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CONTENTS

Editorial

WHAT IS OUR ROLE IN POINTING OUT HISTORICAL BACKGROUND OF DERMATOLOGY IN EUROPE?

Jasna Lipozenčić 151

Short Scientific Article

INTERLEUKIN-2 RECEPTOR γ -CHAIN EXPRESSION IN PATIENTS WITH ALOPECIA AREATA

Ines Brajac, Franjo Gruber, Mladen Petrovečki, Danijela Malnar-Dragojević 154

Clinical Articles

RECURRENCE RATE OF BASAL CELL CARCINOMA AFTER TOPICAL AMINOLEVULINIC ACID-BASED PHOTODYNAMIC THERAPY

Nikolai Naidenov, Rositsa Dencheva, Nikolay Tsankov 157

SENSITIVITY OF INDIRECT IMMUNOFLUORESCENCE TEST IN THE DIAGNOSIS OF PEMPHIGUS

Ines Lakoš Jukić, Branka Marinović 162

Case Reports

UNUSUAL PRESENTATION OF HERPES ZOSTER IN AN IMMUNOCOMPROMISED PATIENT: CASE REPORT

Ivana Kovačević Vojtušek, Mirjana Sabljar Matovinović, Gordana Planinić, Sandra Vučković Rebrina, Ika Kardum Skelin, Mladen Knotek, Dinko Škegro 166

HEREDITARY BENIGN TELANGIECTASIA

Vesna Sredoja Tišma, Ivan Dobrić, Aida Pašić 169

Reviews

FACIAL AND ORAL ASPECTS OF SOME VENEREAL AND TROPICAL DISEASES

Marcia Ramos-e-Silva 173

SKIN DISEASES IN ALCOHOLICS

Krešimir Kostović, Jasna Lipozenčić 181

HISTORICAL DEVELOPMENT OF LOCAL THERAPY OF PSORIASIS VULGARIS

Zlatica Jukić, Ivana Ručević, Vladimira Barišić-Druško, Dujomir Marasović 191

Abstracts 196

News and Comments 221

Reports 230

Marko Polo's Diary 239

Book Review 241

Announcements 243

Instructions to Authors 246

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Aims and Scope

Acta Dermatovenerologica Croatica (ADC) aims to provide dermatologists with up-to-date information on all aspects of the diagnosis and management of skin and venereal diseases. Accepted articles regularly include original scientific articles, short scientific communications, clinical articles, case reports, reviews, reports, news and correspondence. ADC is guided by a distinguished, international editorial board and encourages approach to continuing medical education for dermatovenerologists. ADC is published quarterly. ADC is the official journal of the Croatian

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What Is Our Role in Pointing Out Historical Background of Dermatology in Europe?

It is our duty, when we participate on different dermatological meetings, to discover what dermatovenerology was like long before our times.

We all belong, with all our hearts, to the world of dermatology, and therefore must leave for the generations to come the knowledge of what was before them, before modern technology. What is the point that I want to make? My visit to Department of Dermatology (from 1892) in Wroclaw, Poland (Fig. 1), gave me an idea, and so I want to express my greatest admiration to Prof. Baran, Head of the Department and Congress president, and Prof. Jacek Szepietowski, vice-president of the 10th Congress of the European Confederation of Medical Mycology, which was held in June 17-20, 2004, Hotel Mercure Panorama, Wroclaw, Poland.



Figure 1. The old building of the Department of Dermatology (from 1892) in Wroclaw, Poland.

On June 18, 2004, some of us, active Congress participants visited the Museum, Bibliotheca, and presidential office rooms. What was so special there? "Pupils room" with pictures of former chiefs of dermatology departments, legends in dermatology and venerology: M. Jessner, Köbner and



Figure 2. Albert Neisser, head of the Department of Dermatology in Wroclaw until 1916.

Jaddasohn as well as Korting, A. Neisser (Fig. 2) and Gottron with 5 famous polish dermatologists. Bibliotheca, with the oldest dermatology books and copies of the first issues of journal *Archives of Dermatology*, is situated in an old building from 1892 and has "David's stars" on the ceiling because of the foundation of Jude Committee in Breslow. Albert Neisser, who had been head of the Department until 1916, made a donation to the Department and left his whole property to Wroclaw Museum. During the Second World War, the building was partly destroyed. I enjoyed visiting the Department, where

that special air of the old times mixed well with that of modern ones. The most exciting part of the tour was Museum of Klinika Dermatologiczna, with 404 wax mullages that are unique in Europe, after Vienna and Paris.

Prof. Baran, head of the Dermatology Department, has given me a "dermatology tree" (Fig. 3) with the names of all great dermatologists from Breslow/Wroclaw, including A. Buschke.

Wroclaw spreads over 12 islands connected by 112 bridges. It is known as the "Polish Venice". As one of Poland's oldest cities, Wroclaw has many remarkable architectural sites. Ostrów Tumski (Cathedral Island) is one of the oldest parts of Wroclaw, where traces of the original settlements dating back to the period between the 7th and 9th century have been discovered. Wroclaw is the capital of Lower Silesia, a historical town from 1241 with status of *cavitas* located on an ancient trail linking the West

and South with the major cities of Eastern and Northern Europe. Wroclaw is one of the largest centers of higher learning, research and culture in Poland.

Wroclaw, lying on both banks of the Odra River, is a unique city. Wroclaw had been under the rule of the Czech crown before in 1526, when it was taken by the Habsburg monarchy (renaissance style in Wroclaw). After 1648, the baroque style arrived, and together with gothic it greatly contributed to the city's present architectural beauty. In 1841 the rhythm of life in the city got accelerated, but with destruction of the city, it turned into "Festung Breslow", the over 200 years long German and Prussian rule came to an end. In 1945, around 70% of the city buildings were turned into ruins. In the post-war years, the Old Town and Ostów Tumski were rebuilt and numerous churches were reconstructed. Modern Wroclaw with a population of over 600.000 is a

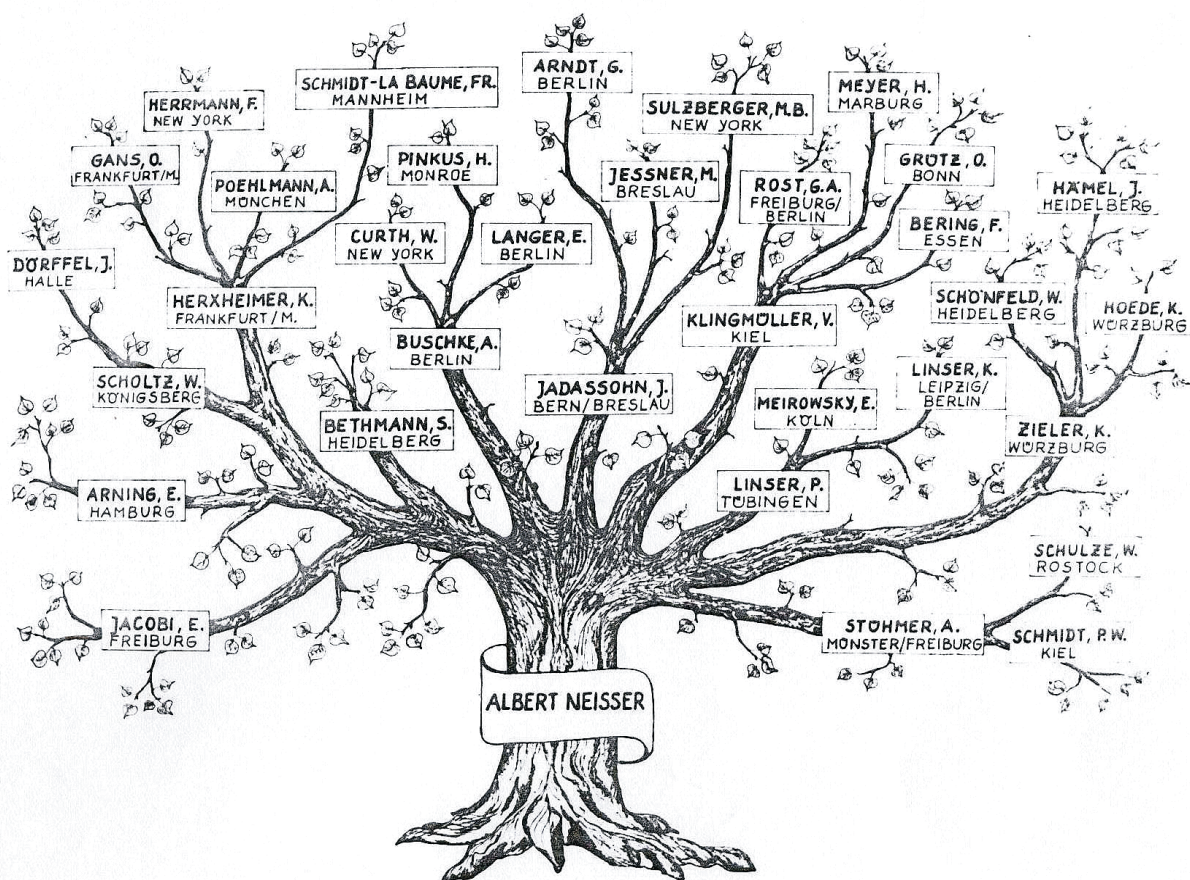


Figure 3. The tree of all famous dermatologists from Breslow/Wroclaw, Poland

seat of many academic and cultural institutions. Nowadays it combines rich thousand years long history with modern life. In 2002, Wrocław University has celebrated 300 years of its existence. I visited Wrocław in June this year, when I participated in the 10th Anniversary and Congress of the European Confederation of Medical Mycology in Wrocław, Poland (June 17-20, 2004).

On Thursday 17, the opening ceremony was held in Leopoldinum Hall of Wrocław University, the most beautiful and grandest hall of Wrocław University with the highest baroque interior in Poland that has been preserved until the present days. Prof. Eugeniusz Baran, Congress President, and Prof. Jacek Szepietowski, Congress Vice-President, opened the event. Prof. E. Baran held a E. Drouhet Lecture: "The wax mycological model collection in Wrocław's Department of Dermatology." We enjoyed in illustrative dermatomycology wax models. Classical music concert given by two young musicians was very nice. Welcome reception took place in Piwnica Swidnicka, a famous old and historical beer hall. It was a pleasure to meet some old friends and make some new ones. I was the only active presenter from Croatia.

On Friday, June 18, 2004, National delegate speakers from Greece, the Netherlands, Turkey, Bulgaria, Russia, Poland, Sweden, Israel, UK, Spain and Germany held their lectures. The main problem among fungal infections today seems to be *Candida albicans* infection and new diagnostic methods for identification of non-candida species, such as *C. dubliniensis*, whose genome will be soon known. All speakers pointed out that identified biological features, virulence traits, pathogenesis, and genomics of emerging new pathogens are extremely important because of prophylaxis of susceptibility of candida infections. The same day I visited the Raclawice Panorama Wrocław as one of the few places in the world that houses a relic from 19th century popular culture: an enormous painting, 120 meters long and 15 meters high. The *Panorama* was painted in 1894 to commemorate the centenary of the Kosciuszko Insurrection and the victory at the battle of Raclawice on April 4, 1794 (Fig. 4).



Figure 4. "The victory in the battle of Raclawice on April 4, 1794."

Saturday, June 19, 2004, there were many parallel sessions: antifungals, taxonomy, epidemiology and ecology; emerging fungal pathogens; dermatomycology; fungal infections in immunocompromised host; veterinary mycology, and a sponsored symposium by Schering-Plough "Facing the future in anti-fungal therapy".

Congress Dinner for all 348 participants was in the Museum of Architecture in Wrocław, where beautiful Dominican claustrum and Museum are, with 200 old Japanese paintings and archeological exemplars.

On Sunday, June 20, 2004, Free Communication took place in a form of parallel sessions: dermatomycology, general mycology; classic and new methods; host fungal relationships. I was happy to have opportunity to give the lecture as only one from Croatia and co-chair the Session.

The plenary lecture at the end of 10th Congress of the European Confederation of Medical Mycology in Wrocław was held by Dr. Hube (Germany), under the title "Transcriptional profiling of *Candida albicans* during infection", followed by a closing ceremony with awarding the best poster from Greece.

Congratulations for organizing the event on such a high scientific and social level for about 70 oral presentations, 200 posters, and 348 registered participants. We hope that the next one in Berlin in 2005 will be equally successful.

Prof. Jasna Lipozenčić, MD, PhD

Editor-in-Chief

Interleukin-2 Receptor γ -chain Expression in Patients with Alopecia Areata

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SUMMARY Interleukin-2 (IL-2) is a lymphokine produced by activated T-cells. Its receptor, IL-2R, is expressed on T-cells. Several clinical and experimental findings point towards IL-2 as a crucial mediator inducing immunologic reaction against human follicle in alopecia areata. The objective of our study was to analyze the expression of IL-2R as a sign of T-cell activation in scalp biopsies of patients suffering from alopecia areata. An immunohistochemical analysis was used to determine the difference in cytokine-regulated expression of IL-2R between 45 patients with active and stable phase of alopecia areata and 23 healthy control subjects. In the patients with alopecia areata in active phase, the expression of IL-2R in scalp biopsies was significantly stronger than that in the patients with stable disease and in controls. The increase of IL-2R⁺ cells in early phase of the disease could suggest that T-lymphocyte activation with IL-2 secretion and IL-2R expression may initiate the immune inflammatory mechanism of alopecia areata.

KEY WORDS Interleukin-2R, alopecia areata, immunohistochemistry

INTRODUCTION

Alopecia areata is a common disease that primarily affects the hair follicle as it enters the prolonged growth phase called anagen (1). There is strong direct and indirect evidence that alopecia areata is an autoimmune disease (2). Expression of CD40, CD54, and HLA-DR was seen in the hair structure including the dermal papilla. Consistent with these observations, interferon-gamma-producing cells were also detected in the perifollicular infiltrate, corresponding to a cytokine pattern of the Th1 T-helper type cells (3). Intraepithelial mononuclear cells positive for IL-2R γ -chain in association with ICAM-1 and E-selectin expression were found in alopecia universalis (4). Their finding adds credence to the view that ICAM-1 and HLA-DR on epi-

thelial cells may be induced secondarily by cytokines derived from activated T-cells (5). Nevertheless, no information is available regarding the levels of IL-2 receptor in the scalp lesions in patients with active vs. those with stable alopecia areata. For this reason, immunohistochemical analysis was used to determine cytokine-regulated expression of IL-2 receptors in different phases of the disease.

PATIENTS AND METHODS

Our study included 45 patients with alopecia areata and 23 healthy control subjects. There were 17 men and 28 women in the patient group, aged between 20 and 65 years. In 29 patients the dis-

ease was active, whereas in 16 patients it was in a stable phase. The active phase of disease was characterized by ongoing hair loss (positive hair pull test) and so-called exclamation point hairs often seen near the margin of enlarging lesions. The disease was in a stable phase if the hairless patches had not increased in their dimension in 3 weeks preceding the study. Patients with stable alopecia areata had also bald circular patches on their scalps, but with no sign of active process.

The control group consisted of 7 women and 16 men, aged between 18 and 65 years.

None of the patients had used any systemic medications for alopecia areata treatment that could have had a prolonged effect on cytokine levels for at least 6 months before the study. We excluded the patients with other types of illnesses, such as autoimmune diseases that could affect the outcome of the study, and those who had received systemic steroid treatment and other immunosuppressive medications. None of the patients had received any kind of medication for at least 1 month before this study, and none, including the controls, had suffered from any viral or bacterial infection for at least 1 month prior to examination.

Scalp Biopsies

From the patients attending an outpatient clinic at the Rijeka University School of Medicine, elliptical biopsies of scalp skin were taken under local anesthesia (lidocaine 1%). Scalp biopsies were performed after obtaining informed consent from the patients as well as controls. Samples of a normal human scalp were obtained from the patients during the routine excision of benign scalp lesions (e.g., epidermoidal cysts or melanocytic naevi). In each case of active alopecia areata, a biopsy was taken from the "active" edge of patch identified by the "hair pull" technique. In cases with stable phase of alopecia areata, without progression and with negative "hair pull test", biopsies were also taken from the edge of the patch.

The tissue samples were immediately snap-frozen in liquid nitrogen and sectioned transversely in their entirety with a cryostat. Consecutive 6- μ m sections were placed on numbered microscope slides and stored at -70 °C until stained.

Indirect Immunoperoxidase

Cryostat sections were processed for immunocytochemistry by using monoclonal antibody against interleukin-2 receptor α -chain (CD25; Dako A/S, Copenhagen, Denmark). Slides were incubated with monoclonal antibody (1:50) in phosphate-buffered saline (PBS) at room temperature for 30 minutes. After three wash steps in PBS, slides were incubated at room temperature for 30 minutes with peroxidase-labeled rabbit anti-mouse IgG (Dako A/S) in PBS (1:40). After being washed twice in PBS, the slides were incubated in 50 mL of diaminobenzidine (DAB) solution (0.5 mmol/L Tris HCl, pH 7.6, 15 mg of DAB, 100 μ L of H₂O₂, 25 mg imidazole) at room temperature for 20 minutes. Finally, the slides were dried and mounted in Canada balsam.

Statistical Analysis

Data distribution between the groups were compared by using Fisher's exact probability test. P value less than 0.05 was considered to be statistically significant. Statistical analysis was performed with MedCalc statistical software (MedCalc Inc., Mariakerke, Belgium).

RESULTS

The expression of IL-2R was significantly higher in the patients during the active phase of alopecia areata than in those during the stable phase of disease ($p=0.037$). The cells positively stained by monoclonal IL-2R antibody in the active phase of disease were graded as positive in 8 out of 29 patients. Expression of IL-2R in healthy control subjects was categorized as negative (Table 1).

There was no significant difference between the expression of IL-2R in patients with alopecia areata in the stable phase of the disease and in control subjects. In the stable phase of disease, and also in the controls, this expression was graded exclusively as negative. This weak expression was very similar in patients with the stable phase of alopecia areata and healthy controls ($p>0.95$; Table 1).

DISCUSSION

According to our findings, it is possible that T-lymphocyte activation with secretion of IL-2 and

Table 1. Expression of monoclonal antibody interleukin (IL)-2R positive cells in different clinical phases of alopecia areata and in healthy controls

| IL-2R | Patients | | | | Controls (n=23) |
|----------|------------------------|-------|------------------------------|-------|-----------------|
| | in stable phase (n=16) | p* | in early/active phase (n=29) | p† | |
| negative | 16 | 0.037 | 21 | 0.999 | 22 |
| positive | 0 | | 8 | | 1 |

*Comparison between patients in stable and early/active phase.

†Comparison between patients in stable phase and controls.

IL-2R expression initiates the immune inflammatory mechanism of alopecia areata and subsequent hair loss. Expression of intraepithelial mononuclear cells positive for IL-2R α -chain in active alopecia areata is consistent with the view that lymphocyte activation by IL-2 is involved in the pathogenesis of alopecia areata (6). Also, the presence of IL-2R+ intraepithelial cells only in early phase of alopecia areata adds credence to the view that HLA-DR and ICAM-1 on epithelial cells may be induced secondarily by cytokines derived from skin-infiltrating, activated T-cells.

Although the etiopathogenesis of disease is poorly understood, evidence is accumulating that it can be regarded as a T-cell-mediated tissue-restricted autoimmune disease, especially expressing the T-helper type 1 cytokines interleukin-2 and interferon-gamma (7). The results in our study are in accordance with high levels of IL-2 observed in scalp biopsies in untreated alopecia areata and high concentrations of sIL-2R in peripheral blood in active phase of disease (3,6). The expression of the IL-2 α -chain is transcriptionally regulated. It is not expressed in resting T-cells. Resting T-cells fail to produce IL-2 or to proliferate in response to antigen, but they are induced to express IL-2R and will proliferate if exogenous IL-2 is present (6). The successful immunotherapy of established melanoma metastases in experimental mice can be achieved by antibody-targeted IL-2 administration. In 20% of such treated animals, the therapeutic effect is accompanied by progressive alopecia, which shows characteristics of alopecia areata. Furthermore, alopecia could be transmitted horizontally by passive transfer of lymphocytes from the treated animals to naïve mice (8). Since cells that have been previously activated continue to express low levels of IL-2R-chains, this would be a particularly attractive way by

which the recruitment of memory T-cells into an immune response might be facilitated. However small the presence of IL-2 R+ cells within the dermal papilla in a stable phase of the disease, as recorded in our study, may be important to maintain a chronic nature of alopecia areata in some patients.

Our hypothesis, based on the data available so far, is that IL-2 is a crucial mediator inducing as well as maintaining immunologic reaction against the hair follicle in alopecia areata.

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Recurrence Rate of Basal Cell Carcinoma After Topical Aminolevulinic Acid-Based Photodynamic Therapy

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SUMMARY Photodynamic therapy with topical 5-aminolevulinic acid is an alternative to the surgical treatment and radiotherapy of different non-melanoma skin cancers, especially basal cell carcinoma (BCC). Advantages of photodynamic therapy include selective destruction of the tumor; lack of toxicity; possibility to perform the procedure easily at any part of the human body; and single application, which is comfortable especially for elderly patients. Photodynamic therapy can be performed repeatedly without side effects and the cosmetic outcome is excellent. It is very convenient for large and multiple lesions and is the only choice for patients contra-indicated for surgery or radiotherapy. Disadvantage of photodynamic therapy is a relatively high recurrence rate of BCC after a single photodynamic procedure, ranging between 0% and 100%. We followed up a group of 60 patients with BCC who were treated with a single photodynamic procedure. The recurrence rate in our patients was 35%. The most probable reasons for the relatively high recurrence rate were the size, localization, and histological type of the lesion; chemical structure of a photosensitizer used; the light source; and the dose. The lowest recurrence rate was observed in superficial BCCs.

KEY WORDS basal cell carcinoma; phototherapy; recurrence

INTRODUCTION

Photodynamic therapy is a new treatment modality that combines photosensitizers and light. It has been increasingly used for the treatment of both malignant lesions and benign chronic skin disorders. Psoralen-containing plant extracts and light had been used for the treatment of dermatological diseases, such as psoriasis or vitiligo, as early as in ancient Egypt, India, and Greece (1-3). The concept, generally known as photochemotherapy, represents a common basis for different treatment procedures, such as PUVA, extracorporeal photophoresis, and photodynamic therapy (3).

Treatment of skin tumors with topically applied eosin and visible light was first proposed by Von

Tappeiner and Jesionek (4) in 1903. A year later, in 1904, the term "photodynamic" was introduced for describing oxygen-consuming chemical reactions induced by photosensitizers in biology (5). In 1974, Petkov, Boyanov, and Tsankov described a method for photodynamic inactivation of herpes simplex after application of eosin and visible light (6).

The clinical use of photodynamic therapy is based on the work of Dougherty *et al* (7), who in 1978 presented data on a successful application of this new technique in the treatment of skin cancer and other malignancies. Since then, photodynamic therapy has gained increasing interest in medicine, representing an experimental tool for the detection

and treatment of tumors located in the lung, esophagus, colon, peritoneum, pleura, urogenital tract, brain, eye, and skin.

Further investigations have been done for expanding the spectrum of clinical entities, benign and malignant alike, that could successfully be treated by photodynamic therapy.

The aim of our study was to evaluate the recurrence rate of basal cell carcinoma after photodynamic therapy combined with 5-aminolevulinic acid.

MATERIAL AND METHODS

We treated a group of 60 patients with basal cell carcinomas (BCCs) for 3 years and then evaluated the response to photodynamic therapy and the cancer recurrence rate. There were 36 men and 24 women. The mean age of men was 70.3 years and the mean age of women was 67.2 years.

Clinical diagnosis of BCCs was histologically confirmed in all patients. Three types of BCCs were distinguished: superficial BCC was diagnosed in 39 patients; BCC planum cicatrisans in 9 patients, and nodular BCC in 12 patients. The average size of the lesions was 9.3 cm².

Photosensitizer was a 20%-aminolevulinic acid (ALA) in a cream base. It was applied under occlusive dressing to improve the penetration into the treated tissue and to prevent undesired degradation of the chemical by visible light. The cream was removed after 4 hours and the lesion was irradiated with a visible light of 635 nm wavelength. The common slide projector was used as the light source in 36 cases and Waldmann photodynamic 1200 lamp in the remaining 24. A single irradiation dose was 150 J/cm² per procedure. The follow-up period lasted 1-3 years and included 4-12 visits (months 1, 3, 6, 12, 18, 24, 30, and 36).

RESULTS

There were three possible clinical results after the therapy: complete response, characterized by full clinical recovery of the treated lesion after photodynamic therapy; partial response, characterized by a decrease in the size and thickness of the lesion; and no response, or no improvement after the photodynamic therapy.

After one treatment session, a complete response was achieved in 37 out of 60 cases, partial response in 19, and in 4 patients there was no response (Fig. 1).

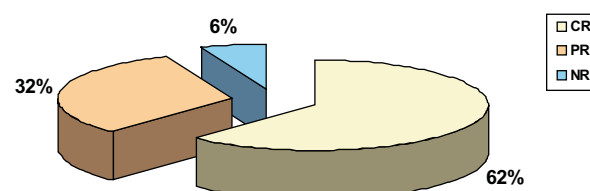


Figure 1. Results after photodynamic therapy of basal cell carcinoma in 60 patients.

The recurrence rate, defined as an appearance of new lesion after a complete response or its enlargement after partial response, was 35% as estimated 24 months after the photodynamic therapy. These 21 patients with recurrent disease were mostly patients who showed a partial response to the therapy (Fig. 2).

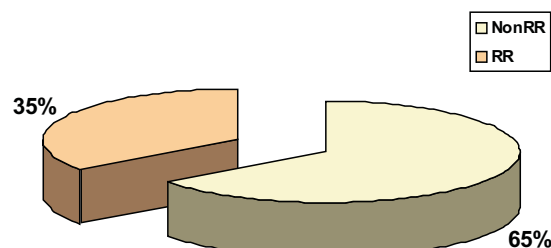


Figure 2. Recurrence rate of basal cell carcinoma in 60 patients after photodynamic therapy.

According to the histological type of BCC, the cancer reappeared in 2 out of 39 patients with superficial BCC (Fig. 3), in 3 out of 9 with planum cicatrisans BCC (Fig. 4), and in 8 out of 12 patients with a nodular type of BCC (Fig. 5).

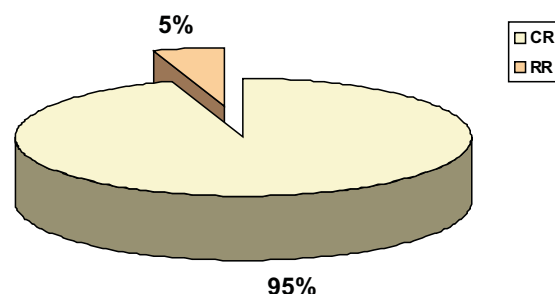


Figure 3. Recurrence rate of superficial basal cell carcinoma in 39 patients after photodynamic therapy.

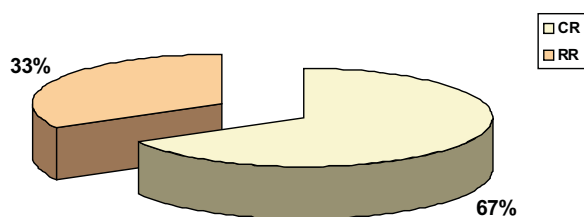


Figure 4. Recurrence rate of superficial basal cell carcinoma, type planum cicatrisans, in 9 patients after photodynamic therapy.

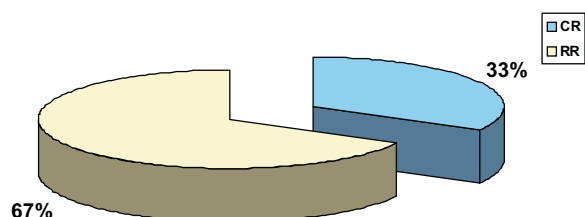


Figure 5. Recurrence rate of nodular type of basal cell carcinoma in 12 patients after photodynamic therapy.

DISCUSSION

The accessibility of the skin to light has led to a frequent use of photodynamic therapy in dermatology. Various precancerous and malignant tumors, preferentially actinic keratoses as well as basal cell and squamous cell carcinomas, have shown partial or complete clinical response to photodynamic treatment (8,9).

Evaluation of clinical response of BCCs to photodynamic therapy depends on many factors. The optimal therapeutic response in the course of the therapy depends on the type of photosensitizer and its accumulation in target cells. Different chemical substances have been used as photosensitizers in photodynamic therapy, such as porphyrins, aminolevulinic acid and its esters, porphines, phthalocyanines, chlorine derivatives, and lutetium texapyrin (Lu-TeX).

Photodynamic therapy with topical 5-aminolevulinic acid is a relatively new method used for the treatment of precancerous lesions (actinic keratoses) and non-melanoma skin cancers. The combination of a photosensitizer, light, and oxygen leads

to the selective phototoxic destruction of tumor cells. ALA is not a photosensitizer, but its topical application leads (*via* biosynthetic pathways) to accumulation of photosensitizer protoporphyrin IX (Pp IX) in tumor cells. The irradiation with light (635 nm) leads to photoactivation of Pp IX and formation of reactive oxygen and free radicals, followed by cytotoxic effect and destruction of the target cells.

The efforts of investigators are now directed for finding new substances or derivatives, suitable for better penetration into the treated lesions. The new derivative of ALA - lipophilic methyl ester shows better tumor selectivity and penetration as well as enhanced porphyrin production, which results in improved effectiveness of the treatment (10).

Basal cell carcinomas represent the most common cutaneous malignancy treated by photodynamic therapy, which is mostly based on the use of topically applied photosensitizers. According to the medical literature, the overall response rate of BCCs to photodynamic therapy varies between 60% and 100% (11-14).

The most important factors that could influence the response of the tumor to the therapy and increase its recurrence rate are histological type, size, ulceration, and localization (15). Patients that failed previous treatment with other modalities are considered to have worse chances for successful photodynamic (16,17).

Our results showed that histological type of the BCC is one of the most important criteria that should be considered when making the decision on applying photodynamic therapy. The best therapeutic results were achieved in superficial BCC, where complete response rate ranged from 79% to 100% (3,18-21). The results observed by us showed a significantly lower recurrence rate with superficial BCC, then with other types. Nodular and nodulo-ulcerative forms of BCC show low complete response rates ranging between 10% and 50% (10,18, 21,22). The sclerodermiform BCC is thought to have the poorest response and the highest recurrence rate (10,14). The limited penetration of ALA into the deeper layers of tumors contributes at least partly to the lack of sufficient response to photodynamic therapy (23,24). The best results of topical ALA-photodynamic for nodular BCC have been obtained by repeated treatment sessions, leading to a

100% complete response rate (25). Repeated treatment sessions lead to a decrease in the tumor size and might reveal deeper tissue layers, enabling the destruction of the entire lesion. The increase of ALA penetration, leading to its accumulation in deeper layers of the tumor, could be achieved by prolonging the application time up to 48 hours, which is considered to enhance the efficacy of photodynamic therapy (5,26).

There is another possibility to increase the penetration of ALA. Orenstein *et al* (20,27) reported that local ALA-photodynamic therapy combined with dimethyl sulfoxide (DMSO) and EDTA resulted in increased complete response rate, probably because of the increased ALA penetration. The concomitant application of DMSO and EDTA with ALA may have increased the Pp IX production and enhanced the complete response rate of nodular BCCs (3,28-30). The inverse correlation of tumor thickness with the response rate to topical ALA-photodynamic was also demonstrated by Morton *et al* (24).

Better distribution of photosensitizers could be obtained after oral or intravenous administration of ALA that could be valuable for recalcitrant nodular and sclerodermiform BCCs (26). This advantage over topical photodynamic is limited by the long-lasting photosensitivity after the systemic application of the chemicals.

Photodynamic therapy could be combined with other therapeutic modalities for improvement of its efficacy. The treatment of nodular BCCs with photodynamic therapy after surgery, electrocoagulation or curettage leads to better results. The local or regional cell nests could be found on the site after radical removal or curettage of the lesion and cause further recurrences (10). Thus, the reduction in the size of tumor is recommended for better penetration of chemical agents, followed by ALA-photodynamic therapy, which would destroy the remaining tumor cells and diminish the possibility for recurrences.

There are several more factors that should be considered about possible reasons for higher BCC recurrence rate: the dose of light and the duration of irradiation as well as the sort of light source. It is not clear whether high intensity of light and shorter exposure or a lower intensity and longer exposure should be used (15,16). It seems that the light

source does not influence the recurrence rate as long as the wavelength is 635 nm. It is important to remember that the light intensity in the center of the lesion and on its periphery is different. When multiple lesions are located on a convex surface, it is necessary to deliver light from multiple directions to insure the illumination of all lesions.

Based on our data and the review of the literature, we suggest photodynamic therapy as an effective treatment of superficial BCCs. Conventional treatment modalities of BCCs, such as surgical excisions, curettage in combination with electrocoagulation and irradiation have lower recurrence rates (31). Photodynamic therapy should be considered as an alternative therapy for patients who are unable to undergo surgery for medical reasons or have been previously treated with radiation therapy, or for those with superficial BCC. The very good results and acceptable cosmetic outcome are proving that photodynamic therapy is a promising alternative in the treatment of BCCs.

CONCLUSION

To be able to correctly estimate the BCC recurrence rate it is important to consider the clinical and histological type of the tumor, previous treatment failures, type of photosensitizer, and additional chemical substances that could improve its penetration and time between application and irradiation. Additional therapeutic modalities could be combined with photodynamic therapy for better results. The indications for this management method in dermatology are constantly enhancing and it is a useful complement of the established therapeutic schemes for benign and non-melanoma malignant tumors as well as for other dermatological disorders.

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Sensitivity of Indirect Immunofluorescence Test in the Diagnosis of Pemphigus

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SUMMARY Indirect immunofluorescence testing of sera from patients with pemphigus produces a positive intercellular staining on a variety of epithelial substrates with different sensitivity. We aimed to determine the sensitivity of indirect immunofluorescence (IIF) test in detecting pemphigus antibodies, using two different substrates: guinea pig lip and human skin. IIF detected antibodies in 66 out of 109 patients with different types of pemphigus. Sensitivity of IIF performed with guinea pig lip was 40%, while with human skin it increased to 69%. However, we found that neither human skin nor guinea pig lip was sensitive enough to make an IIF test reliable for the diagnosis of pemphigus.

KEY WORDS indirect immunofluorescence; pemphigus; substrate

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INTRODUCTION

The diagnosis of a bullous disease relies on three independent sets of criteria: clinical, histologic and immunologic criteria. The pemphigus group of diseases encompasses a spectrum of autoimmune bullous skin diseases characterized clinically by the development of blisters on skin and mucous membranes, histologically by intraepidermal acantholysis, and immunologically by the production of antibodies directed against desmosomes (1). Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are characterized by autoantibodies to desmosomal glycoproteins desmoglein 3 and desmoglein 1, the cadherins that extend from the desmosomal plaque into the intercellular space where they joint desmogleins from adjacent keratinocytes. Desmoglein 1 is expressed throughout the epidermis, more intensely in the superficial layers, whereas

desmoglein 3 is expressed in the lower part of the epidermis, mainly in the basal layer. In the mucous membrane, desmogleins 1 and 3 are expressed throughout the squamous mucosal epithelia, but expression of desmoglein 1 is much lower than that of desmoglein 3 (2). The autoantigen in IgA pemphigus is desmocollin 1, another desmosomal cadherin. The main target antigen for pemphigus herpetiformis (PH) is most often desmoglein 1 (3). Patients with paraneoplastic pemphigus (PNP) have polyclonal antibodies against antigen complex of different proteins of the plakin family, including desmoplakins 1 and 2, bullous pemphigoid antigen 1, periplakin, and envoplakin (4). Indirect immunofluorescence (IIF) study is a test in which a patient's serum is examined for the presence to a defined antigen. According to literature, indirect

immunofluorescence test (IIF), performed on different substrates, is positive in approximately 85-90% of patients with active PV, in 60-70% patients with PF, and in 50% patients with IgA pemphigus (1,5,6).

Our aim was to determine sensitivity of indirect immunofluorescence test in detecting pemphigus antibodies, using two different substrates: guinea pig lip and human skin.

PATIENTS AND METHODS

During a 7-year-period, from 1997 to 2003, 109 patients with various type of pemphigus were hospitalized at our Department. Eighty two sera from PV patients, 9 from IgA pemphigus, 16 from PF, one from a pemphigus herpetiformis (PH), and one from a pemphigus paraneoplasticus (PNP) patient was tested for presence of pemphigus antibodies.

Serum specimens submitted for IIF were collected without anticoagulant and centrifuged. The serum was incubated at an initial dilution of 1:10 with 4-5 m-thick frozen sections of the epithelial substrate for 30-40 min at room temperature in moist, dark chambers. After 10-15 min, the sections were washed in phosphate-buffered saline (PBS), incubated with a fluorochrome-labeled animal serum prepared against human immunoglobulins, and finally, after a second wash in PBS, examined under a fluorescence microscope. The fluorochrome used was fluorescein isothiocyanat.

During 1997-1998, IIF testing was performed on guinea pig lip (Hartley strain), whereas in 1999-2003 period, human skin (HS), which was obtained from surgical specimens from the neck and axillae, was used as substrate.

Sensitivity was calculated as true positive/true positive + false negative.

RESULTS

Pemphigus antibodies were detected by IIF in 66 (61%) out of 109 patients with different type of pemphigus, while 43 (39%) IIF tests were negative. Considering IIF substrate, IIF studies done on guinea pig lip (1997-1998) were negative in 19 out of 32 patients, whereas those done on human skin (1999-2003) were negative in 24 out of 77 patients (Table 1).

Table 1. Sensitivity of indirect immunofluorescence (IIF) tests performed with two different substrates

| Substrate | No. of patients | IIF (%) | |
|----------------|-----------------|----------|----------|
| | | positive | negative |
| Guinea pig lip | 32 | 13 (41%) | 19 (59%) |
| Human skin | 77 | 53 (69%) | 24 (31%) |
| Total | 109 | 66 (6%) | 43 (39%) |

In 1997-1998 period, there were 24 patients with PV and 5 patients with PF, and in 1999-2003 period, there were 58 patients with PV and 11 patients with PF. Pemphigus foliaceus antibodies reacted more strongly on guinea pig lip (60%) than pemphigus vulgaris antibodies (38%), while human skin appeared to be more sensitive substrate in detecting pemphigus vulgaris antibodies (69% vs. 64%; Table 2). The sensitivity of IIF studies done with sera of IgA pemphigus patients was 50% on guinea pig lip as a substrate, compared with 57% on human skin. IIF evaluation of the sera of patients with PH and PNP performed on human skin was positive in both cases.

Table 2. Sensitivity of indirect immunofluorescence tests in pemphigus vulgaris and pemphigus foliaceus on two substrates

| Substrate | No. of patients with | | |
|----------------|----------------------|---------------------|-------|
| | pemphigus vulgaris | pemphigus foliaceus | total |
| Guinea pig lip | 9/24 | 3/5 | 29 |
| Human skin | 40/58 | 7/11 | 69 |
| Total | 49/82 | 10/16 | 98 |

DISCUSSION

Indirect immunofluorescence is a more sensitive assay when human skin is used as a substrate. In our study, it was much higher than when guinea pig lip was used. A statistically relevant comparison, however, was not possible because the number of sera investigated with human skin as a substrate was more than twice the number of sera investigated with guinea pig lip. Although there was a small number of sera from PF patients, human skin was a more sensitive substrate in patients with PV than in patients with PF.

The understanding of pemphigus as an autoimmune disease of the skin began with the discovery

of circulating antibodies directed against the cell surface of keratinocytes. While these antibodies are not species-specific and react with human, monkey, guinea pig, and rabbit epithelial substrates, they are organ-specific and react only with squamous epithelium (7). Detection of circulating antibodies can be achieved by IIF performed on different epithelial substrates with characteristic intercellular space fluorescence pattern (Fig. 1.). Substrate specificity can be used to determine the type of pemphigus in IIF. Many authors have concluded that monkey tissues are superior to other substrates, e.g., of rabbit, human or guinea pig origin, for the detection of PV antibodies, whereas rabbit tissue has seemed better for the detection of PF antibodies (8-10). Harman *et al* (11) compared sensitivity of monkey esophagus and human skin in detecting circulating antibodies in pemphigus vulgaris and pemphigus foliaceus. Overall, the sensitivity of IIF was 83% on human skin and 90% on monkey esophagus. In PF patients, the IIF sensitivity was 100% on human skin and 67% on monkey esophagus. In contrast, IIF sensitivity was greatest on monkey esophagus in PV, i.e. 100% compared with 75% on human skin. The findings correlated well with the clinical phenotypes of pemphigus patients; human skin, desmoglein 1 rich substrate, was a better substrate in patients with cutaneous disease only, while monkey esophagus, a mucosal substrate rich in desmoglein 3, was more sensitive in patients with mucosal lesions. IIF performed on both human skin and monkey esophagus improved the diagnostic sensitivity in pemphigus compared with using either substrate alone (11). However, guinea pig esophagus, also a mucosal substrate, was more sensitive than monkey esophagus for detecting antibodies in PF and less sensitive for de-

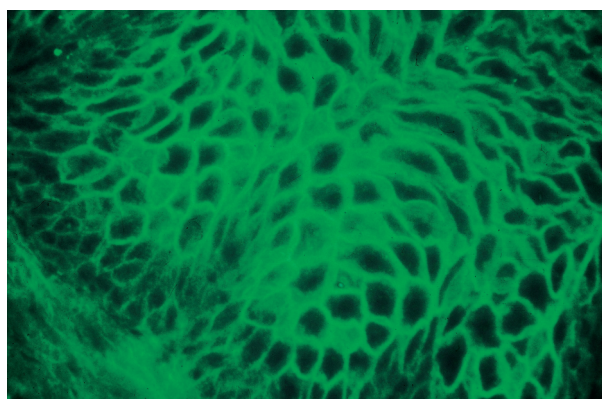


Figure 1. IIF. Intercellular fluorescence.

tecting PV antibodies, probably because of a stronger expression of desmoglein 1 (9). Matis *et al* (12) reported that adult human skin from the head or neck or neonatal foreskin is a more sensitive substrate than monkey esophagus in IIF for PV and PF antibodies, especially when used with a buffer supplemented with 5 mmol/L calcium chloride. It is unclear whether calcium acts by facilitating binding of the pemphigus antibody to the pemphigus antigen or by protecting the pemphigus antigen against proteolysis. Another factor that can influence the sensitivity of human skin as a substrate for IIF is regional expression of pemphigus antigen. Sison-Fonacier and Bystryń (13) found that the skin from the head, neck, armpits, and legs had greater antigen expression, whereas the skin from the back and groins had lesser expression of antigen. Sera from patients with paraneoplastic pemphigus reacted not only to the cell surfaces of skin and mucosa in a pattern typical of pemphigus, but also to simple, columnar and transitional epithelia, which is why IIF on rat bladder epithelium is an adequate screening test with a sensitivity up to 89% (14).

The failure to demonstrate pemphigus antibodies in sera of some patients with active disease may be due to their species or organ specificity, to prozones, to interference by other antibodies, or to errors in technique. Prozone phenomenon might be due to the presence of intercellular antigens in sera, the presence of blocking antibodies or due to enzymatic degradation of labile intercellular antigens or by the serum activation of enzymes present in the cryostat cut sections, which serve as a substrate. Interference phenomenon seems to be caused by the consumption of the labeled antiglobulin by one of the reactive tissue antibodies to the exclusion of the others (15). False positive results can be produced by sera containing antibodies to cell-surface antigens. These pemphigus-like antibodies have been described in patients with extensive burns, penicillin allergy, trichophyton rubrum infection, cicatricial and bullous pemphigoid. These antibodies produce dull intercellular fluorescence pattern limited to the lower epithelial layers (10).

No matter which substrate is used, there are some patients with pemphigus in whom antibody titer may be low in the presence of extensive lesions or in whom antibody titers may be high in the absence of skin changes. Use of IIF titers to monitor

disease activity may not be justifiable in an individual patient because of wide variations in titer. However, there is a positive statistical correlation between disease severity and titer when groups of patients are considered (10).

In cases where IIF findings are not conclusive, more sophisticated tests may be used, such as immunoelectron microscopy, immunoblotting and immunoprecipitation, and enzyme-linked immunosorbent assay (ELISA). Cozzani *et al* (1) showed that IIF performed on monkey esophagus had the same high sensitivity as immunoblotting for the detection of circulating PV antibodies, but IIF performed on rabbit lip was more sensitive than immunoblotting for the diagnosis of PF. The similar results were reported by Jiao and Bystryń (16).

CONCLUSION

Our study showed that neither human skin nor guinea pig lip is sensitive enough to make an IIF test reliable for the diagnosis of pemphigus. The literature data strongly suggest that at least two substrates should be used for IIF testing: one rich in desmoglein 1, such as human skin, and the other rich in desmoglein 3, such as monkey esophagus. This combination of substrates should not only increase the sensitivity of detecting pemphigus antibodies, but will aid in differentiation of PV from PF. Thus enhanced diagnostic sensitivity might be more useful for disease monitoring. Other tests for detecting pemphigus antibodies (immunoblotting, ELISA) are more time-consuming and expensive, so IIF will continue to remain one of the gold standards for the diagnosis of pemphigus.

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Unusual Presentation of Herpes Zoster in an Immunocompromised Patient: Case Report

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SUMMARY We present a case of an immunocompromised patient with unusual presentation of herpes zoster infection. After having been treated with corticosteroids for several weeks, the patient developed the zoster infection with atypical clinical course and skin localization. Parenteral treatment with acyclovir for 10 days resulted in a complete clinical resolution of the skin lesions. Similar cases of unusual presentation of herpes zoster have been described in immunocompromised patients.

KEY WORDS herpes zoster; immunosuppression

INTRODUCTION

Infection with varicella-zoster virus presents with two distinct syndromes: chickenpox (varicella) and herpes zoster. Chickenpox is a benign manifestation of primary infection with the virus and usually occurs in childhood as an epidemic among susceptible children. The subsequent reactivation of latent varicella-zoster virus in dorsal-root ganglia results in a localized cutaneous eruption, herpes zoster. The manifestation of herpes zoster infection may occur at all ages, but its incidence is the highest among the individuals between the sixth and eighth decade of life. The well-defined risk factor for the development of herpes zoster is altered cell-mediated immunity, which occurs as a consequence

of the aging process, immunosuppressive illness, or immunosuppressive treatment (1-3).

During the prodrome of herpes zoster, patients usually report headache, photophobia, and malaise. Fever is present in rare cases. The disease begins with abnormal skin sensations localized within a dermatome and often associated with severe pain. These sensations precede the development of visible skin lesions in a form of an erythematous maculopapular rash. Clear vesicles, which continue to appear over three to five days forming the clusters, evolve to pustules, ulcers, and crusts (4). The dermatomes from the T3 to L3 are most frequently involved (5).

In the immunocompromised patient lesions continue to form over a week, and scabbing in most cases usually completes only after 3 weeks (5,6). These patients usually have a disseminated form of the disease, with extensive skin lesions (1,7).

CASE REPORT

A 56-year-old Caucasian male patient, previously diagnosed with undifferentiated collagenosis and treated with corticosteroids for four weeks, was admitted to the hospital three days after the onset of the skin symptoms. For two years, the patient had had inflammatory polyarthritis with positive serum rheumatoid factor, but did not meet the American College of Rheumatology classification criteria for rheumatoid arthritis. He had been occasionally treated with non-steroid anti-inflammatory drugs. The analysis of serologic markers of autoimmune diseases was positive to nuclear extractible antigens, and negative to antinuclear factor, anti-Sm, and anti-RNP antibodies. The identification of anti-SS-A and anti-SS-B was not performed due to the technical difficulties but these markers were presumed positive, because the antibodies to whole group of nuclear extractible antigens were positive. Four weeks before the onset of skin symptoms, the patient was admitted to hospital because of high fever, newly diagnosed nephrotic syndrome, dysmorphic erythrocyturia, and renal failure (serum creatinine, 131-155 mol/L). As he refused to undergo kidney biopsy, he was administered a daily dose of 80 mg metilprednisolon IV. This corticosteroid IV therapy was continued after his discharge from the hospital under the supervision of his general practitioner. During the course of the corticosteroid therapy, the patient observed red spots with vesicles on the skin of the internal side of his left thigh and front side of the shin. He also felt pain in this area, which he described as itching and burning. He did not take any analgesics because the pain was tolerable, but he had a fever (39°C), which was the main reason for rehospitalization.

On admission, the patient was prostrated, dehydrated, and febrile (39.3°C), with the arterial blood pressure of 100/60 mm Hg. Physical examination revealed a normal cardiorespiratory status, except for sinus tachycardia (100/min). Dermatological changes included erythematous plaques with areas of ulcerations and crusts covering the internal side



Figure 1. Red spots with vesicles on left thigh.

of the left thigh (Fig. 1). Similar changes, but without crusts and ulcerations, involved most of the left shin. Only a few vesicles on the erythematous macules were found in the sacral and right gluteal region (Fig. 2).



Figure 2. Vesicles and macules in the sacral and right gluteal region.

Laboratory findings revealed normal white blood and differential blood count. Both C-reactive protein and erythrocyte sedimentation rate were increased. The blood and urine cultures were sterile on several occasions.

Chest X-ray was normal, abdominal ultrasound showed a mild enlargement of the spleen, and several enlarged lymph nodes in the para-aortal region, already noticed during previous hospitalizations and explained as a part of the undifferentiated autoimmune diseases.

Cytological examination of the vesicles revealed a cytopathic effect with intranuclear inclusions, which are a typical finding of herpes virus infections (Fig. 3).

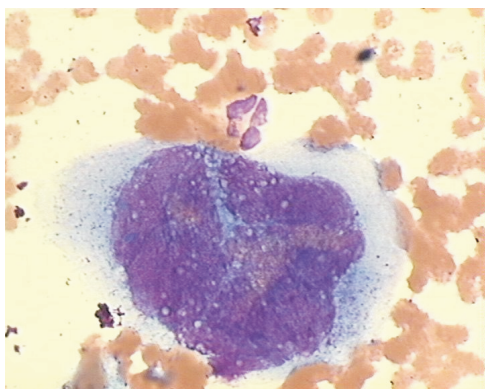


Figure 3. Intranuclear inclusions in cytological examination.

Serological identification of varicella-zoster virus by enzyme-linked immunosorbent assay (ELISA) was negative for IgM on day 1 and 12, but there was a positive dynamics of the IgG titer.

The neurologist found the skin lesions in the innervation area of medial, intermedial and partially posterior branch of the femoral nerve, which covered the dermatomes L4-S1.

DISCUSSION

The patient was first suspected of having a vasculitis, as a new clinical event in the course of his undifferentiated connective tissue disease. However, this possibility was excluded as highly improbable because the skin lesions were unilateral. However, high fever, absence of severe pain, and localization of the skin lesions did not fit into the classic clinical picture of zoster infection. On admission, only a few vesicles and necrotic detritus covered a large area of the skin. The neurological examination confirmed that skin lesions were in the dermatomes of the femoral nerve and its branches, which is not a frequent localization for zoster infection (5). There were two predisposing factors for such infection present in our patient: the modified cell-mediated immune response as a part of the autoimmune disease and the depressed immune response as a result of corticosteroid therapy (8,9). Systemic corticosteroid therapy increases morbidity even in patients without other immunocompromising conditions, especially when administered during the incubation period of the disease (1,10).

After 10 days of parenteral acyclovir therapy the lesions partially resolved, and complete clinical recovery was achieved one week later (Fig. 4). Steroid therapy was tapered off to 40 mg per day, and



Figure 4. Partially resolved lesions after 10 days acyclovir therapy.

then switched to alternate-day therapy with the same dose.

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Hereditary Benign Telangiectasia

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SUMMARY Hereditary benign telangiectasia is a very uncommon disorder characterized by generalized telangiectasias and angiomatic lesions of the skin. The diagnosis should be suspected in patients with such cutaneous signs, positive family history, no associated bleeding problems, and no mucosal involvement. We present a 74-year-old woman with typical clinical features of hereditary benign telangiectasia.

KEY WORDS diagnostic criteria; hereditary benign telangiectasia; prognosis

INTRODUCTION

Hereditary benign telangiectasia was first described as a separate clinical entity by Ryan and Wells in 1971 (1). The condition occurs in kindred in which numerous family members have widespread cutaneous telangiectasias unassociated with signs of systemic disease (2).

The reported genetic findings in cases of hereditary benign telangiectasia (1,3-7) speak in favor of the autosomal dominant hypothesis. The etiology and pathogenesis of the disease, however, remain unknown (2,3). Angiogenetic factors or estrogen and progesterone hypersensitivity in the affected lesions have been suggested (3,4), but not proven.

The lesions are not present at birth but develop during childhood, often before adolescence, particularly involving the upper part of the body. As with all generalized telangiectasias, the individual le-

sions are highly variable, ranging from small pin-head-sized macules to mats or complex intertwining vascular aggregations. They tend to more often occur on the skin exposed to light. The predilection sites is the face, including the vermilion border of the lips, then neck and upper parts of the trunk (4,6,8).

The lesions are distinguished from many other primarily telangiectatic disorders on the basis of morphologic appearance, age at onset, and absence of associated symptoms (2,3). The most important differential diagnosis is from the more serious hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease) (3,5,6). The initial sign of hereditary hemorrhagic telangiectasia is the presence of recurrent epistaxis in youth, which may be associated with hematuria and intestinal bleeding. In

contrast, hereditary benign telangiectasia is a disorder without mucosal involvement. Many lesions that appear in this condition are indistinguishable from cherry angiomas, but differential diagnostic considerations also include multiple spider nevi, multiple angiokeratomas, angioma serpiginosum and generalized essential telangiectasia. Various telangiectatic syndromes, such as ataxia-telangiectasia (Louis-Barr syndrome), unilateral nevoid telangiectasia, congenital telangiectatic erythema (Bloom syndrome) and congenital poikiloderma also have genetic disposition, but each of them is inherited as an autosomal recessive trait (2,3,8).

Histology and electron microscopy show dilated vessels of the superficial reticular dermis with thick walls but no dehiscence. This finding has been used to distinguish this condition from hereditary hemorrhagic telangiectasia (6). According to some authors (6), videocapillaroscopy (VCP) of the nail fold and labial mucosa can be used as a simple, noninvasive method to detect microscopic abnormalities and to provide additional data to complete the diagnostic evaluation of patients affected by hereditary benign telangiectasia (6).

CASE REPORT

A 74-year-old woman was admitted to Outpatient Center within our Department with numerous telangiectatic lesions and angiomas involving the face, neck, trunk and extremities (Figs. 1-4).

The disease started in adolescence with the occurrence of angiomatous lesions on the flexor aspect of the arms, and then spreading to the neck, low neck, breast folds, back, and legs. The cutaneous lesions worsened over the years and resulted in numerous telangiectasias and angiomas highly variable in size, especially on the ventral aspect of the upper trunk segment and breast folds. The patient had never had nosebleeds, hematemesis, melena, hematuria, hemoptysis or bleeding from cutaneous lesions. She had never observed telangiectasias on the oral mucosa or conjunctivae.

Family history revealed that the patient's mother had had the same skin changes, and both of the patient's daughters also showed numerous but less extensive telangiectasias and small angiomas on the neck and upper part of the trunk, without mucosal involvement or bleeding episodes.



Figure 1. Diffuse flushing with numerous radiating and arborizing telangiectasias on the nose and left cheek of a 74-year-old female patient with hereditary benign telangiectasia.



Figure 2. Typical clinical features of hereditary benign telangiectasia with numerous telangiectatic lesions and angiomas involving the upper part of the trunk.

The patient was diagnosed with hereditary benign telangiectasia in 2000, when she visited a dermatologist for evaluation of her skin changes. Three years later she was admitted to our Department because she was worried about the worsening tendency of her skin lesions, occurrence of the same skin changes in both of her daughters, and the course, prognosis, and treatment options of the disease. Another reason for admission was worsening of hypostatic dermatitis seven days before the hospitalization, with erythema, scaling, and burning on the distal parts of the legs. After only few days of

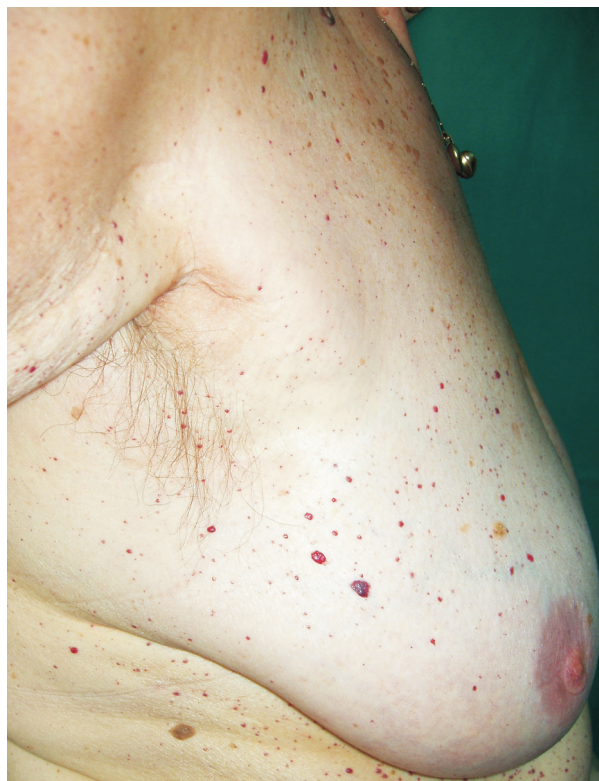


Figure 3. Teleangiectatic lesions highly variable in size, ranging from small punctuate deep red maculae to sized, elevated, dark red soft papules.



Figure 4. Multiply dark red angiomas on the back of the patient with hereditary benign telangiectasia patient.

topical therapy with aclo methasone cream, which was recommended by a dermatologist for home care, the inflammatory changes showed signs of regression. The patient had also had a medical history of hypertension for over 20 years, for which she had been taking amlodipine and furosemide. Many years before, she had suffered chronic venous in-

sufficiency and hypostatic dermatitis. Since 1994, she has atrial fibrillation, for which she was taking amiodarone and prophylactic anticoagulation ethyl biscoumacetate.

Physical Examination

Physical examination on admission showed absolutely arrhythmic heart action. Her blood pressure was 170/100 mm Hg and her pulse was 90/min. She had bilateral ankle edema. Other somatic findings were normal.

Dermatologic Examination

The cutaneous changes were characterized by numerous telangiectatic lesions and angiomas of highly variable size ranging from small punctuate deep red maculae on the flexor aspect of the arms to sized, elevated, dark red soft papules involving presternal region, breast folds, upper segment of the abdomen, lower back, arms and legs (Figs. 2-4). On the nose and left cheek, there was diffuse flush with numerous radiating and arborizing telangiectasias (Fig. 1). A dark red elevated papular lesion, 6 mm in diameter, was observed in the left preauricular region, and a small, dark red papule, 2 mm in diameter, on the chin.

On the neck and upper part of the trunk there were numerous round and oval, elevated, sharply bordered, yellow-brown lesions varying in size, with scaling and rough surface. One of the lesions, dark brown, elevated by 2 mm, 9x5 mm in diameter, was found on the lateral side of the left upper leg. On the extensor surface of the lower legs, the skin showed brown discoloration and mild scaling, with edema and phlebectasias above the ankles. Physical examination of the oral mucosa was normal.

Laboratory Findings

Laboratory tests showed erythrocyte sedimentation rate of 10/21 mm/h; leukocytes 5.6×10^9 ; erythrocytes 4.47×10^{12} ; hemoglobin 135 g/L; hematocrit 0.4 l/L; platelets 272×10^9 ; eosinophils 1%; segmented granulocytes 58%; lymphocytes 39%; monocytes 2%; blood glucose 4.8 mmol/L; urea 6.4 mmol/L; creatinine 84 mmol/L; aspartate aminotransferase 27 U/L; alanine aminotransferase 21 U/L; gamma-glutamyltransferase 19 U/L; alkaline phosphatase 116 U/L; prothrombin time 0.23 s; activated partial thromboplastin time 33.2 s;

and fibrinogen 3.5 g/L. Urine findings were normal. Antistreptolysin O (AST-O) titer was 35 I.U./mL and antistaphylolysin (ASTA) titer 2.0 I.U./mL. Venereal Disease Research Laboratory (VDRL) test was negative as well as *T. pallidum* hemagglutination (TPHA) test and both KOH examination and fungi culture from leg skin samples.

Treatment

Local neutral creams (dexpanthenol) were applied on the hypostatic lesions on the distal parts of the legs throughout her hospital stay, because there were no visible inflammatory changes anymore. The patient also received her usual medicaments. On discharge, the patient was recommended cryotherapy for large angiomatic lesions and seborrheic keratoses at our Department of Dermatological surgery, because she refused laser therapy.

DISCUSSION

According to the Pub Med database search results, by September 2003, several articles had been published about this rare condition. To the best of our knowledge, our case report of hereditary benign telangiectasia is the first one ever documented in Croatia.

The condition probably often remains unrecognized because of minor attention paid by some members of the affected families, and may therefore be more common than generally appreciated (2,5,6).

In our patient, the diagnosis of hereditary benign telangiectasia was made on the basis of several findings. There was positive family history: patient's mother and both of her daughters had similar cutaneous lesions, without mucosal involvement and episodes of nosebleeds or internal bleeding. Patient's medical history showed no nosebleeds or internal bleedings. Her physical and dermatologic examination revealed diffuse telangiectatic and angiomatic lesions without mucosal involvement. Finally, laboratory tests showed no evidence of anemia. Based on these criteria, we believe that the four members of three generations in this family represented cases had hereditary benign telangiectasia.

The cutaneous lesions are asymptomatic (5). They usually require no therapy, although they can be destroyed with electrosurgery, laser or a combination of the two. Systemic tetracycline therapy has been reported to be successful in the primary telangiectatic condition (3,8).

The prognosis of this disorder is usually good as it causes only cosmetic disability (7).

In 2001, Onishi *et al* (4) reported on 10 patients with hereditary benign telangiectasia who also had arteriovenous malformation. That was the first report of yet unknown association of hereditary benign telangiectasia with any other disorder. A coexistence of familial glomerulonephritis and benign cutaneous telangiectasia has also been described (9). Additional studies are necessary to confirm any possible associations with other disorders. Therefore, careful clinical observation of patients with hereditary benign telangiectasia seems reasonable.

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Facial and Oral Aspects of Some Venereal and Tropical Diseases

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SUMMARY Diseases of the tropical areas include some venereal diseases, and they are still very prevalent in some countries; Brazil is one of them. Very few cases are originated in large cities, as Rio de Janeiro, but at the University Hospital of the Federal University of Rio de Janeiro we also see those patients who come from the interior of the State of Rio de Janeiro or from other states to seek medical care at better equipped hospitals for this type of investigation and therapy. Venereal and tropical dermatoses have many different cutaneous manifestations and may affect skin in several locations. The face is one of the affected areas especially when the disease has a predilection for cartilage, oral and/or nasal mucosa. Alterations observed on the skin of the face and on the mucosa of the mouth of some tropical diseases, such as leprosy, leishmaniasis, paracoccidioidomycosis, donovanosis, and syphilis, as they are observed in Brazil, are presented and discussed in this article.

KEY WORDS Tropical medicine; Leprosy; Leishmaniasis, mucocutaneous; Paracoccidioidomycosis; Sexually transmitted diseases;

LEPROSY

Leprosy is caused by *Mycobacterium leprae*, an intracytoplasmic parasite of macrophages and Schwann cells and, in the tissue, it can be found alone or forming globoid masses called globia. This disease is still very frequent in Brazil and lesions of all forms, lepromatous, borderline, tuberculoid, and indeterminate leprosy frequently involve the face, and sometimes the mouth.

Leprosy affects man, but the disease can be found and reproduced in the armadillo, monkey and

mouse. The structures mostly involved are skin and peripheral nerves, sparing the central nervous system. Its incubation period is very long, between two to seven years. The bacillus is spread from the nasal drops and open lesions of the bacilliferous patient, and it is still viable in the exterior in dry secretions, after one to seven days. Inoculation is through the nasal mucosa or open skin lesions. The specific cell-mediated immunity eliminates the bacillus in most people and can be detected by the lepromine test. The clinical form depends on this late immunity response; with the disease being able to progress without restraint, limit itself or cure spontaneously. Humoral immunity is difficult to eva-

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luate but it is increased in forms with low cell mediated response (1,2,3).

Lepromatous leprosy, which is the more contagious form, shows its first sign on the skin. There can be multiple, erythematous macules, papules, nodules and plaques, with ill-defined borders (Fig 1). Lesions are usually bilateral with a tendency to symmetry. It affects mostly the face, legs and buttocks, and the patients can show infiltration of the skin of the forehead, which gives a leonine aspect. The patient can have madarosis, bilateral infiltration of the earlobes and xerotic skin on the legs. Some peripheral nerves may be thickened and there is bilateral anesthesia in boot or glove, bone reabsorption and eyes alteration.

Borderline form has intermediate features between lepromatous and tuberculoid forms (Fig 2). It is asymmetrical, there can be a unilateral earlobe infiltration, with the severity of skin and nerve alteration depending on the side of the spectrum the patient is. No hair grows on the lesion.

Tuberculoid form also affects skin and nerves, with few lesions and it can also be only neural. Lesions are papules or plaques with well-defined borders and depressed centers (Fig 3). In black skin, they are usually hypopigmented, while being erythematous in white skin. There are sensibility alter-



Figure 2. Borderline leprosy showing erythematous patches on the face with an aspect of lupus erythematosus.

ations, the lesions are also hairless and there can be unilateral bone reabsorption (4,5).

The diagnosis of the disease and its forms is confirmed by the finding of the bacilli in cutaneous lymph and nasal secretion. Ziehl-Neelsen stain is used and only the presence of globia is diagnostic. They are found in 100% of lepromatous leprosy,



Figure 1. Lepromatous leprosy with numerous nodular lesions on the face.



Figure 3. Tuberculoid form with a single hypopigmented lesion with erythematous and well defined borders.

75% of borderline and only in 5% of tuberculoid. Evaluation of the thermic, pain and tactile sensitivity, histamine, pilocarpine and Mitsuda test may be needed. Skin biopsy must be performed and sometimes also nerve biopsy (3).

Today, multidrug therapy is used, following recommendation of the World Health Organization, and, for this, bacilloscopy is performed in three to five different sites in the skin. The patient is considered paucibacillary if no bacilli are found being then treated with rifampicin and sulfone for six months, remaining in observation for two years. If there are one or more bacilli, the patient takes rifampicin and clofazimine for two years and stays in observation for five years. There is another option using only sulfone and clofazimine.

New drugs are in research for leprosy as pefloxacin and ofloxacin, which seems to be able to cure leprosy in 30 days, as well as claritromycine, minocycline and ansamycines (5)

Leprosy can be defined as a chronic curable disease, which has a good prognosis related to life expectation but can be very incapacitating. It is very important to make early diagnosis and to exam the patients' contacts (1,2,3,4).

LEISHMANIASIS

Leishmaniasis is an infectious disease caused by a protozoon of the genus *Leishmania*. It is transmitted by the bite of an infected female mosquito, mainly of the genera *Phlebotomus* and *Lutzomya*. It is very prevalent in Brazil where it produces cutaneous, mucosal and lymphatic lesions, sometimes very destructive, and usually it does not affect internal organs or central nervous system. Visceral and anergic form are not common.

There are two types of transmission: one where wild animals act as reservoir and man gets infected when he goes into the tropical forests. The other has domestic animals as reservoir and this biological cycle occurs in the domicile or peri-domicile area.

The parasite's biologic cycle begins with the promastigote or flagellated form, called leptomonas, being transmitted to the animals or healthy man by the female mosquito, in need for warm blood to mature its ovarian follicles. In affected man or animal, it

changes into amastigote or ovoid aflagellated form, called leishmania that can again be transmitted to a female mosquito. Amastigote is also the form that causes the disease (5)

The first lesion that appears occurs at the site of inoculation, three to four weeks after the bite of the infected mosquito and predominantly on the legs.

There is a presence of erythema, edema, papule, tubercle or ulcer. The size is very variable and a discrete lymphangitis and adenopathy can also occur (Fig 4). Leishmaniasis can produce facial lesion after inoculation or after hematogenic dissemination (6)

Mucous membranes also can be affected after hematogenic dissemination. Mouth, nose, larynx and pharynx are mostly involved. There are infiltrative, ulcerous, vegetating and atrophic-crusted le-



Figure 4. Two sisters with different types of inoculation lesions of leishmaniasis on the face.

sions (Fig 5). Infiltration of the upper lip and nasal region can give a tapiroid appearance. The fall of the tip of the nose by destruction of the septum and sub septum can produce a bulldog facies. The appearance of parrot beak nose is caused by partial destruction of the sub septum and, when oral and nasal cavities form a unique cavity, it is called a gangosiform aspect. Deforming osteoarthritis occurs when there is severe ulcero-cicatricial involvement (7).



Figure 5. Lesions of leishmaniasis on the palate and on the lip.

Diagnosis depends on the patient's origin, the clinical aspect of the lesion and the laboratory. The parasite can be seen on the direct exam. Giemsa stain is used to find amastigota, leishmania or flagellated form, inside macrophages, and it is 100% positive in recent lesions. Promastigota, leptomonas or flagellated form of the parasite can grow in NNN medium. Histopathology of the lesion also shows leishmania in macrophages. For Montenegro intradermal test, a suspension of leptomonas or antigenic fractions of leishmania is used. Reading is made 48 to 72 hours after the injection and it stays positive for the rest of the life after infection (8).

Patients can be treated with intramuscular glucantime, intravenous amphotericin B, intramuscular pentamidine and also paromycin, which is in trial for topical and systemic applications.

Combat to the animal reservoir and to the mosquito, treatment of human infection sources, protection of the healthy individuals and a preventive vaccine are the most important actions to achieve prophylaxis of leishmaniasis (5,7,9).

PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis, South American blastomycosis or Lutz's Mycosis is a chronic granulomatous disease, caused by a dimorphic fungus, *Paracoccidioides brasiliensis*, which affects mainly lungs, oral, nasal and gastrointestinal mucous membranes and the lymphatic system.

The disease was first described by Lutz in 1908, who also isolated the etiologic agent. The parasite is an eukaryotic cell, has a chitin wall and, in lymph nodes, it appears as round cells, with a double refringent wall, single or multiple budding, and 5 to 25 μm in diameter (10).

This disease is a rural endemy, which affects mainly male rural workers between 29 and 40 years old, in a proportion of fifteen men to one woman. Man is the only natural host. It is endemic in South America, except Chile, where no case has been reported, and Central America. In Brazil, the larger incidence is in the state of Sao Paulo. Invasion is mainly pulmonary by spore inhalation and inoculation by trauma on skin and mucous membrane is also possible. It can affect the skin of the face directly or by spread from the oral or nasal mucosa (5,11,12)

The immunological state of the patient will determine the degree of severity of the disease. The patient can have the infection without disease; a benign, localized disease, that can cure spontaneously and has an epithelioid granuloma with few fungi in histopathology; or a severe, chronic, generalized disease, which is the most common form. The patient with this form has a poor prognosis, depressed late immunity, negative paracoccidoidin and unspecific tests, and the biopsy shows necrotic areas, less formation of granuloma and numerous multiplying fungi.

In mucous membranes, the characteristic lesion is an erythematous ulcer, with hemorrhagic and granular dots. There can be macrocheilitis, infiltrations, vegetations and ulcerations. Sialorrhea is frequent. In the skin, lesion of inoculation is rare; in this location, it is usually caused by hematogenic spread. There can be papules, tubercles, vegetations and ulcers. The ulcer's base shows the characteristic hemorrhagic dots (Fig 6).



Figure 6. Paracoccidioidomycosis lesions outside and inside the mouth.

There is regional or generalized adenopathy and the lymph nodes undergo fistulisation. Pulmonary paracoccidioidomycosis occurs in eighty to ninety percent of the cases, usually is bilateral and located in the lower half of the lungs. There is an association with tuberculosis in 12 percent of the cases. Other organs often involved are gastrointestinal system, liver, spleen, central nervous system and adrenals (13).

Diagnosis is made by direct exam, where we can see the round parasites, with double contour membrane, single or multiple budding and the cryptosporulation that gives a "pilot wheel" appear-

ance. Media used for culture are mainly agar-Sabouraud and agar-blood. Histopathology shows the granuloma and, with Grocott and PAS stains, fungi can be easily visualized. Paracoccidioidin test can be useful, but it is also positive in unapparent infections.

For treatment, oral sulfadiazine or sulfamethoxyypyridazine, intravenous amphotericin B or micronazole, and also oral ketoconazole or itraconazole are mostly used, with good results (14,15,16). Treatment control can be done by precipitin test that detects the activity of the disease and a complementary fixation test that measures the quantity of fungi (13).

SEXUALLY TRANSMITTED DISEASES

The sexually transmitted diseases can be divided in 3 groups by their epidemiology: essentially, frequently and eventually transmitted by sexual contact. In the first group, syphilis, gonorrhea, chancroid, lymphogranuloma, and AIDS; in the second, donovanosis, non-gonococcal urethritis, herpes simplex, genital warts and candidiasis, trichomoniasis, phthiriasis, and B hepatitis; and in the third, other non-exclusive diseases, as molluscum, scabies, etc.

Two sexually transmitted diseases with mouth and facial involvement will be discussed here. They are syphilis and donovanosis.

Donovanosis

Donovanosis is caused by a Gram-negative bacterium, *Calymatobacterium granulomatis*, mostly observed in the tropics. It is predominantly genital and perianal. The painless lesions are initially papules or nodules, and slowly expand over weeks or months, resulting in extensive destruction (17) (Fig 7). It may lead to elephantiasis (18).

It mainly affects homosexual men, especially those with low economical status and poor hygiene (19).

The positive direct exam shows small rods in macrophages and the differential diagnosis is made with many other infectious diseases, including leishmaniasis, which also shows small parasites in macrophages.



Figure 7. A rare case of oral lesion by donovanosis. (Courtesy Cleide Ishida, MD)

The patients can be treated with one of several antibiotics, among them sulfamethoxazole-trimethoprim and doxycycline, usually for 3 weeks (17).

Syphilis

Syphilis is caused by *Treponema pallidum* and can affect all organs. There are two forms: the sexually transmitted, divided into recent, latent and late; and the congenital, divided in recent and late.

It is universal, does not have any predilection factors, is increasing all over the world, and penetration is mainly through mucosa and semi-mucosa, soon reaching the lymphatic system and the blood. This disease increases with changes in human sexual behavior (18)

Primary syphilis occurs at the inoculation site and is a hard ulcer, with red base and serous exsudate, called hard chancre or Hunter's chancre. It appears 18 to 30 days after inoculation and is a vasculitis of the Arthus type. This lesion is usually unique, painless and its hard base is caused by plasmocyte infiltrate. Usually painless, it shows re-

gional and bilateral micropolyadenopathy. The most common sites are the balano-preputial sulcus or inner shaft of the prepuce in man; and uterine collum (unnoticed), labia minora and majora, clitoris in woman. Sometimes there are extra genital lesions as on the anus, rectum, tongue, finger and lip. Spontaneous involution occurs usually in 1 to 4 months.

In secondary syphilis, there is a monomorphic, generalized eruption of small lesions; mostly on the trunk without pruritus, and of variable severity. Micropolyadenopathy, muscle pain, discrete fever, headache, pharyngitis, palmo-plantar involvement may be present. Recent syphilids show an erythematous (roseola), papular, papulosquamous (psoriasisiform), or follicular (lichenoid) eruptions. Late syphilids, on the other hand, are characterized by pustular eruptions, called malignant syphilids. Venus Collar (*leukoderma colli* – on the neck) is usually observed. In black patients a circinate or annular configuration may be present (Fig 8). At this stage, mucous membranes are, in general, affected with multiple erosive lesions on the mouth (mucous patches), erosive, vegetating syphilids (condyloma latum) on the anus and vulva. Later, alopecia, madarosis, and paronychia appear (17,18,19).



Figure 8. Facial lesions of secondary syphilis on a black patient.

Secondary syphilis occurs after 2 to 3 months after the infection. Alterations are due to immune complexes similar to a serum sickness disease. After 2 to 4 years, it may become latent syphilis.

Recurrent recent syphilis is characterized by few papular lesions with tendency to circination. It is infectious and is an intermediate stage between secondary and tertiary syphilis. Unapparent and latent syphilis are the phases of clinical silence with positive serology; unapparent syphilis is in the recent phase but in the interval of episodes, while latent is in the late phase, which is already non-infectious (5 to 50 years) (17,18).

Tertiary syphilis only occurs after 2 years of infection. There are few, non-contagious and destructive lesions with vasculitis and necrosis. Fifteen percent are tegmental lesions. The lesions can be:

1. tuberous-circinated or nodular lesions, usually on the arms, face and back of trunk;
2. gumma: cutaneous or mucous lesions on the scalp, face and sternal region.
3. juxta-articular nodules of Jeanselme.

Leukoplakia, perforation of hard palate, superficial and interstitial glossitis, and destruction of the central portion of face may be present. (Figure 9)

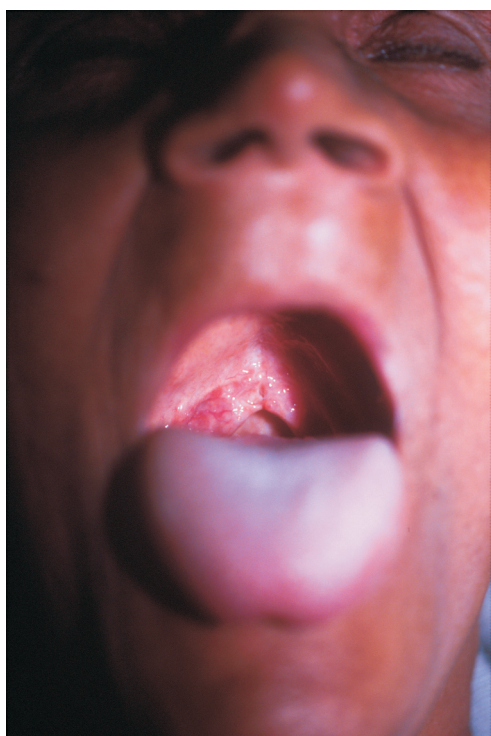


Figure 9. Destruction of the uvula by tertiary syphilis.

There is aortitis (10%), and bone lesions (Charcot's joints), aneurysm, neurosyphilis (6%), showing general paralysis, tabes dorsalis, and optical nerve atrophy.

Syphilis can be transmitted to the offspring anytime during pregnancy, but it is more frequent after the fourth month of pregnancy. Infection at the beginning of pregnancy will lead to spontaneous abortion and later to stillborns or premature births. Severity depends on the time of infection and on the mother's immunity. Babies can be healthy at birth (days or months) or be born with congenital syphilis.



Figure 10. Recent congenital syphilis with generalized desquamation, hoarse crying, senile face, and profuse nasal secretion.

lis. If the mother is treated during pregnancy, the baby will not have syphilis (17,19).

Recent congenital syphilis occurs before 2-years of age. The child has low weight, senile face, hoarse cry, hemorrhagic rhinitis, maculopapular eruption, mucous patches, condyloma latum, perioral and anal radiated fissures, palmoplantar blisters or in other areas (syphilitic pemphigus, which is rare), micro adenopathy, osteochondritis (Parrot's pseudoparalysis: paralysis caused by pain), and hepatosplenomegaly (Fig 10).

Late congenital syphilis begins in children over 2-years of age (until 16). There is interstitial keratitis, nodular syphilids, gumma, periostitis, painless synovitis (Clutton's bilateral hydrarthrosis), palate perforation, deafness, and tabes dorsalis.

Congenital syphilis has some typical features known as stigmata. They are: 1. Hutchinson's teeth, characterized by small and conical incisive teeth, with chamfer on the free border; 2. Hutchinson triad, composed of Hutchinson teeth together with keratitis and deafness; 3. saddle nose; 4. saber tibia; 5. perioral scars; 6. curved palate; 7. "salt and pepper" eye fundus; 8. Higoumenakis sign, a unilateral thickening of the internal third of the clavicle; 9. Parrot's cranial nodules; and 10. "strawberry" molar (17,19).

CONCLUSION

All of these diseases may sometimes be seen in Brazil; fortunately not as often as in the past. The importance of an early diagnosis in most of them and combat to the transmission agent in some of them is the key feature to the avoidance of late sequelae and also transmission to healthy people.

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Skin Diseases in Alcoholics

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SUMMARY Alcohol abuse is associated with many health problems, especially skin changes. As a small, water- and lipid-soluble molecule, alcohol reaches all tissues of the body and affects most vital functions. Cutaneous diseases are now emerging as useful markers of alcoholism detectable at an early and possibly reversible stage of the disease, thus being of substantial importance to dermatologists and general practitioners. The most common skin manifestations of alcoholism presented in this review article are urticarial reactions, porphyria cutanea tarda, flushing, cutaneous stigmata of cirrhosis, psoriasis, pruritus, seborrheic dermatitis, and rosacea.

KEY WORDS *alcohol abuse; health effects of alcohol; alcohol and the skin*

INTRODUCTION

Alcoholism is a chronic, progressive and potentially lethal disease characterized by alcohol (ethanol) dependence and multiorgan dysfunction, with genetic, environmental and psychosocial factors playing the main role in its development. The disease is characterized by the loss of control of alcohol intake and continuation of the habitual alcohol intake in spite of its deleterious consequences (1). Social concerns have brought the issue of substance abuse into the very focus of medical interest. Dermatologists in particular regularly encounter patients seeking help for cutaneous manifestations of alcohol or drug abuse. The lifetime prevalence of alcohol abuse has been estimated to 13.7% (2). Nearly 12.5 million Americans (approximately 5-10% of all alcohol drinkers) develop ethanol dependence. In untreated alcoholics, life expectancy is reduced by 12-15 years (2).

In the absence of gastrointestinal diseases or food intake, 80-90% of ingested ethanol is absorbed within 30-60 minutes. The absorbed ethanol is oxidized in the liver by the aldehyde dehydrogenase enzyme, and excreted *via* renal and respiratory pathways and perspiration. Although rather low, respiratory excretion proportionally reflects the blood concentration of alcohol, which is why breath sampling can be used to measure the level of intoxication.

Many interactions can occur when alcohol is taken in conjunction with drugs. These interactions can be antagonistic (effects are blocked or reduced), additive (sum effect), or supra-additive; hypersensitivity may also be present.

The skin is not spared from the detrimental effects of alcohol abuse. Alcohol can cause patho-

logic skin changes directly or through dysfunction of various organs. Alcohol-induced skin pathology may be due to a direct toxic effect or consequential to personal neglect, environmental factors, or inappropriate diet. However, there is no skin lesion specific for alcoholism (2). The disease imposes great financial burden on the health care system. Alcohol drinks, primarily beer and wine, are best described in the literature. Beer and wine are naturally fermented beverages with maximal alcohol concentration of 3% and 8-12%, respectively. The prevalence and severity of some skin diseases are increased in patients prone to excessive alcohol intake. According to Rosset and Oki (3), the prevalence of skin diseases is 43% in male and 33% in female alcoholics.

Alcohol use/abuse is associated with significant health problems. Alcoholism is an important cofactor in many diseases. It is often associated with exposure to venereal diseases and human immunodeficiency virus (HIV) infection. Chronic alcohol abuse can lead to liver cirrhosis, which ultimately affects all body systems. Endocrine tissues and organs are damaged by alcohol abuse rather than by consequential hepatic dysfunction or chronic malnutrition.

ETHYLIC FACE (FACIES AETHYLICA)

Chronic alcoholics tend to look older and have "dull expression". The skin of the face appears smooth, oily and shiny, while the color of the skin may be sallow or grayish blue. The conjunctivae may be reddened, with thickened eyelid margins. Poikilodermal changes on the neck and trunk are commonly seen (2).

FLUSHING

Flushing is the most common skin manifestation of acute alcohol intake, defined as the occurrence of transient redness of the face and neck associated with the feeling of heat. The face, neck and upper trunk are the regions characteristically involved by flushing, which occurs due to vasodilatation (4). It appears as congestive erythema of the skin and may be accompanied by weakness, sweating, pruritus, and headache. Flushing may also be a normal physiologic response (blushing caused by emotional reasons) or a menopausal symptom.

CUTANEOUS MANIFESTATIONS OF ALCOHOLIC CIRRHOSIS

The cutaneous changes associated with alcoholic cirrhosis are well documented, ranging from spider nevus to petechiae, which are classic stigmata and dermatologic signs associated with alcoholic cirrhosis.

Spider Nevus

Spider nevus (*nevus araneus*) is the site of dilatation of superficial cutaneous arterioles surrounded by fine branching radiations. Pressure upon the central arteriole leads to the development of this lesion. Spider nevi are generally found on the face, neck, upper trunk, shoulders, forearms and dorsal aspect of the hands, and are the most common and classic vascular abnormalities of liver disease and alcohol abuse (5). They may also occur during pregnancy and estrogen therapy.

Palmar Erythema

Palmar erythema is characterized by warm, light-red patches on the thenar, hypothenar and finger pads. It is usually bilateral and symmetric, with sharply delineated peripheral margins, and can occur during pregnancy and in a number of chronic diseases (5). Palmar erythema has been attributed to hyperestrogenism in chronic liver disease.

Nail Changes

Terry's nails characterized by opaque white nail plate with the exception of the distal part, which retains its normal, pink color, are frequently seen in cirrhosis patients (6). These patients may also show transverse white strips, "clubbed nails" or koilonychia (spoon nails). White nails are also described in patients with cirrhosis, systemic scleroderma, and some other conditions (5).

Hair Changes

Hair changes are quite common, mostly in men. Axillary, pubic and chest hairiness is reduced and development of the female type of pubic hairiness is frequently seen.

Caput Medusae

Caput medusae are dilated umbilical veins due to portal hypertension.

Petechiae and Ecchymoses

Petechiae and ecchymoses occur due to prothrombin deficiency consequential to impaired liver function. They mainly occur on the lower limbs in patients with end-stage alcoholic cirrhosis.

Other skin diseases associated with alcoholism and alcoholic cirrhosis include Dupuytren's contracture, vitiligo, disseminated superficial porokeratosis, nutritional deficiencies, pellagra and pellagroid dermatoses, and skin infections.

PSORIASIS VULGARIS AND ALCOHOL INTAKE

Epidemiology

Most epidemiologic studies carried out in the last decade have confirmed the association of psoriasis and excessive alcohol intake. A study of the prevalence of psoriasis relative to alcohol and liver diseases found psoriasis to be more common in individuals drinking more than 50 g alcohol daily irrespective of liver disease (7). Another study showed a higher prevalence of alcoholism in hospitalized psoriatics, especially men, than in patients with other skin diseases (8). A questionnaire study conducted in Norway, revealed that psoriatics drank alcohol more frequently and in greater amounts than nonpsoriatic patients (9). An Italian study confirmed the excessive alcohol intake to be more common in psoriatics than in the general population (10). Higgins and duVivier (11) found 39% of psoriatics to habitually take excessive amounts of alcohol, whereas the prevalence of psoriasis in the alcoholics included in rehabilitation programs was 10-fold that recorded in the general population (12). Most of these studies did not take into consideration the possible additive factors, such as cigarette smoking, that may have influenced the results. None of these studies explained whether alcohol abuse increases the risk of the development of psoriasis, or it is just a phenomenon associated with the chronic course and nature of the disease (4). Indirect evidence for the possible etiologic association of alcohol intake and psoriasis has been provided by Stern and Lange (13), who found cirrhosis to cause more deaths among psoriatics than among other patients. These findings could possibly be explained by the fact that alcoholic cirrhosis is more common

and/or more severe in psoriatics than in nonpsoriatics.

Severity, Course and Prognosis

Generally, alcohol intake is associated with a more severe form of psoriasis and lower therapeutic responsiveness. Monk and Neill (14) found that excessive alcohol consumption was significantly more common in men with psoriasis who had a more severe form of disease. In their studies conducted in 1990 and 1994, Poikolainen *et al* (15,16) found an association between alcohol abuse and severity of the disease in both male and female psoriatics. Exacerbation of psoriasis was considerably more common in psoriatic patients with excessive alcohol intake irrespective of sex than in patients with other skin diseases. According to Higgins and duVivier (11,12), alcohol abuse is associated not only with a higher incidence and severity of psoriasis but also with a different nature and distribution of skin lesions. Thus, the patients could be classified into two groups: one with severely inflamed skin and few scales, typically involving the face, inguinal region, axillae and other flexures, and the other predominated by hyperkeratotic foci, especially on the extremities. Little data are available on the effect of alcohol consumption on therapeutic results. In their study, Gupta *et al* (17) investigated the relationship between alcohol consumption and therapeutic success in 94 hospitalized patients with moderate to severe psoriasis. Their results showed an average daily intake of 80 g ethanol to be more frequently associated with lower therapeutic success in men, but not in women. According to Vincenti and Blunden (18), abstinence from alcohol consumption can lead to remission, whereas resumption of drinking habit results in exacerbation of psoriasis.

Pathogenesis

The main question is whether the relationship between alcohol intake and psoriasis is causative or simply a phenomenon associated with the chronic course of the disease and its social and psychological burden (19). There are several hypotheses on the effect of alcohol on psoriasis, most of them based on theoretical postulates and only a few on the findings of psoriatic patient tissues. The majority, if not all researchers, believes that alcohol influences psoriasis through the immune system. Alco-

hol consumption has adverse effects on all immune system components, thus rendering alcoholics susceptible to infection. As infections, especially streptococcal, act as trigger factors for psoriasis, the effect of alcohol may imply an increased susceptibility of these psoriatics to infection (19). A co-cultivation model with keratinocytes obtained from psoriatic patients and T-cell lymphoma (HUT-78) cell line was developed in a study performed by Ockenfels *et al* (20). In this model, HUT-78 cells were co-incubated with keratinocytes from psoriatic patients and cultivated for 24 h with or without the addition of ethanol. The levels of interleukin (IL)-2, IL-6, IL-8, interferon- and transforming growth factor (TGF)- were determined in supernatant culture. The levels of interferon- and TGF- were increased by 150-175%, whereas the levels of IL-2, IL-6, and IL-8 showed no significant changes in the cultures with the addition of ethanol in comparison with control cultures. These findings may explain the exacerbation of psoriasis associated with alcohol intake. This study is highly relevant for research into psoriatic keratinocytes, whereas the majority of other studies did not tackle the direct immune impact of alcohol on the skin.

PORPHYRIA CUTANEA TARDA AND ALCOHOL INTAKE

Molecular Basis of Disease

Uroporphyrinogen decarboxylase (UROD) deficiency is the main biochemical disturbance underlying porphyria cutanea tarda (PCT). UROD catalyzes uroporphyrinogen decarboxylation to coproporphyrinogen. In PCT, the hepatic activity of UROD is less than 30% of normal values. The accumulated porphyrinogens are readily oxidized to porphyrins, which cause phototoxic reaction upon being transported from the liver *via* plasma to the skin. There are three types of PCT. One is the sporadic form (type 1), accounting for 80% of patients, where UROD deficiency is restricted to the liver. The second one is the familial form (type 2), inherited as an autosomal dominant trait, seen in the majority of the rest of patients, with seminormal UROD activity in all tissues; only 10%-20% of these patients have clinical symptoms of PCT. The third form, type 3, is the most infrequent form and biochemically similar to type 1.

Alcohol and Other Risk Factors for PCT

Alcohol. Elder (21) found excessive alcohol intake to be a factor commonly associated with the development of PCT. Alcohol abuse defined as the intake of >40 g alcohol daily is found in 30-90% of PCT patients. However, PCT is not a common complication of alcoholism, as only 2% of cirrhotic alcoholics have PCT. Obviously, alcohol is an important factor in the pathogenesis of PCT, but not the main cause of the disease.

Iron. Iron metabolism abnormalities are frequently seen in PCT. Total body iron store is increased in 60-65% of cases (22). Alcohol may contribute to the pathogenesis of PCT by increasing iron absorption (23,24).

Other risk factors. Hepatotropic viruses (hepatitis B and C) and estrogens are important factors for PCT.

Alcohol and PCT Pathogenesis

Alcohol and hepatic UROD. Excessive alcohol intake can temporarily reduce UROD activity in red blood cells (25). However, neither the measurement of urinary excretion of porphyrin (25-27) nor the measurement of hepatic porphyrin concentration (28) indicates the hepatic UROD activity to be frequently decreased in alcoholics.

Alcohol and hepatic heme synthesis. Alcohol increases urinary excretion of coproporphyrin III. In nonalcoholics, this effect is short-lived and directly dependent on alcohol dosage (27,29-31). In chronic alcoholics, the excretion of coproporphyrin is frequently increased (26,31,32). The mechanism by which alcohol increases the excretion of coproporphyrin III is not clear. It is believed that an increased coproporphyrin III excretion reflects its enhanced hepatic production (21). The increased synthesis of coproporphyrin III and hemoprotein requires induction of hepatic 5-aminolevulinate (ALA)-synthase, the enzyme regulating the rhythm of heme synthesis. Occasional high ethanol doses lead to transient enhancement of hepatic ALA-synthase in PCT patients (33,34). The activity of ALA-synthase is less increased in chronic alcoholics with liver cirrhosis (23). In alcoholics, changes in the porphyrin metabolism are more common than PCT. In the pathogenesis of PCT, these changes

may lead to UROD inactivation in predisposed patients.

ROSACEA AND ALCOHOL INTAKE

Rosacea is a chronic cutaneous disease typically involving the middle parts of the face, characterized by mild flushing, permanent erythema and telangiectasia (35). In more severe forms, papules, pustules and rhinophyma may occur. According to these symptoms, rosacea is classified into four grades: I, mild flushing; II, permanent erythema and telangiectasia; III, papules and pustules; and IV, rhinophyma and tissue hyperplasia.

The factors known to act as triggers of flushing in rosacea include emotional stress, warm drinks, spiced food, and alcohol (36). Alcohol can precipitate the progression of rosacea and, like in other skin diseases, contributes to a depressed therapeutic response (2,37). Psychogenic factors are also considered to play a role in rosacea.

A relationship of skin disease and stress is presumed in 90% of patients, whereas the association of stress and alcohol consumption has been definitely established (38). There is strong clinical and histologic evidence for sunlight to contribute to the development of rosacea (35,39). Also, UV light in combination with recurrent flushing appears to lead to rosacea grade II (40).

Less is known about the triggers leading to progression to the papulopustular form of rosacea (grade III). Implication of immunoregulatory mechanisms has been postulated (39). In alcoholics, depression of the cell-mediated immunity is found, which may account for the progression of rosacea in chronic alcoholics (40,41). Recently, the interest has been focused on the possible role of *Helicobacter (H.) pylori* in the pathogenesis of rosacea. However, the available results are contradictory (42,43). It has been definitely demonstrated that *H. pylori* has a central role in the development of duodenal ulcer. The increased incidence of peptic ulcer in alcoholics may explain the possible causal relationship between *H. pylori* and rosacea (40). In the study by Rebora *et al* (43), 84% of rosacea patients were *H. pylori* positive. There is a higher rate of *H. pylori* association with grade II (erythematous) than with the more advanced grade III (papulopustular) rosacea. The patients with excessive alcohol intake

had an increased level of collagen III propeptide, a marker of enhanced collagen metabolism (44). Amplified skin collagen was detected in histologic studies in the skin of alcoholics (3), and may play a role in the mechanism of hyperplasia observed in grade IV rosacea (40).

ACNE VULGARIS AND ALCOHOL INTAKE

Acne may be precipitated or aggravated by alcohol consumption in some patients (2). *Propionibacterium acnes* is known to be responsible for the pustular component of the disease. Skin infections, including folliculitis, are more common in alcoholics. The bacteria and yeasts produce reactive and toxic acetaldehyde in the presence of high amounts of alcohol (45), which could account for the adverse effect of alcohol in skin diseases implying an infective component (40). Furthermore, the incidence of acne in alcoholics aged around 40 years can reach 26% (46,47). Nevertheless, any direct causal relationship between alcohol consumption and acne has been denied. Oral retinoid therapy is the treatment of choice in the most severe forms of acne. The dosage and clinical effects of oral retinoids are limited, and the risk of side effects is increased by excessive alcohol intake (48).

SEBORRHEIC DERMATITIS AND ALCOHOL INTAKE

Strong association seems to exist between seborrheic dermatitis and alcohol consumption. Although seborrheic dermatitis is also quite common among nonalcoholics, excessive alcohol intake has been demonstrated to potentially lead to precipitation and exacerbation of the disease (49). Parish and Fine (46) reported that 11% of alcoholics in their study suffered from seborrheic dermatitis. Rosset and Oki (3) found seborrheic dermatitis of the scalp in 10%, and seborrheic changes on the face and other body surfaces in 7% of alcoholics, i.e. in twice more patients than expected.

NUMMULAR ECZEMATOUS DERMATITIS AND ALCOHOL INTAKE

Nummular eczematous dermatitis is more common in patients prone to alcohol abuse. More so,

nummular eczematous dermatitis has been considered a significant indicator of the possible excessive alcohol consumption. In one study, excessive alcohol intake was recorded in more than 90% of patients with nummular eczematous dermatitis (11). As differentiated from patients with other inflammatory dermatoses, hepatic functional tests are frequently elevated in these patients (50). Also, abstinence is associated with clinical improvement of nummular eczematous dermatitis, whereas continuation of habitual drinking may lead to therapeutic difficulties and frequent disease relapses (40).

ALCOHOL AND INTOLERANCE SYNDROMES, URTICARIAL AND ANAPHYLACTOID REACTIONS

Intolerance syndromes associated with alcohol intake include flushing syndromes and urticarial reactions, which are characterized by different pathologic mechanisms and clinical manifestations (Table 1).

Table 1. Intolerance syndromes, urticarial and anaphylactic reactions

| |
|--|
| Flushing syndromes |
| acquired: |
| drug-alcohol flush reactions |
| malignant diseases |
| genetic: |
| oriental flush syndrome |
| Urticarial reactions: |
| contact urticaria |
| generalized urticarial reactions/anaphylaxis |
| contact dermatitis |

There are two groups of alcohol dependent flushing syndromes: drug-alcohol flushing syndromes associated with concomitant use of particular drugs and alcohol (51,52), and simple alcohol flushing not associated with drugs. Simple alcohol flushing is found in 3-29% of westerners and 47-85% of easterners (mostly Asiatic), which is why it is named "oriental flushing" (53,54).

In flushing syndromes, erythema develops several minutes upon alcohol intake predominantly on the face and trunk, whereas the symptoms resolve within 1-2 h. On the other hand, the severity of

drug-alcohol flushing does not increase with the increasing amount of alcohol consumed, the severity of simple alcohol flushing depends on the amount of alcohol ingested (51,52). Both groups of flushing syndromes can be accompanied by nausea, dizziness, headache, vomiting, and somnolence. Drug-alcohol flushing syndromes occur with concomitant intake of alcohol and the antidiabetic chlorpropamide, antibiotic cephalosporin, and antimycotic griseofulvin (52,55-59). Acquired flushing syndromes can also occur in Hodgkin's disease and other malignant tumors, mastocytosis and hypereosinophilic syndrome (60).

Urticarial reactions accompany various clinical conditions and are considerably less common. Contact urticarias are restricted to the site of alcohol contact, whereas anaphylactoid reactions are systemic and occasionally life-threatening events that follow oral ingestion of very small amounts of alcohol. Within several minutes, erythema and urticarial changes involve the upper trunk, and are followed by asthma, hypotension and loss of consciousness.

Although the intolerance syndromes may occur early in life, their initial manifestation may occur after years of asymptomatic alcohol consumption (61).

Pathogenetic Mechanisms

Modifications in alcohol metabolism have been well documented in flushing syndromes, both acquired and genetic. In patients with oriental flushing, there is a hereditary defect of the aldehyde dehydrogenase enzyme (61-65). Prostaglandins, endogenous morphins, and abnormal susceptibility to mastocyte release of histamine are candidate cofactors for its occurrence (66).

The effect of chlorpropamide in drug-alcohol flushing has been investigated in many studies. Different pathogenetic mechanisms have been proposed, but it seems most likely that the genetic basis is involved. In addition to an increased drug concentration in the circulation, particular iso-enzymes may be sensitive to the inhibitory effect of chlorpropamide (55,56,67); however, aldehyde dehydrogenase is not altered.

In contact urticaria, immune, nonimmune and other forms have been identified. Immune forms are

characterized by positive skin tests and positive Prausnitz-Küstner reaction (68,69). In nonimmune forms, positive skin reactions are induced by aldehydes and low aliphatic alcohols (70). In alcoholic contact dermatitis, direct irritative effects of alcohol are considered to play a substantial role (71-73).

Alternatively, positive epicutaneous tests might point to a delayed immune reaction (60). In alcohol-induced urticarial and anaphylactic reactions, the effects of prostaglandins, endogenous morphins and mastocyte degranulation are considered to be the main pathogenetic factors (74-76). IgE mediated type 1 allergic reaction has also been discussed (77).

Allergologic Testing for Alcohol Intolerance Syndromes, Urticarial and Anaphylactoid Reactions

Comprehensive allergologic testing should be done to differentiate the type of alcohol intolerance, to assess the severity of disease, and to exclude other potential causes (e.g., other alcohol drink ingredients, food, or food additives) (Table 2).

Table 2. Allergologic testing for alcohol intolerance syndromes

In vitro tests:

total/specific IgE
in vitro histamine release

Prick tests and scratch tests:

ethanol (96%)
acetaldehyde
acetic acid (0.96%-9.6%)
citric acid (0.1%)

Oral challenge:

food additives
ethyl alcohol (10-20 L/0.01-10%) (v/v)
pure ethanol in water

Therapy

Avoiding any contact with alcohol and its metabolites, especially alcohol ingestion, is the most important measure in therapy for alcohol intolerance. The medications used include oral or parenteral antihistaminics and corticosteroids.

PRURITUS AND ALCOHOL INTAKE

Some 40% of patients treated for alcohol dependence complain of pruritus (78), which mostly occurs due to impaired liver function. However, pruritus may precede liver cirrhosis, and it seems that it does not necessarily have to be related to hepatic functional impairment itself (40). A crawling sensation under the skin that may precipitate delusions of arthropod infestation may be experienced by some cocaine abusers, as well.

SKIN INFECTIONS AND ALCOHOL INTAKE

Alcohol abuse predominantly inhibits T-lymphocytes and reduces cell immunity, at the same time reducing the function of neutrophils and killer cells. That is why skin infections are more common in alcoholics. According to literature reports, aspergillosis, disseminated candidiasis, human papillomavirus infection, sporotrichosis, erysipelas and other streptococcal cutaneous infections are more frequently observed in alcoholics (2). The prevalence of tinea pedis, onychomycosis and other forms of dermatomycoses is higher in alcoholics because of their suppressed immunity, poor hygiene, and unfavorable socioeconomic conditions (46).

CONCLUSION

Comprehensive research and numerous studies have demonstrated that the effects of alcohol are implicated in many skin diseases. Therefore, physicians should take alcohol abuse as the possible causative factor for skin diseases in consideration in their daily practice. Dermatologists should appraise the effect of alcohol and drug abuse on the etiology of their patients' skin diseases and compliance with treatments. Also, dermatological tests should be part of medical examination in patients suspected to take excessive amounts of alcohol.

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Historical Development of Local Therapy of Psoriasis Vulgaris

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SUMMARY Throughout the history people have used various remedies for the treatment of psoriasis. Some of them were bizarre, some ineffective and harmful, and some have survived until today and are still in use. Salicylic acid, anthralin, coal tar, corticosteroids, vitamin D3 analogues, retinoids must be mentioned as remarkably effective ones. Phototherapy and laser therapy are both promising techniques, as well as immunomodulators. Underlying mechanisms of psoriasis and mode of action of therapeutics that have been elucidated over the time allowed for the development of more potent and promising therapy of psoriasis

KEY WORDS psoriasis vulgaris; local therapy; historical development

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INTRODUCTION

Psoriasis is a common chronic, inflammatory, hyperproliferative skin disease affecting about 2-3% of Caucasian population (1). Patients with psoriasis are often frustrated because the illness may cause significant physical and emotional discomfort, and in the past centuries, it was a "stigma".

In its beginning, the treatment of psoriasis was empirical and consisted of a wide range of therapies and techniques, successful in varying degrees. It seems that the earliest record of the therapy of psoriasis are medical notes of old Egyptians, contained in the famous Eber's papyrus, 20 meters long and 30 centimeters wide, which consisted of 700 magical formulas and folk remedies, 877 recipes, and 400 drug prescriptions (2). Skin diseases and prescribed remedies in Eber's papyrus were divided into three categories: irritative, exfoliative, and ulcerative, and were featured in paragraphs 90-95 and 104-118 (3). The application of cat or

dog's dung and the berries of the xet plant for the "sculf", the mixture of onions, sea salt and urine, or goose oil and semen, or wasp's dung in the milk of sycamore was recommended (4). In a way, the Egyptians established the principle of photo(chemo)therapy – they recommended the plant *Ammi maius* (Bishop's weed) be rubbed directly into the skin or taken orally and then to stand naked in the sun (5).

Although the disease had been first described by a Greek physician Hippocrates (460-377 BC) and later on introduced by Galenus (201-131 BC), it received the name *psoriasis* only centuries later (6,7).

Old Greeks were familiar with squamous dermatoses, which they all called "lepra" (7). People could not distinguish the infectious leprosy from the non-infectious psoriasis. The description of leprosy in

the Bible does not resemble any known infectious disease. Indeed, Biblical leprosy seems to resemble most closely a scaly flaking skin disease (8). Thus, psoriasis was confused for leprosy for many centuries and patients suffering from psoriasis, together, with the lepers were ostracized from the society. The church sometimes declared them officially dead (6). However, after the development of the microscope and the recognition of infective causes of inflammatory skin diseases, the disease started to be discerned from other skin disorders and understood better and better.

In the 18th century, a French dermatologist Astruc described many dermatoses including psoriasis (8). The first classification of skin diseases was given by G.G. Planck, dermatologist from Vienna, in his *Doctrina de morbis cutaneis* from 1776. Robert Willan (1757-1812), the “father of British dermatology”, identified two types of psoriasis, which von Hebra unified into a single disease (9). Willan believed that decoctions of various wood barks, such as elm, sarsaparilla, willow, sassafras, and juniper were adjuncts to therapy. Febrile acute psoriasis was managed with ipecacuanha and colomel (mercury) with gentle purgation, a light moderate diet, frequent washing and abstinence from fruit juices and fermented liquors. In all forms of psoriasis, moderate diet, relief of flatulence, and cleansing in water gruel were thought to be beneficial (4). Alibert (1768-1837), the “father of French dermatology”, classified psoriasis together with the scaly eruptions and termed it *herpes furfureux circinée* (4). His first line of treatment were spa baths, whereas for more resistant cases he recommended mild cauterization with fused silver nitrate. Ointments for the treatment of psoriasis contained ammoniated mercury, zinc and lead oxides, sulphurated tin, calcium, and potassium (4).

Pustular psoriasis was described by Schaffer in 1921 and later on by MacLeod. Pustular psoriasis of the extremities was described by Barber and Ingram (10).

Local therapy in the 19th century was based on plants, antibiotics from corn mould, phenols, arsine, iodine, phosphorus, sulfur, bismuth, antimony, iron, gold, zinc, silver, manganese, tar in different prescription (9), vitamins (A, B2, B12, C, D, E) (11), long sleep, sedation, prolonged sweating, and diets

without potassium, fats, carbohydrates or some other components. Thyroid treatments and suprarenal substitution treatment were tried out but without any success (7). From 1914, autohemotherapy was used for the treatment of psoriasis and some other skin diseases (4). Implantation of placenta according to Filatov was performed, and Bogomolev serum and “psorin”, extract from the psoriatic scales, applied (11). Poisons, like strychnine, pilocarpine, cantharides were used as “potential therapeutics” (7). In the 20th century, salicylic acid, sulfur, resorcinol, mercury, anthrobin, cignolini, sapocalinus (black and green), podophyllum, colchicum, and metotrexat were added to the list of psoriatic therapeutics (7). The famous ointments were Dreuer’s, Siemen’s, Leyden’s and Jadasson’s ointments (7).

The results of different therapies ranged from effective to ineffective as well as from toxic to non-toxic treatments.

REMARKABLE LOCAL THERAPEUTICS

Arsenic

Thomas Fowler first produced famous mineral solution of potassium arsenite in 1786, first used for the treatment of malaria (4). It acted as an inhibitor of oxidative processes and was prescribed in a form of pills, solution, and injection (11). The most famous was “Asiatic pill”, promoted by Hebra and Kaposi. It was a combination of arsenic acid and pepper with acacia (4). The pigmentation effects and carcinogenic potential were recognized early (10).

Salicylic Acid

Salicylic acid is a remedy that has been used for the treatment of psoriasis over a 100 years. The main effect of this acid is the removal of scales, as it facilitates the separation between the cells of the stratum corneum (4). It is a double-acting substance: 1-2% salicylic acid always has keratoplastic effect, whereas 5-20% has keratolytic activity (11).

Anthralin/Dithranol

Anthralin derives its origin from the herbal remedy Goa powder, which was used for refractory skin diseases in India and Brazil (12). Later on, during World War I, it was synthesized as a substitute of

chrysarobin, a primary component of Goa powder (4). It produces a characteristic skin staining and irritation. The time consuming aspects and the difficulty of using dithranol at home prevented that therapy from becoming popular.

Some brand new dithranol ointments, which can be washed off easily, are presumed to be better for outpatient treatment. Today, it is well known that autoreactive T cells are supposed to mediate inflammation and hyperproliferation in the epidermo-papillary compartment and have a positive feedback on the expression and accessibility of decisive antigen structures (13). Recently, an epitope within cytokeratin 17 (K 17) has been described as a putative psoriasis autoantigen up-regulated by the influence of proinflammatory interferon (IFN)-gamma, which is abundantly detected in psoriatic plaques. The data indicate that a part of dithranol antipsoriatic mode of action may be related to a direct down-regulation of putative psoriasis autoantigen structures (14).

In Europe, dithranol was first used in Germany, and introduced in Great Britain in 1939 (15).

Coal Tar

Coal tar for treatment of cutaneous conditions was described by a Greek philosopher Dioscorid nearly 2000 years ago (16). Because coal tar contains as many as 10.000 different chemical compounds, its precise mechanism of action is not clear. It seems to have antiproliferative and anti-inflammatory action. It is useful in combination with UVB radiation and has been successful in cases refractory to other treatment modalities (17). In addition to its unpleasant odor, it can also stain clothing and bedding. In rare cases, it may cause severe bronchospasm in atopic patient with asthma after being inhaled (18).

Goeckerman (1925) introduced application of crude coal tar (*pix lithanthracis*) for several hours up to 24 hours. After the removal of tar with olive oil, phototherapy with a mercury vapor lamp was performed (19).

Corticosteroids

Corticosteroids are the most common used topics today. Sulzberger and Witten (20) reported the first moderately successful use of topical cortico-

steroids. Topical corticosteroids have antiinflammatory, immunosuppressive, and antimitogenic action. They inhibit the 5-lipoxygenase pathway of arachidonic acid metabolism, inducing dose-dependent inhibition of leukotrienes. In addition, they inhibit the production of cytokines and chemokines, such as TNF- α , IFN- γ , IL-1, and IL-8 (12).

They penetrate skin easily and cause vasoconstriction and sealing of the superficial vascular plexus, decreasing of the exudation of fluid and inflammatory cells and normalizing terminal differentiation of keratinocytes (12). But the remission induced by corticosteroids is short-term and lesions treated with corticosteroids are less responsive to other methods. Local side effects, such as atrophy, striae, purpura, hypertrichosis, and teleangiectases must be kept in mind (19). They are used in a form of cream, ointment, and lotion.

Photo(chemo)therapy

UVB. The history of phototherapy reaches back to the 6th century BC. In 525 BC, Herodot described the positive effect of sunlight on bone growth in Egyptians (19). In 1895, Niels Finsen (1860-1904) was the first who treated lupus vulgaris skin lesions with a carbon-arc (20 amperes) lamp. The work of Finsen represented the first therapeutic use of artificial light sources and marked the beginning of modern phototherapy (19).

In the late 1970s, more selective broadband type of UVB (300-320 nm) was introduced - the so-called selective ultraviolet phototherapy (SUP) by Saalman in 1986 (19). Therapeutic optimum for psoriasis was achieved after the development of the Philips TL-01 fluorescent lamp (21). Parrish and Jaenicke (1981) demonstrated that wavelengths between 300 and 313 nm caused the greatest remission of skin lesions (21). Narrow-band 311 nm UVB therapy is a very effective, safe and easily administered phototherapy. It can be combined with corticosteroids, vitamin D analogues, salt-water baths, and psoralen baths. UVB light affects cell proliferation, mediator release and the immune system (22).

P(UVA). Topical exposure to sunlight and extracts, seeds, and part of plants that contain natural psoralens was known as a remedy in ancient Egypt and India thousands of years ago. First oral psoralen was produced in 1948 (23). In 1974 it was

confirmed that the combination of orally administered 8-methoxypsoralens (8-MOP) and exposure to UVA radiation source was effective treatment for psoriasis (24). The interest in the molecular effects of PUVA on the psoriatic skin has been first focused on the photobinding of psoralens to DNA of keratinocytes (25). Psoralens from photoproducts with proteins are leading to the damage of membranes and microsomal P-450 system and inactivation of certain enzymes, morphological, and functional effects on immunocompetent cells contribute to the therapeutic efficacy for psoriasis (25).

The dose of UVA radiation given to the patient is the variable in PUVA therapy, the dose of methoxalen and the interval between ingestion of the drug and exposure to UVA radiation are both fixed in any given patient (26). A variety of schedules for PUVA therapy are used and none is ideal for every patient. The therapist must select the most efficient one for the individual patient. Photochemotherapy was first applied in Boston (27). In Croatia, PUVA was for the first time administered in Rijeka, and later in Zagreb (28).

Vitamin D Analogues

Vitamin D plays an important role in the differentiation of epidermal cells. Human keratinocytes possess receptors for 1,25-(OH)₂-D₃, whose stimulation leads to a reduction of basal cell proliferation and acts as a trigger for cells to differentiate into corneocytes (12). Improvement of psoriasis by 1,25-(OH)₂-D₃ was demonstrated in a patient with osteoporosis who received it orally (29). The anti-proliferative effect is predominant due to excessive expression of VDR. Proinflammatory cytokines IL-1, IL-6, IL-8, and RANTES are all suppressed by 1,25(OH)₂D₃, possibly explaining why the sterol is topically effective in the treatment of hyperproliferative skin disorders such as psoriasis (30). Potential side effect is hypercalcemia, so the treated body surface area should not exceed 30% and the amount used per week must not exceed 100 g (12). Vitamin D can cause local irritation. Vitamin D₃ analogues (calcipotriol and tacalcitol) are used alone or in combination with other topical agents as well as with phototherapy. They are available in a form of creme, ointment, and solution (31). Sequential therapy is a combination of calcipotriene and corticosteroids according to the schedule (31).

Retinoids

Retinoids include calcipotiol, tacalcitole, and tazarotene. In 1925, Wolbach and Howe (32) first described tissue changes caused by retinoids. In 1962, Stüttgen and Baer (32) discovered the use of retinol acid for topical treatment. A recent topical analogue is a third-generation retinoid, tazarotene. Tazarotene is available in the form of 0.01% gel and seems to be effective for mild to moderate psoriasis. Retinoids influence proliferation, keratinization, and differentiation of epithelial cells, effects cellular and humoral immune response, and possess anti-inflammatory activity (32).

308-Excimer Laser

308-excimer laser treatments seems to offer relapse-free periods for localized psoriatic changes that are comparable or better than those offered by standard topical therapy regimens (33). In contrast to traditional phototherapy techniques, this excimer laser UV B therapy is selectively directed on the skin lesion (33).

NEW APPROACHES

Mexacalcitol is a vitamin D₃ analogue that is approximately 10 times more effective in controlling keratinocyte proliferation *in vitro* than calcipotriol and tacalcitol (34). Tacrolimus is an immunosuppressant that is used to prevent the rejection of solid organ transplantation. Topical preparation is a form of ointment is still on a trial (35).

Basic and clinical research is constantly providing new information on the pathogenesis, which is used to develop new approaches to the treatment of psoriasis. Recent researches are leading to the development of immunotherapy that targets specific steps and molecular mechanism in the underlying immunologic causes of psoriasis.

CONCLUSION

The treatment of psoriasis has come a long way. Psoriasis is a common disease, so trial and error attempts in therapy have provided a long list of treatment modalities. Underlying mechanisms of psoriasis are elucidated, raising hope that potent antipsoriatic therapy can and will be designed.

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1st Croatian Congress on Psychodermatology

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Book of Abstracts

Oral Presentations

Service Provision for Psychodermatology

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Psychodermatology service provision remains rudimentary in most, if not all, health care systems. An overview with recommendations will be offered, with particular reference to the UK experience. While psychodermatological conditions are common in community and primary care, the expertise for dealing with such conditions is largely at the secondary care level, where it is split between different services. Tertiary level specialist psychodermatology liaison/consultation services remain few and far between. The results of a recent key-informant survey to map UK psychodermatology services are presented. Psychodermatology needs to be established as an essential element in the curriculum for trainee dermatologists and general practitioners with a special interest in dermatology. Service provision can then be expected at both primary and secondary (dermatology) care levels. Specialist liaison/consultation clinics need to be available for tertiary referral, but especially for the provision of training opportunities for those practitioners working at primary and secondary care levels.

Liaison Psychiatry and Psychotherapy in Dermatology

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In the long history of medicine, body and mind were inseparable. The same may be said for dermatology and psychiatry – they are inseparable, especially because the skin and psyche have the same embryological origin, and the connection between the skin and psychological aspects is especially significant. The visibility of dermatitis gives it a special psychological meaning. At the same time, some of the person's psychological characteristic (like hysteric behavior and exhibitionism) can be manifested through changes on the skin. Psychodermatology deals with dermatological symptoms caused by psychiatric disease; dermatological diseases with psychosomatic etiology; and dermatological diseases with complications caused by emotional and psychical disturbances. Duties of the liaison psychiatrist at a dermatology department are primary, secondary and tertiary level of prevention; continuous education of the health care team to see each patient as bio-psychosociologically unique; and suggesting structural changes in department. The goal of psychotherapeutic approach in dermatology is to remove conflict situations that may influence the therapeutic process, to reduce the resistance to therapy, to reduce the tendency to be passive or infantile, to ensure that the patient has an active approach to the present and future problems, to motivate the patient, and teach him or her how to integrate and accept their illness.

Psychological Experience of Skin Disease in Children

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The psychological problems associated with a child's medical condition have long-term implica-

tions regarding both social and emotional development. Such addressing of these problems can be even more crucial with children than with adults. This presentation will highlight possible relationship difficulties that may arise within a family after a child is diagnosed and focus on how counseling techniques can be applied to working with young dermatology patients and their families.

Liaison Psychiatrist in the Treatment of Dermatovenereological Patients

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A joint approach of dermatovenerologist and psychiatrist plays an important role in the process of diagnosis and treatment of patients with certain dermatoses. Case reports of patients with urticaria, psoriasis, and other skin diseases show the importance of the liaison psychiatrist in the successful treatment of patients with these dermatoses. They also reflect the difference between a simple consultation and the liaison approach.

Anxiety and Depression in Dermatological Patients

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The hypothesis that links skin diseases with anxiety and depression has long been a subject of debate. The aim of our study was to screen outpatients for anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). The subject group consisted of a 1,000 outpatients at the Ernest Lluch Hospital in Calatayud, who were asked to complete the HADS questionnaire and a socio-demographic form. The co-morbidity between anxiety and depression and skin diseases was slightly lower than those observed in other similar studies. Patients with skin cancer and other serious skin problems scored highest in depression, while pa-

tients with visible unsightly skin disorders scored highest in anxiety. Our results showed that one out of four patients had clinical scores for anxiety and/or depression. We consider that this information is extremely valuable for planning our patients' course of treatment. The HADS is very reliable and valid, as it is simple and fast to apply and interpret.

Improvement of Acne Quality Life Index (AQLI) and Global Acne Grading System (GAGS) in Acne Patients After Treatment

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Acne vulgaris is a disease of the pilosebaceous unit where abnormally adherent keratinocytes cause plugging of the follicular duct followed by accumulation of sebum, keratinous debris, and bacteria within this structure. It remains one of the most common inflammatory dermatoses among adolescents. The psychological impact of acne is one of the most important aspect of this disease, which can significantly worsen the patients' quality of life. One hundred patients with mild, moderate, and severe acne (comedonal and inflammatory) were followed up at our Department. They were clinically and psychologically evaluated with a Global Acne Grading System and an Acne Quality of Life Questionnaire, respectively. The Global Acne Grading System (GAGS) attributes a different score to each area of face (forehead, nose, chin, left cheek, and right cheek) and to each lesion. The score of the lesions depends on the percentage of the surface in which lesions are localized. The sum of the scores forms the Global score, that correlates with the degree of acne severity. Quality of Life Questionnaire (QoL) is a self-administered questionnaire developed to assess the effects of acne on QoL and the impact of treatment on these QoL parameters. This questionnaire contains 19 questions, which are organized into four domains (self-perception, role-social, role-emotional, and acne symptoms). QoL and GAGS have been administered to all patients at baseline, during and at the end of treatment. Our

results have demonstrated a significant improvement of GAGS and of QoL in about all patients.

Influence of Corrective Cosmetics on Quality of Life of Patients With Acne Vulgaris

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Acne vulgaris is the most common skin disease. The condition affects mostly young people during the adolescence, at a time when they are undergoing maximum social and physical changes, and can produce significant psychological scarring. Emotional impairment due to disfigurement by the disease is almost undisputed and has been thoroughly investigated. Camouflage therapy is a system of cosmetic techniques designed for patients to cover their disfigurement and to help them cope with the psychological and physical trauma of their disfigurement. The goal of this study was to assess the effect of camouflage therapy on patient's perceived quality of life. Forty patients aged between 15 and 25 years were included in the study. Twenty of them were instructed how to use camouflage therapy and applied it daily for 4 weeks. Other 20 patients were only given therapy for their condition, but were not introduced to camouflage therapy. The dermatology specific quality of life questionnaire (DSQL), APSEA, and general questionnaire (age, sex, and other diseases) were applied before the beginning of the therapy and after 4 weeks. The clinical status was documented on photographs before and after the use of camouflage therapy. The first results show significant improvement of quality of life after the use of camouflage therapy and indicate it can be used as a complement to the treatment of acne vulgaris.

Psychological Status and Quality of Life in Patients with Acne Vulgaris

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Acne vulgaris is based on follicular keratosis of the sebaceous glands which occurs mainly during puberty but also during adolescence. It is one of the most frequent clinical pictures in dermatology. Although it doesn't hurt general health or overall well being, having acne can seriously damage psychological well being. It can be highly painful condition in an emotional sense. For teenagers whose self-esteem and identity are still in a formative stage, even a mild case of acne may have negative psychosocial effect. Acne can have strong impact on health related quality of life, anxiety, depression, self-consciousness, embarrassment, low self esteem and social withdrawal. The goal of this study was to investigate effect of acne on our patients and potential improvement of psychological status after the improvement of acne condition. This study included 50 patients with mild to severe acne vulgaris (22 female and 18 male patients), aged 14 to 23 years. General data on sex, age, and other diseases were collected and Dermatology Specific Quality of Life questionnaire (DSQL), APSEA, Beck's depression inventory (BDI), MPS, and STAI were applied before the beginning of the therapy, after 5, 10, and 16 weeks of therapy, and after discontinuation of the therapy. The results showed significant influence of acne on quality of life, depression and anxiety, as well as an improvement of psychosocial status and quality of life after a successful therapy.

Isotretinoin and Its Influence on Psychological Status of Patients With Acne Vulgaris

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The extent to which severe acne affect patients' personality and emotional life is still undetermined.

The patients with severe acne vulgaris frequently report feeling self-conscious, anxious, and socially isolated. Isotretinoin is the drug indicated for severe, recalcitrant nodular acne that has proved unresponsive to other therapies. Isotretinoin's link to psychiatric adverse events is controversial. For the last 15 years, there has been a debate over whether isotretinoin could be causing depression and subsequent suicide in teenagers. Although depression and suicide are important health problems for teenagers, there is as yet no good evidence that isotretinoin contributes significantly to either. Numerous clinical investigations have failed to identify an association between the use of the isotretinoin and the development of psychiatric disorders. The causal relationship between isotretinoin therapy and depression has not been clearly established and needs further study. Acne may be associated with low self-esteem and poor self-image, problems that can eventually lead to serious psychological conditions. Since isotretinoin is an effective treatment for acne, it may help reduce associated psychological disturbances. The goal of this study was to investigate the influence of isotretinoin on psychological status of acne patients during and after treatment. The following work describes the benefit of using a questionnaire as a clinical tool to identify acne patients who have developed psychological sequelae as a result of the disease process. Fifty patients (23 men and 27 women) with moderate to severe form of acne vulgaris were prospectively examined for psychological, emotional, and dermatological symptoms. A variety of standardized psychometric inventory were used, such as DSQL, APSEA, BDI, MPS, and STAI, which were applied at the beginning of the therapy, as well as after 5, 10, 16 weeks, and at the end of the treatment when the disease had been effectively brought under control. The subgroup of 25 patients (15 men and 10 women) has received isotretinoin taking in consideration the severe, recalcitrant form of papulopustular or nodulocystic acne. The results showed significant decrease in depression and anxiety as well as an improvement of psychosocial status and quality of life after successful treatment in both groups of patients. The use of oral isotretinoin was very effective therapy and no influence on psychological disturbances was observed. However, monitoring patients for depression, depressive symptoms, and suicidal ideation can help identify those

who may be at risk and improve patient care by facilitating appropriate diagnosis and treatment of patients experiencing clinical depression.

Psoriasis: Stress, Depression and Pruritus

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Psoriasis is a chronic inflammatory disease. The aim of this presentation is to give an overview of psychodermatological aspects of this disease based on own studies and experience. Over 60% of psoriatic patients reported the presence of at least one stressful life event within one month before psoriasis exacerbation. The severity of psoriasis (PASI) was significantly higher ($p < 0.001$) in patients who experienced stressful life events compared with those without stress. Depression was diagnosed in 17% of the patients. Among them, reactive disorders were found in 77%, moderate in 8%, and mild depression episodes were recognized in the remaining 15% of subjects. Itching was found in 80% of psoriatic patients. Severity of psoriasis in pruritic patients was significantly increased compared with non-pruritic subjects ($p < 0.004$). Significant correlation was found between PASI scores and intensity of itching, assessed by both VAS and the questionnaire method ($p < 0.01$ for both analyses). Generalized itching was reported by 29% of pruritic patients. The most common sites of itching were lower limbs (50%), trunk (49%), upper limbs (49%), and scalp (35%). Face appeared to be the least commonly affected skin area (only 1.2%). Patients who experienced heavy or extremely heavy stress suffered from pruritus significantly more often ($p < 0.05$). Significant correlation between severity of stress and intensity of itching was observed among examined patients ($p = 0.015$). No relationship was found between psoriatic pruritus and plasma concentration of both histamine and SP. The mean value of CGRP concentration in the plasma of pruritic psoriatic patients was significantly higher than in control subjects ($p < 0.01$). This was not observed when the non-pruritic subjects were compared with healthy individuals. A significant correlation was found between itching intensity

and CGRP plasma concentration in the male subjects ($p=0.03$).

Influence of Stress and Psychological Characteristics of Patients with Psoriasis Vulgaris

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Psoriasis is a chronic disease with lesions that are often extensive and disfiguring. Patients suffering from severe psoriasis report high levels of personal distress and disability as a result of their disease. Emotional factors and specific personal traits have been implicated in predisposing or perpetuating psoriasis. The aim of this clinical study was to accomplish an accurate assessment of the patient's psychological condition, which would prove to be important altered psychological status, as the history of many patients suggested. We also determined the relationship between psychological status and the age of the onset and duration of psoriasis. We examined whether certain psychopathological traits were more frequently associated with *early onset* (up to age of 40 years) or *late onset* (after age of 40 years) psoriasis. The psychological status of 70 psoriatic patients and 70 controls was evaluated by using the following psychometric instruments: Beck Depression Inventory (BDI), State and trait anxiety Inventory (STAI-T, STAI-S), General Health Questionnaire (GHQ), Social Support Appraisals Scale (SSAS), Psoriasis Life Stress Inventory (PLSI) and Minnesota Multiphasic Personality Inventory (MMPI-201). The severity of psoriasis has been assessed by using standardized (Psoriasis Area Severity Index) PASI index measure. It has been verified that the *late onset* psoriasis is comorbid with greater psychopathology than the *early onset* psoriasis. The *late onset* psoriasis patients have more prominent symptoms of depression and show "descending neurotic profile" in

MMPI-201, which refers to the conclusion that those patients have tendency to somatization with converse way of reaction. The results showed higher score in BDI and PLSI for the late onset group, as well for both groups in BDI score comparing with control. According to the self-perception, stress was the precipitating factor for the onset or exacerbation of the disorder in 62% of psoriatic patients.

Self-Perception in Patients with Psoriasis

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Negative changes in self-perception are often present in psoriatic patients. Problems are present at the level of self-consciousness, self-esteem, and the perception of the public self. The relation of the psoriatic patients towards themselves often disturbs their intraphysical reactions and relations with other people, which has negative effects on the development of the basic dermatological illness. We studied characteristics of the personality structure and traits of 30 psoriatic patients by using ROSCHACH test and self-perception scales. We also analyzed the results of the group psychotherapy with psoriatic patients that was conducted at our Department, which showed that patients had problems with self-perception and perception of their own body.

Psoriasis as Reaction to Experience of Being Rejected

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A case of a patient who developed psoriasis after a period of stressful adaptation to an unfamiliar situation, characterized by feelings of humiliation and belittling is presented. Because of the depressive reaction, the patient came in for psychotherapy. As he is a foreigner, he did not speak the language when he arrived to Croatia. In the new envi-

ronment with very poor empathy abilities, he felt unaccepted. The patient's wife felt guilty for the situations he found himself in and thought that psychotherapy (which is still going on) should help him. There were many details showing unfriendly and frustrating environment to which the patient reacted depressively. He developed aggression toward himself, since he could not have shown an open aggression to the external environment, which represented for him a bad mother. These unconscious sadistic-masochistic conflicts as a basis of dermatosis are clearly seen in the crisis of psoriasis as sadistic impulses turn against the proper ego. Non-relieved sadistic wishes as guilt for the hostility to family figures usually influence the skin pathologically. The disturbed economics of libido influences the blood vessels in the skin through humoral and nervous alterations, and chemical processes create changes that provoke sensations of urgent character, such as skin scratching. The inflow of blood in the scratching spot is increased, which probably represents the reminder of a deeper biological reflex, which represents a psychological relief. At psychotherapeutical session, I indicated to the patient the sadistic character of his super-ego with an expectation that he would become able to externalize his aggression more to the outside world and in this way diminish the psoriatic reaction of his skin.

Psoriasis Vulgaris and Psychotic Disorders

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We have investigated incidence of psoriasis vulgaris and psychotic disorders at three psychiatric departments: forensic-psychiatric, psychiatric subacute, and chronic psychiatric department of Neuropsychiatric Hospital in Popovača. According to the data in literature, skin psoriasis vulgaris ranges from 1-2% among the general population. Pilot investigation, which we carried out at the three departments, showed the following results: the incidence of psoriasis vulgaris at the forensic-psychiatric department was 1.5% (n=200), at the subacute

department around 8% (n=75), and at the chronic psychiatric department around 2.7% (n=75). According to the obtained results, with the reference to the general population, the considerable aberration is evident in relation to the average at the subacute psychiatric department.

Psychological Aspects of Alopecia Areata

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Alopecia areata is one of the skin pathologies frequently associated with psychopathology. Our study group consisted of 35 patients with alopecia areata. A multidimensional profile of the patients was obtained by using the Derogatis SCL-90-R Symptom Checklist, which contributes to a clearer symptomatic context and enables concrete behavior patterns of psychopathological manifestations to be interpreted. Data on epidemiological parameters such as age, sex, type of alopecia, and degree of the disorder were obtained as well as the 9 dimensions explored by the SCL-90-R: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychotism. The SCL-90-R proved to be an excellent instrument for screening, allowing both a better understanding of patients with alopecia areata and facilitating an integral treatment.

Sexual Problems in Patients with Psoriasis and Atopic Dermatitis

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During their consultation sessions, people with skin diseases increasingly talk of sexual problems. However, up to now, only a few studies have been performed on this topic. We wanted to determine what are the sexual characteristics of patients affected by the most frequently occurring chronic skin diseases: atopic dermatitis and psoriasis. Hypo-

thetically, it was assumed that patients with atopic dermatitis would report about increased sexual problems due to mucous membrane involvement. The study included 31 patients with psoriasis vulgaris and 38 patients with atopic dermatitis. A healthy control group consisted of 33 people. All subjects were tested with Snell's Multidimensional Sexual Self-Concept Questionnaire (MSSQ), which measures 20 variables that reveal sexual self-concept of a person. In comparison with controls, the patients with atopic dermatitis had lower sexual self-efficacy, lower sexual motivation, and increased sexual anxiety, whereas the patients with psoriasis indicated a higher external sexual control, lower sexual self-control, and lower sexual motivation and capability. Compared with patients with psoriasis, the patients with atopic dermatitis had less sexual self-respect and increased sexual anxiety. It seems that the sexual behavior of patients with psoriasis or atopic dermatitis is reflected differently. However, patients with atopic dermatitis indicated more sexual problems. This emphasizes a need of patients with chronic skin diseases for sexual consultation, which is expected to increase their life quality.

Anxiety and Depression in Children with Vitiligo

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In the study conducted between 2001 and 2003 at the Institute for Health Care of Children and Youth in Novi Sad, 33 children aged 10-15 years with vitiligo diagnosis were assessed, as well as 51 healthy children of same age. The questionnaire for depression and anxiety was applied, as well as the Risk Scale to control the studied groups in relation to the existence of stress factors that could potentially impact some of measured variables. Obtained results showed no significant differences in relation to the emergence of anxious and depressive characteristics between the children with vitiligo disease and control group.

Psychosocial Aspects of Condylomata Acuminata

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The aim of this investigation was to evaluate the knowledge, attitudes and behavior of patients who suffered from one of the most common sexually transmitted diseases, *condyloma acuminatum*, and to compare their cognitive representation of sexuality (sexual self-schema) and their self-esteem with those of healthy controls. Participants were 46 patients (8 women and 38 men) with *condylomata acuminata* (mean±SD age=29.8±10.6 years) and 43 patients (23 women and 20 men) with contact dermatitis (mean±SD age=27.3±7.2 years) as a control group. All patients were from the outpatient clinic of the Department of Dermatovenereology, Rijeka University Hospital Center. Questionnaires were administered to collect sociodemographic and medical data, inventory of readiness to behave in a health beneficial way, as well as psychological self-assessment scales including Bezinović's Sexual Self Schemas Inventory and Rosenberg's Self-Esteem Scale. Results showed that only 54% of the patients knew something about their disease and about possible way to treat it; 60% of the patients saw their disease as moderately stressful and 28% as extremely stressful. Furthermore, patients were 100% sure that they would prevent the symptoms to recidivate by following medical advice and by using appropriate protective measures. They were almost 100% sure that they would regularly visit their physicians. There were significant differences between the patients and controls in some aspects of sexual self-schema (readiness to engage in sexual activities and sexual well-being): patients with *condylomata acuminata* were less ready for sexual action and more satisfied with their sexual life comparing to controls. The results of this investigation were discussed regarding psychosocial impact of the disease and its treatment.

Eczema in Bulimic Patient

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We present the case of a 24-year-old woman undergoing psychotherapy because of eczema alterations on her hands and palms. Her medical history also revealed that she was bulimic. She was the second child in the family with the strict and abusing mother and the weak father who was mostly absent from home. In the psychoanalytical therapy, the first author tried to understand the dynamics causing eczema on the skin. The therapy has shown that eczema symbolized the conflict between dependence and independence, i.e. her wish to be independent and her mother's wish to make her dependant was projected on the skin. Her incapability to make the difference between the inner and the outer world was the result of unsolved symbiotic relationship with the mother. Through eczema, the patient tried to solve her conflict and had the need to take care of her skin. In that way, the dermatological symptom was a compromise symptom between her need to remain a little child and her wish to become a grown-up. The eczema first appeared when she was 15 and entered the vocational school for hairstylists, following her mother wish, although she herself wanted to become a teacher. She started her first sexual relationship when she was 13 with a man who was 5-6 years older than she. They married later on when she turned 18. She had a child whom she breast-fed for three years. At that period, the eczema completely disappeared. Although the patient eczema was intermittently present all the time, the fact that the eczema disappeared at the time of the breast-feeding confirms our hypothesis that the feeling of rejection and not being loved was a provocative factor for the outbreak of eczema on both hands. A 3-month psychoanalytical psychotherapy has enabled the patient to experience the so-called therapeutic symbiosis through a massive positive transfer with the psychotherapist; her eczema completely disappeared.

The "Third Ear" of the Dermatologist. What Does it Consist of?

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Patients not being aware of psychiatric alterations who consult dermatologists for disorders not considered as psychocutaneous may suffer slight states of anxiety, with or without masked depressive alterations. Only in a very reduced number of cases obsessive tendencies are found and slight phobias in a few. None of them have important psychiatric alterations. If they had, they would have previously consulted a psychiatrist. Masked depression, which is frequently hidden in dermatological consultations, is characterized by the lack of sadness, the typical symptom of depression. Patients with masked depression frequently somatize their problem. Those who do so in the skin consult the dermatologist. During the visit of some of these patients it is evident that if they had not been anxious or depressed they would not have felt it necessary to consult. Perceptive dermatologists open to the psychological aspects of their patients have a "third ear", which allows them to "hear" beyond what the patient is explaining and makes them automatically suspect an alteration in the psychological state of their daily patients. The suspicion is established for the general attitude of some patients, what they say but, above all, the way in which they explain. A systematic and specific questionnaire helps to accept or reject a suspected psychological alteration. Patients seen in hospitals can easily accept the transfer to a liaison center. It is easy that they reach the psychiatrist who is the only expert. On the other hand, patients visited in private offices should be psychiatrically treated by the dermatologist as, due to the stigma of mental illness in our society, these patients would never accept to see a psychiatrist. The patient would be lost, without psychiatrist, nor dermatologist, without being cured of either his dermatosis or improvement of his psychological alteration. The necessary therapeutic management could be made with psychotropic drugs or not. In some of these patients a type of psychiatric treatment is the only way to cure their dermatosis. And, in all of them, this treatment improves the patient's psychological quality of life. The only person who could give them this improvement is the consulted dermatologist.

Localized Hyperhidrosis Treated With Botulinum Toxin Type A: Improvement of Quality of Life Index

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Primary local hyperhidrosis is a common condition with excessive sweating, most often of the hands, feet or armpits. Symptoms may give rise to serious emotional and social problems as well as functional impairment with consequences for professional life. Current treatments, which include topical application of acids, aldehydes and metal salts, iontophoresis, and systematic therapies, are often ineffective or produce improvements of short duration. Surgical treatment, such as sympathectomy and removal of the sweat glands by liposuction or curettage, may provide relief for longer periods of time, but these methods carry significant risks. Recent studies have demonstrated that Botulinum toxin type A (BTX-A) injections into the axillae or the hands result in dramatic reductions in sweat production. The BTX-A acts by blocking the release of acetylcholine from the presynaptic cholinergic nerve fibers innervating sweat glands. Thirty-five patients affected by palmar and axillar hyperhidrosis were followed up at our Department. All patients were evaluated by the Minor Test and by the Dermatology Life Quality Index (DLQI) questionnaire, and underwent Botulinum toxin type A treatment (100 UI for axillae or palms), with follow up at 1 week, and 1, 3, 4, 5, 6 and 9 months. We found a significant improvement of the Quality Life Index in all patients evaluated by the Minor test and DLQI. Thus the Botulinum toxin type A must be considered a valid way in the treatment of patients affected by palmar and axillar hyperhidrosis.

Quality of Life in Patients With Pemphigus

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Pemphigus is a group of chronic autoimmune blistering diseases that can result in a significantly reduced quality of life. Measuring quality of life by using different questionnaires can be valuable for clinical practice. In dermatology, there are well-established questionnaires about quality of life of patients with psoriasis, atopic dermatitis or acne, but there are not many studies about the quality of life of patients with blistering diseases. Although patients with pemphigus are quite rare, there should be investigations into their quality of life due to the severity of disease itself, often a life-long therapy, and side effects of therapy. Special attention should be given to actual manifestations of the disease, location of the lesions, prognosis of disease, pain and burning, treatment of disease and side effects of therapy.

Quality of Life in Chronic Skin Disorders

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On the basis of population means, people's satisfaction with their own lives (or subjective quality of life) is within the range of 70-80% of the measurement scale maximum score (%SM). According to homeostatic model, the subjective quality of life (SQOL) is strongly influenced by the homeostatic system. Individuals who report a SQOL level which is less than 50% SM can be considered to be experiencing the homeostatic failure. Homeostatic failure can be caused by different factors.

The aim of this study is to assess the subjective quality of life and to identify psychosocial predictors of SQOL among patients with a variety of dermatological diseases.

First results show that the group of patients remained within the normal range of subjective well-being expected by the homeostatic model. Dermatological disease alone does not result in a homeostatic failure. Psychological variables, especially the anxiety level, play the major role in maintaining the homeostatic balance. This finding suggests the importance and necessity of psychological support in treatment of dermatological illnesses.

Dysmorphophobia

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Dysmorphophobia is another name for body dysmorphic disorder (BDD), a psychiatric condition that was described more than a century ago. It is marked by a fixation on an imaginary flaw in the physical appearance. Male to female ratio seems to be equal and the disorder usually occurs in adolescent age. However, average age in people receiving dermatologic care is 33.7 years. Heredity may contribute to development of the illness. Dermatologic or plastic surgery treatment frequently fails to improve dysmorphophobic symptoms. Serotonin re-uptake inhibitors (SRIs) have proved to be the most effective medications in the treatment of dysmorphophobia. Non-pharmacologic psychiatric treatment may prove effective in the treatment of people with BDD. People with BDD frequently develop major depressive episodes and are at risk of suicide. They also may exhibit violent behavior toward treatment providers. People with BDD frequently desire a cosmetic medical or cosmetic surgical approach but demonstrate unrealistic expectations. Medical pitfall is to combine surgical treatment with psychiatric therapy when treating a person with BDD.

The delusion of parasitosis – myth or reality?

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Delusional parasitosis (DP) is a syndrome in which the patient falsely believes he or she is infested with parasites, for example, lice or worms, despite clear evidence to the contrary. Patients spend much time trying to get rid of the bugs and suffer from these symptoms. Such a patient is not satisfied with assurances or test results that no par-

asites are present, but is so convinced that he or she will go as far as to bring the parasites in matchboxes to a physician. Subjectively worried, the patient may try to pick the "parasites" out of the skin, in order to prove his/her "reality" causing cutaneous lesions and even ulcerations. Patients prefer to go to dermatologists, rather than psychiatrists, because they have a strong conviction over the presence of a somatic disease and do hardly accept any psychiatric advice for their complaints. DP can be sometimes (5-15% of cases) associated with "Folie à deux" or shared psychotic disorder. Delusions of parasitosis, though uncommon, are an important cause of distress for affected patients and frequently of frustration for their physicians. They occur primarily (but not exclusively) in middle-aged or older women.

A few patients with a delusion of infestation by insects over the body (including the external genitalia) and with a delusion of insects crawling over the scalp are briefly presented in this paper from the dermatological point of view. These patients have been referred to the Mycological and Parasitological Reference Laboratory of our Department in order to rule out the real parasitic skin disorder. However, no one of these patients wanted to accept the negative results of the parasitological testing, moreover, almost of all these patients have persisted in "supporting the evidence" of their "serious parasitic skin disorder" in the manner previously described. All of them had an impression that their difficult "skin infestations" have not been taken seriously enough. In general, the management of the complexities of DP requires a comprehensive biopsychosocial understanding. Though, we have the impression that this route is still very difficult and frustrating and the therapeutic results in most cases not satisfactory enough.

Trichotillomania and Anorexia Nervosa in Adolescent Female: Case Report

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Trichotillomania, a disorder characterized as a recurrent failure to resist impulses to pull out one's own hair that results in noticeable hair loss, was first described by Hallopeau in 1889. It is described as a rare chronic condition, primarily affecting females, with an onset in early childhood or adolescence. According to DSM-IV, it is considered an impulse control disorder, but some experts believe it to be a symptom of obsessive-compulsive disorder. It has been associated with a number of psychiatric disorders, with more than 20% of trichotillomania patients suffering from eating disorders, most commonly *bulimia nervosa*. We describe a 16-year-old girl with a 4-year history of an eating disorder and a 2-year history of hairless areas. Six years ago she lost 11.5 kg in only 6 months. She developed secondary amenorrhea and denied vomiting or using any medications. After hospital treatment, her weight returned to normal. About 2 years after the onset of eating disorder, she started noticing hair loss. At the time of assessment, she had irregular areas of incomplete hair loss over the frontal, temporal occipital, and parietal areas of her scalp and she denied pulling out her hair. Physical examination and all laboratory data were normal and she was sent to a psychological testing. Psychologist started cognitive-behavioral therapy, which she attended for almost a year. She also started visiting psychiatrist who prescribed psychotropic medications.

Dermatitis Artefacta in Adolescent With Emotional and Conducted Disorder

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Dermatitis artefacta is a self-inflicted dermatologic injury. The patient creates skin lesions to satisfy an internal psychological need, usually a need to be taken care of. The highest incidence of onset is in late adolescence and early adult life. Female to male ratios range from 3:1 to 20:1. The psychological tests reveal patients with artifact dermatitis to be in a state of considerable depressive-aggressive tension without being able to handle their emotions and impulses in an adequate manner. Both, the depressive adolescent and adolescent with conduct

disorders have a basic problem with aggressive impulses. They show strong intrapsychic tension, inhibition of aggression, low frustration tolerance, and self-aggressive tendencies. Self-inflicted injuries to the skin have different functions: by causing pain to themselves the patient tries to feel their body boundaries and to avoid fragmentation of the body-self. The artifact should draw the attention of the surroundings to the emotional suffering of the patient. Sometimes to confront the patient with artifact dermatitis with their psychical background may be counter-productive, but usually combined psychiatric dermatologic approach brings best results. Psychiatric treatment consists of cognitive behavioral treatment and psychotropic drugs. The upper dose of selective serotonin re-uptake inhibitors and low dose of atypical antipsychotic agents may be effective. Prognosis is variable but seems to correlate directly with the duration of the illness.

Differential Clinical Expression of Dermatitis Artefacta

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Dermatitis artefacta is a mutilation of the skin induced by the patient who usually denies it. The condition is rare, prevalent mostly in women patients. The patient creates skin lesions to satisfy an internal psychological need, usually to be taken care of. They may look and act normal in every respect, although frequently there is a strange and bizarre personality behind. The patient's denial of psychic distress, and negative feeling aroused in healthcare personnel, make management difficult. The skin lesions consist of scars, ulcers, erosions, blisters. The shape of the lesions may be linear, bizarre shapes, geometric patterns, single or multiple, and rarely occurring on the face. The lesions do not conform to the configuration and distribution of any recognized pattern of dermatologic disease, even though there may be an attempt to simulate them. It is important to rule out every possible cause and perform a biopsy before assigning the diagnosis of *dermatitis artefacta*. We describe a several cases.

Dermatitis Artefacta: Usual and Unusual Cases

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Dermatitis artefacta is frequently seen in individuals with immature personalities when faced with a stressful life situation. The visible skin lesions can be interpreted as an attempt of non-verbal communication, actually a silent appeal for help. Many of these patients display a rather neurotic emotional disorder, not psychosis. Since in more severely affected patients the recurrences are frequent, a long-term and intensive psychotherapy by experienced analytically oriented therapist is recommended. We followed 40 patients with usual and unusual clinical pictures of *dermatitis artefacta* (3 males and 37 females) during longer period of time. The skin lesions were different in configuration, shapes, single or multiple, and found on skin areas accessible to patient's hands, mostly face, chest, and limbs. All lesions healed rapidly under the occlusive dressing. The diagnosis of *dermatitis artefacta* was made on the basis of bizarre case history and quality of dermatological lesions. In 17 patients, histological analysis was also performed. Twenty-four patients firmly denied that they had caused the lesions, while others admitted to have caused the skin lesions by scratching, abrasions, burning, applying chemicals and plant extracts, and even injecting some ingredients under the skin (such as sawdust). All that provoked heavy irritative dermatitis with erythema, erosions, and sometimes ulcerations. The psychological profile of 9 of our patients was within normal limits, 3 had a low intellectual level, one had mental retardation, 19 had neurotic disorders, and 8 were borderline personality disorders.

Etiological Factors in Dermatitis Artefacta

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Out of a total of 15,500 patients hospitalized at the Department between 1982 and 2001, 28 (0.18%) were diagnosed with artifact dermatitis. The aim of this study was to determine the total number of the patients diagnosed with artifact dermatitis during this 20-year period, and their distribution according to sex, age, epidemiological and clinical data, and etiological factors. Of 28 patients diagnosed with artifact dermatitis, 26 were women and 2 were men, aged between 17 and 72 years. Epidemiological data indicated that all patients were urban residents and most were highly educated. Routine clinical laboratory data did not indicate any deviations from standard values. Multiple *acar* and *phthyr* tests were negative. In 20 patients (71.5%) prior to the appearance of artifact dermatitis, the following conditions were noted: cystitis (n=9), sinusitis (n=4), gastritis (n=3), and adnexitis (n=4). Four patients had psychiatric problems, while the remaining 4 patients did not suffer from any prior severe disease. In the 4 psychiatric cases, stress-reactive anxiety disorder, major depressive episode, depressive syndrome and anorexia as well as depressive-anxiety disorder were recorded. Investigating the etiological factors, the possible cause of artifact dermatitis in 71.5% of patients could be a prior inflammatory process, in 14.3% of patients it could be psychiatric illnesses, while in 14.3% of patients it was impossible to determine the cause of this entity.

Incidence of Dermatitis Artefacta During Last 10 Years in Hospitalized Patients at the Department of Dermatovenereology in University Hospital "Sestre milosrdnice"

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Dermatitis artefacta is mutilation of the skin induced by the patient who creates skin lesions to satisfy an internal psychological need. The inci-

dence and prevalence of dermatitis artefacta is thought to be underreported. We examined the incidence of *dermatitis artefacta* in a 10-year period among our hospitalized patients. The diagnosis of *dermatitis artefacta* was based on the clinical picture and evolution of the lesions, on the patient's borderline personality, on the objects found in his possession, and eventual admittance of being involved in the aggravation of the lesions. The obtained results showed <1% prevalence of *dermatitis artefacta* among the hospitalized patients at our Department. Most patients with *dermatitis artefacta* were women. Our study results confirmed that *dermatitis artefacta* was uncommon. For the better management and the treatment of the patients with *dermatitis artefacta* in the future, we recommend a supportive consultations with the psychiatrist, physician, and psychosocial worker.

Forensic Psychiatric Patients and Self-inflicted Skin Injuries

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Skin problems may represent problems of the contact and communication with the environment. While working at the Institute of Forensic Psychiatry at Neuropsychiatric Hospital in Popovača, we meet a lot of people who committed criminal offences in a state of mental incompetence due to the psychopathology of basic illnesses. Different skin changes and diseases have been observed in these patients. With forensic patients, self-inflicted skin injuries can be an indicator of their difficulties in communicating with the environment, but also of their personal problems. We investigated the consequences of self-inflicted skin injuries and on the change of the patients in their perception of their own.

Stress-related Hormone Status in Psoriatic Patients Treated With Naphtalan Oil

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Psoriasis is a chronic, genetically predisposed, erythematous squamous disease. Stress is a common trigger for initiation and exacerbations of psoriasis. Chronic stress may decrease adrenal activity; level of cortisol in blood and urine is lower than normal in patients exposed to chronic stress. The aim of the study was to compare the blood and urine level of cortisol in psoriatic patients before and after naphtalan therapy to cortisol blood and urine levels in healthy volunteers. The study included 19 male patients and 17 healthy volunteers. Twenty-four-hour urinary cortisol, circadian cortisol rhythm at 8 am and 5 pm, and cortisol in dexamethason suppression test by standard radioimmunoassay were determined in all study subjects. Results of the study showed lower cortisol levels in psoriatic patients before the therapy compared with control subjects, corresponding to the cortisol level in a state of chronic stress. After therapy introduction, there was a statistically significant increase in urine cortisol level, but not in the blood cortisol level. Pre-therapeutic blood cortisol showed stronger circadian rhythm than after therapy introduction, pointing to improvement with higher cortisol supplies during the day. It should be noted that it was impossible to determine whether these results were a consequence of patients' isolation from the stressful environment or to therapy *per se*. The results are, however, intriguing and additional studies are needed to elucidate them.

War Stress and Skin Cancer in Karlovac County, Croatia

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War stress and conditions and higher incidence of various malignancies was first observed among the United States Army war prisoners during World

War II, with higher incidence of melanoma. After Vietnam War, a higher incidence of uterine and prostate cancer was observed in military personnel. In Croatia, higher incidence of breast carcinoma was observed after the Homeland 1991-1995 war. The aim of this study was to investigate possible etiological role of war stress in the development of skin cancer. We retrospectively analyzed Karlovac General Hospital cancer registry data on 3,355 patients, of whom 705 had skin cancer. We compared incidence of skin cancer in our patients during and after the war. For statistical analysis, student t-test and proportion tests were used. The incidence of skin cancer in Karlovac region was found to be significantly higher ($Z=7.93$; $p<0.001$) in the postwar 1996-1999 period then during the war. The incidence of all other types of cancer in Karlovac region was also significantly higher in postwar period ($Z=3.63$; $p<0.001$). Increased incidence of skin cancer was mainly due to a higher proportion of older people, changes in behavior including recreational insolation, and depletion of ozone layer. Thus, war conditions and stress may be included among the causes of higher incidence of skin and all other types of cancer.

Alcoholism and Dermatological Diseases

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Alcohol is one of the most used addictive substances in the world. Wide accessibility and low price of alcoholic drinks contribute to the problem as well as more liberal attitude of the surroundings regarding consumption of alcohol in everyday life. In the last 40 years consumption of alcohol increased twofold and with it the risk of addiction and the frequency of other alcohol induced disorders. Alcohol directly and indirectly influences dysfunction of organs and body systems and causes a series of health disorders. The most common are changes on the skin in alcoholics. Some researches have found skin changes present in as many as 44% of male and 33% of female alcoholics. The changes vary from minor superficial skin changes resulting from the acute effect of alcohol

on the skin blood vessels (flush) or, in case of protracted consumption of alcohol, in the form of more permanent facial redness. This is a result of the toxic action of alcohol on the blood vessels and its consequential effect on the gastric mucous membrane, which by way of vegetative system stimulation causes facial redness (postprandial erythema). Presence of rosacea is the result of direct effect of alcohol on skin blood vessels as well as on chronic gastric musous membrane damage. Long-term use of alcohol leads also to malnutrition and it is direct cause of certain skin changes, particularly due to the vitamin B group deficiency (pellagra, seborrhea, and others). Some of the changes on the skin are direct consequence of cirrhosis of the liver and therefore, they become a part of the overall diagnostic system in alcoholology (spider nevus or caput medusae).

Skin diseases in alcohol-induced disorders represent a group of widely spread and present health disturbances caused by consumption of alcohol. Such disturbances by themselves can initiate further drinking due to the negative cosmetic effect that causes person to "release internal pressures" and to "self-heal" accumulated tension and dissatisfaction by drinking. Abstinence from drinking brings rapid positive change on the skin of alcoholics shown first as an improvement and then healing up of skin diseases.

Alcohol Intake and Psoriasis

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Most studies conducted in the last decade support positive association between alcohol consumption and psoriasis. There are several theories on how alcohol may affect psoriasis. Most of them are based on our theoretical knowledge on how alcohol affects different organ systems. It is not known whether the association between alcohol consumption and psoriasis is causal, mediated by some biologically plausible mechanism, or merely an epiphenomenon indicating some external confounding differences between alcohol drinkers and

nondrinkers. It is also possible that some yet unknown genetic link exists between the predisposition to alcohol abuse and psoriasis. The presented case will help us discuss these questions.

Rosacea-Cutaneous Stigmata of Alcoholism

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The classical cutaneous stigmata of alcoholism that have been well recognized for over a century are plethoric faces (facial flushing), persistent erythema and teleangiectasia, papules and pustules and specific shape of nose (rhinophyma and tissue hyperplasia). Rosacea, as a chronic skin disorder, typically affecting the central face, is considered a multiphase disease, therefore sometimes inequitably stigmatizes persons that are not alcoholics, especially women in which she is more often as well. Etiology of rosacea is still unknown, as it can be caused by constitutionally weak little blood vessels, disturbances of the vegetative nervous system and endocrine influence at the vascular level, cold whether, hot beverages, as well as psychogenic factors like stress, high anxiety neuroses and, very often, alcohol consumption. Alcohol is proved to be in some cases the factor responsible for the disease, especially in triggering the easy flushing and afterward, alcohol may accelerate the progression of the disease and contribute to the treatment resistance. Alcoholism itself includes high level of anxiety, stress and high frequency of feelings of guilt. Diagnostically clear and noticeable in alcoholics are third and fourth stages of rosacea, while in lower stages we can also diagnostically consider other alcohol-associated skin diseases (seborrheic dermatitis connected with changes of the fat metabolism), as well as the other alcohol-associated conditions often found in alcoholics; plethoric faces, ethanol-induced vasodilatation, vegetative hyper-reactivity and hypertension caused by hypervolemia. We report on a case of the fourth stage of rosacea in a male alcoholic patient, showing simultaneous development of rosacea and alcoholism. Our 45-year-old patient started to consummate alcohol when he was 15. Over the past 20 years he daily

drank two or three bottles of beer or 1 or 2 liters of homemade wine. He is in a drop of tolerance, with distinctive psycho-organic changes and aggressive behavior when drunk. Ten years ago, the patient started to have facial flushing and teleangiectasia, 5 years ago the papules and pustules appeared. A dermatologist has treated him with no improvement for a past 5 years, which can be contributed to his constant alcohol consumption. On admission, the patient was showing medial withdrawal symptoms with strongly pronounced rosacea. Laboratory results indicated liver failure, as gamma-GT was 431, and abdominal ultrasound revealed enlarged liver and spleen. Esophagogastroduodenoscopy showed chronic gastritis, ventricular erosions as well as esophageal varicose of the I/II level. The diagnosis made by internist was diffuse toxic lesion of the liver, possible liver cirrhosis. During the treatment, the patient abstained from alcohol and his psychophysical condition normalized as well as the laboratory results. Simultaneously, the patient was treated dermatologically and already after a month, the remarkable improvement of rosacea was noticed. Simultaneous treatment of rosacea and alcoholism yielded results very soon, with noticeable improvement of rosacea. Therefore, the dermatologist should insist on instant, constant and complete alcohol abstinence in persons suffering from rosacea, and recommend the treatment of alcoholism, if alcoholism is diagnosed. Such measures also contribute to the prevention of development of alcoholism.

Occurrence of the Alcohol Consumption in Patients with Psoriasis Vulgaris

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Psoriasis is a multifactorial chronic skin disease induced or exacerbated by various endogenous and exogenous factors ("trigger factors"). Several reports have suggested that environmental stimuli, including alcohol use and emotional stress, may have deleterious effects on the increased morbidity of psoriasis. We have pointed to the significance of

the patient's alcohol consumption as it relation to psoriasis outcome. The aim of this study was to explore the alcohol consumption as a risk factor in psoriasis. We assessed the effects of the alcohol consumption as a common environmental trigger factor and evaluated the clinical occurrence of the disease. We collected the data from our patients with psoriasis to determine whether there was an association between the alcohol consumption and psoriasis. The obtained results showed that the proportion of psoriasis patients using alcohol was much higher than that of the normal population. It was also observed that alcohol consumption, especially in men, was often associated with psoriasis outcome. An accurate history of alcohol intake will facilitate recognition of the disease and treatment resistance of psoriasis. This association is important mostly for the physicians who work with the psoriasis patients, as it seems there is a possibility that simple reduction in alcohol consumption may reduce both the prevalence and severity of psoriasis.

Emotional Language of the Skin

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Basic psychosomatic concepts such as integrity of mind and body, alexithymia, and an inordinate need for affection are worth considering when discussing treatment and diagnosis of psychocutaneous disorders. The skin is a target organ because it is the very first communication channel in our identity-structuring processes. Thus, the skin language would mean talking about the basics of our body ego formation. Understanding the emotional skin language also represents a very important topic for consultation-liaison psychiatry, with the possibility for applying the biopsychosocial model to skin diseases.

Psychic Envelop and Its Relation To Skin

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The hypothesis of French authors about the skin-self shows the importance of the auditory environment in the earliest development of the Self. The primal function of the skin of the baby and of its primal objects is to assure the most primitive binding of parts of the personality not as yet differentiated from parts of the body. It can be readily psychodynamically studied in its relation to problems of dependence and separation in human relations. Clinical case will show how the containing object is experienced concretely as the skin. Disturbance in the primal skin function through which dependence on the object is replaced by a pseudo-independence through the inappropriate use of certain mental functions, could serve the purpose of creating a substitute for skin container function. In fact these observations have led French authors to formulate the hypothesis of a skin-self and that of the ego constituted as a containing envelope and a protective barrier as well as a filter of exchanges where the result of epidermal and proprioceptive sensations are of leading importance for the internalization of skin identifications. Moreover, as a result of the experience of the fixation of the flow of vocal sounds to phonemes which are fundamental to the mother tongue so-called 'sound bath', self-emerges as an envelope of sound (concomitant to the self as a suckling). This bath of sound pre-figures the skin-self, with one half of its double face turned to the inside and the other half to the outside. Since the sound envelope is composed of sounds coming alternatively both from the environment and the baby, this combination of sounds produces a primary image (spatio-auditive) of the immanent body, and a link of actual fused reality with the mother (without which the imagined fusion with her later on would not be possible).

Forensic-Psychiatric Patients and Dermatological Diseases

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Patients under the compulsory hospitalization are placed at the Institute of Forensic Psychiatry at

Neuropsychiatric Hospital Dr. Ivan Barbot in Popovača, according to the article 44 of the Law on Protection of Persons with Mental Disorders. They usually spend a longer period of time at the Institute, which may sometimes last even a few years. In raising the standard of living of patients with mental disorders, beside personal hygiene, skincare and the care of the whole body are also the imperatives, but negligence and inadequacy of living conditions are being reflected on skin and visible mucous membranes changes. The research has been made and a number of skin changes and diseases have been observed. All that difficulties leave the mark on quality of life of mental patients, as will be discussed in this work.

Adolescent's Crisis with Conflict on the Skin

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Adolescence is a normal developmental period characterized by crises during which self-identity is formed, and adolescent's social position is defined, and partnership relations are made. Our investigation into the adolescent crisis and its finish included 153 students from the Split University, Croatia. Ninety students were treated by counseling and 63 were a control group. The students took 1-2 initial therapy sessions and were examined after 12 months. In the diagnostic procedure, Hampstead Index and DSM-IV Multiaxial evaluation were used, which allowed better insight into personal functioning. The control group did not differ from the treated patients in age, sex, or diagnoses. The treated students had better personality functioning after the 12-month treatment, although many single functions showed more serious disturbances in the beginning. Thus, counseling may be considered a good therapeutic method. As an example, a female student with persistent skin changes refractive to every skin treatment is presented. Two years after her skin changes appeared because of anxiety disorder, she started counseling, by which her adolescent crisis was resolved. As her ego became stronger, her anxiety decreased and the skin changes withdrew. In adolescent's assessment, it is neces-

sary to take a view of the whole person, because looking at only one aspect, and due to the different development of different personalities and the pace at which it occurs, a wrong conclusion may be reached. Therefore, it is useful to make more than one diagnostic assessment.

Psychodermatosis in War Veterans with Posttraumatic Stress Disorder

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Our study involved 1,000 war veterans with the posttraumatic stress disorder (PTSD). Frequency and sort of psychodermatosis were determined. An experimental group of war veterans with psychodermatosis and PTSD was formed. Fifty randomly chosen war veterans with PTSD, without evident physical illnesses, composed the control group. Psychological profiles of patients with psychodermatological diseases were tested by MMPI 2 personality questionnaire. The intensity of PTSD symptoms was detected by M-PTSD scale. Statistically significant differences between experimental and control groups were estimated.

Body Decorations: Fashion or Something Else?

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The spectrum of body decoration incorporates body painting, body adornment, and body modification. Some are temporary, like body painting and body adornment, but others are permanent. Body modification includes piercing and tattoos, scarification or branding and inserts objects of various shapes under the skin. All of these categories have

been practiced for thousands of years in all cultures.

The number of body decorations has increased dramatically over the last decade. In past the prejudice was that tattoos and piercing are associated with psychiatric patients, military personnel, gangs and prisoners. Today these procedures become more common in adolescents and young adults. Some of them truly see it as art and beauty or as applications of their creativity and love for their body. Body piercing and tattoos are always ways to get attention from other, a way to transmit messages to others but also people use body modification as a form of self-injury. Results of recent survey suggest that young persons with tattoos and/or body piercing are more likely than their contemporaries to engage in high-risk behaviors, such as drug use, sexual activity, and violence.

The continuum of body art continues to expand, and more of the areas on the continuum are now considered a normal part of society. It is important to have on mind that body decorations are part of play in our culture but body modification with body mutilation is potential for psychopathology.

Psychotropic Medication in Dermatology

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Why, when and how should dermatologists use psychotropic medications? A practical guide will be offered, with brief review of the nature of the conditions being treated. A successful pharmacological approach to any illness needs to take account of non-pharmacological factors, including the quality of the doctor-patient relationship. Current use of selected anxiolytics, antidepressants, antipsychotics, drugs for obsessive-compulsive disorder, and drugs with direct dermatological effects will be summarized, with reference to indications, advantages, and disadvantages. Liaison between specialties provides opportunities for cross-fertilization of ideas. There is also a need for multi-centered randomized double-blind trials, especially with long-term follow up.

Counseling Dermatology Patients and Use of Cognitive Behavioral Therapy

Papadopoulos L

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Psychological therapies have long been used with dermatology patients in an attempt to address both the physiological and psychological symptoms of skin disease. This presentation will track the development and efficacy of using various psychotherapeutic approaches including cognitive based therapeutic models in order to counsel dermatology patients. Protocols and techniques that have proven effective in this area will be outlined and a critique of the methodological means used to assess the efficacy of therapy within psychodermatology will be discussed.

Treatment of Pruritus in Advanced Diseases

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Treatment modalities reducing pruritus associated with systemic diseases are presented. The group of international experts at a symposium in Oxford proposed treatment guidelines for pruritus in advanced diseases (published in Quarterly Journal of Medicine 2003). According to the research results, pruritus is the most common symptom in dermatology. It can occur with and without visible skin lesions. Pruritus constitutes a major problem in several chronic systemic diseases, such as chronic renal insufficiency, cholestasis, lymphomas and Hodgkin's disease, and solid tumors. Itching may also be provoked by opioids (opioid-induced itch). Opioid antagonists relieve itch caused by spinal opioids, cholestasis and, possibly, uremia. Ondansetron relieves itch caused by spinal opioids in some uremic subjects, but not in patients with cholestasis. Other drug treatments for pruritus include rifampicin, cholestyramine, and 17-alkyl androgens (cholestasis), thalidomide (uraemia), cimetidine

dine and corticosteroids (Hodgkin's disease), paroxetine (paraneoplastic itch and polycythemia vera) and indometacin (some HIV-positive patients). If the specified remedies fail, paroxetine and mitrazepine should be considered. Ultraviolet B therapy, particularly narrow-band UVB, may be superior to drug treatment for pruritus in uremia.

Family Psychodynamics and Vitiligo

Jeličić J

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The family is often the source of the most beautiful events and achievements, both in psyche and body life. The family is, however, also the source of destructive forces and events, both on physical-body and mental level. Alexithymia, as a symptom central in psychosomatic disorders, implying the impossibility to read and register emotions and feelings, present over several generations in family dynamics, conditioned the appearance of dermatopsychological disorders (vitiligo, lupus, and psoriasis) in alteration with psychotic disorders (schizophrenia and depression) among descendants. This paper presents such a family, which also spent two years in psychotherapy.

The Use of Psychotropic Agents in the Hospital Treatment of Burn Patients

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Burn injury is one of the most severe forms of trauma. There is the growing evidence for the need of holistic approach to pharmacotherapy of severely burned patients, including psychotropic agents for the sedation and amelioration of psychosocial problems associated with burns. The expression of emotional problems and psychological disorders in burn patients may range from minimal reactions of fear and anxiety to, in rare instances, severe psychotic behavior. The purpose of our study

was to retrospectively review the records of adult burn patients regarding the use of psychotropic agents in their treatments. The study included 193 inpatients with severe burns treated during 2003 at the Clinic of Traumatology, Zagreb, Croatia. There were 121 (63%) male and 72 (37%) female patients aged between 14 and 96 (mean age, 50 years). The hospital stay ranged from 1 to 180 days (median, 21 days). The majority of patients sustained heat burns (95%). The extent of their injuries ranged from small (63%, n=122), to large (29%, n=56), and extensive (8%, n=15). The mean burned total body surface area (TBSA) was 27%. The depth of the burns ranged from first-degree (1%, n=2), second-degree (IIA 23%, n=45; IIB 35%, n=67), third-degree (39%, n=75), to fourth-degree (2%, n=4). The mortality rate was 7% (n=13). On the basis of medical records, we analyzed the classes of psychotropic agents prescribed to these patients as well as their average daily doses. We also checked whether the patients had previous psychiatric history, as well as the localization of burns. Psychotropic agents were prescribed to all patients (100%). Among psychotropic agents, patients were treated with anxiolytics, hypnotics, antidepressants, anticonvulsants, and antipsychotics. The class of medication most frequently prescribed was anxiolytics, most often diazepam. Midazolam was readily utilized in the preoperative treatment. Among antipsychotics, patients with psychotic symptoms were mostly treated with haloperidol, and some of them with fluzepam and risperidon. Other psychotropic medication applied for treating delirium was meprobamat. The seriously burned patients need psychotropic agents from the time of injury to full recovery. This need is increasing as modern burn centers are dramatically improving survival rates. In the modern treatment of burns, it is necessary to have a multidisciplinary approach, not only for the successful treatment of large burns and their complications, but for the necessary rehabilitation and psychological support required for readjustment back into society. Psychopharmacotherapy alone is rarely sufficient to provide complete remission of psychological disturbances of burn patients. Burn patients would likely benefit from conscious, systematic assessment and treatment decisions regarding psychological problems.

Flurazepam-induced Stevens-Johnson Syndrome?

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Stevens-Johnson syndrome is a rare but occasionally severe mucocutaneous disease often associated with drug consumption. We present a 30-year-old female patient with primary diagnosis of schizophrenia, who developed extensive epidermal detachment 3 days after initiating flurazepam therapy. Mucocutaneous changes were life threatening and required intensive life support measures. Clinical assessment and objective diagnostic findings incriminated flurazepam as the main cause.

Psychotherapeutic Treatment of Persons With Chronic Dermatological Illnesses

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Skin is one of the organs we make contact with the environment. Thus, skin problems might also represent problems of the contact and communication with the environment. Goals of presentation are to accentuate the importance of psychotherapeutic procedures with persons having chronic dermatological illness and to emphasize the importance of their early inclusion in some form of psychotherapeutic procedure. The inclusion of a psychotherapist in the medical treatment from the beginning also influences the process of the treatment with other methods. Early inclusion in self-supportive groups and self-protection and encouragement to gain knowledge and experience in treatment of skin illnesses also play a significant role. The goals and problems of psychotherapy of chronic dermatological illnesses will be discussed, as well as problems with facing and accepting the illness and long-term treatment. Work with family members, mutual support of similar patients in the group, and individual psychotherapy are part of the whole treat-

ment process. The types of psychotherapy procedures include supportive procedures, such as individual or group psychotherapy with the aim of self-helping and self-protection, and behavioral psychotherapy with the aim of changing the patient's lifestyle. Group and individual psychotherapy, the expected contribution in psychotherapy of persons with chronic dermatological illnesses, improving the quality of life of persons with chronic dermatological illnesses, lowering the anxiety and depression, overcoming fears and fantasies, longer preservation of working and family functioning, and unusual ways of human communication will receive due attention in this presentation.

Poster presentations

Nutritional Assessment of Patients with Epidermolysis Bullosa

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The term epidermolysis bullosa (EB) describes a number of rare, genetically determined blistering disorders characterized by excessive fragility of the skin and mucous membranes. Complications in the mouth, esophagus, and anus, combined with chronic skin infections and blood loss can severely compromise nutritional status, leading to a prolonged malnutrition and extreme growth failure. We assessed the quality of food intake and nutritional status of 16 patients with epidermolysis bullosa (4 with EB simplex and 12 with dystrophic EB) aged 2-34 years (7 male and 9 female patients). The nutritional status was assessed by a) calculation of the body mass index (BMI), b) the position of the weight in percentile distribution, c) the position of the height in percentile distribution, d) the position of the BMI in percentile distribution. According to the position of the weight and height in percentile distribution, 12 patients had weights at or below the fifth centile, and 5 patients had height at or below the fifth centile. In 10 patients the weight centile was lower than height centile, and 10 patients had BMI below the fifth centile. Patients with dystrophic EB

have many problems that affect their appetite and their ability to eat. Because of their eating difficulties, the majority of patients has inadequate food and energy intake. For many of these patients eating is painful, which is the reason why they tend to show certain trends in terms of likes and dislikes in relation to food. These trends are reflected in the results of the dietary assessments. Our patients suffered from the effects of chronic malnutrition. Our study results provided a strong argument for the value of nutritional assessment and intervention. The prevention of malnutrition depends on more active and continuous nutritional support, starting at very early age. This may require the use of additional procedures, such as nasogastric or gastrostomy feeding.

Differences in Dietary and Living Habits Among Adolescents With and Without Acne

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The aim of this study was to describe the prevalence rate of acne among adolescents and to evaluate the possible influence of foods, smoking, drinking and living habits on acne prevalence. The study included 420 students (161 male and 259 female) aged 14 to 15 years from Zagreb, Bjelovar and Split. They were examined for acne during physical examination by school doctors, and completed a questionnaire on life style habits. The prevalence of acne was 54.8%, i.e., 55.6% among girls and 53.4% among boys. Among students reporting no alcohol drinking, 44.4% had acne. Among those reporting occasional drinking, acne prevalence was 63%. We found 52% non-smokers with acne and 53% smokers with acne. More frequent consumption of chocolate, fast food, and soft drinks was not associated with higher prevalence of acne. Dietary habits (chocolate, fast food, and soft drinks) and tobacco smoking was not significantly associated with acne, whereas alcohol drinking and nail biting was associated with higher prevalence of acne.

Hospitalization of Psoriatic Patients Improves Patients' Quality of Life

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Psoriasis is a chronic, recurrent, and often disfiguring skin disease that has a negative impact on patients' quality of life. Treatment of psoriasis, including hospitalization, addresses both the cutaneous manifestations of the disease and their impact on quality of life. In pilot study 20 in-patients with psoriasis were asked to complete the Dermatology Life Quality Index (DLQI) before treatment and four weeks after discharge from hospital. The DLQI is a self-administered questionnaire designed to measure the impact of skin diseases on patients' quality of life. The instrument contains ten items dealing with the subject's skin. The 10 items were based upon the most commonly identified impacts upon dermatology-specific health-related quality of life (HRQL) that were elicited from patients with skin disease. The score on the DLQI has a possible range of 0 to 30, with 30 corresponding to the worst HRQL. The DLQI was developed to contain 6 subscale scores: symptoms and feelings; daily activities; leisure; work/school; personal relationships; and treatment. Our patients with psoriasis showed overall a significant decrease in impairment of life quality following in-patient treatment.

Trichotillomania in Childhood

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Trichotillomania is an impulse disorder where patients pull their hair from the scalp and/or other sites. Although the clinical presentation is characteristic, it can be confused with some other types of alopecia, particularly alopecia areata. This disturbance is most common in children aged between 4 and 10 years, although it is not infrequent in adults

either. Trichotillomania is usually considered a sign of an underlying emotional disorder and has been categorized as an obsessive-compulsive neurotic reaction. However, it can be a minor neurotic trait as well as a sign of serious psychiatric disorder. During a three-year period, we observed 39 children with trichotillomania (22 girls and 17 boys) aged 2 to 13 years. The lesions were mostly located in regions accessible to child's hands, such as parietal region (n=26), temporal region (n=9), frontal region (n=2), occipital region in (n=1), and in one patient we found diffuse loss of hair. Parents of 11 children noticed the child's habit of playing with hair and pulling it, while onychophagia was observed in 2 patients. Five children were previously hospitalized for some other diseases, and 2 were permanently separated from their parents for social reasons. Treatment involved psychiatric consultation, although in most cases a detailed explanation to the parents might have been sufficient to terminate the hair-pulling.

Alopecia Areata in a Female Patient Suffering from Borderline Personality Disorder With Co-occurring Mood Disorder and Depressive Episodes

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We report on a case of a 44-year-old female patient, a highly educated woman employed as a custom clerk and a mother of three sons aged 19, 15, and 11, respectively. According to DSM-IV diagnostic criteria, the patient is suffering from borderline personality disorder with co-occurring mood disorder and present depressive episodes. She has been in a psychiatric treatment since 2000 and hospitalized in our hospital four times. Her previous diagnosis was bipolar disorder (severe recurrent major depressive episodes with psychotic features for manic episodes). She was and still is treated with risperidon, Na-valproat and alprazolam or diazepam in different dosages, depending on the clinical picture. She has been on different antidepressants over the years and usually unsatisfied with the therapeutic effects because she has not been taking

her medications properly. She is also constantly complaining of her chronic feeling of emptiness and loneliness. Since November 2003, the patient has been taking sertralin. She is regular at her psychiatric controls and has been attending group psychotherapy for two years. At group sessions, she was at first making monologues but gradually learned to listen to other members as well. Somatically, she has been under medical control since 1998 because of tachycardia and palpitation; she was hospitalized once and has been taking sotalol regularly. In 2003, she underwent neurological examination because of the pain in the neck and headaches. She lost her first child in the fifth month of pregnancy in 1982, when she had taken ill with hepatitis B. In the previous 3 years, she has been going through a divorce. The situation escalated six months ago, when the patient left her husband, taking the children and moving into a rented apartment in the same town. Due to her previous psychiatric diagnosis and treatment, the children were supposed to remain under their father's care. Over the years, the patient's complaints against this court decision were rejected and she had to give up her children; after that, the divorce procedure was over soon. Her husband was forbidding children to visit their mother. The patient felt she had lost her children, family, and home. The situation firmed her belief that her surroundings were uncaring and she experienced intense abandonment fear and inappropriate anger when she was faced with a realistic time-limited separation from her children. The feelings that followed the anger were shame and guilt for her children and contributed to her feeling of being evil or bad. She started spending time writing to the various organizations and social services, trying to get help and support on gaining her children back, but in vain. She was displaying extreme sarcasm, enduring bitterness and verbal outbursts. She quit at free will her psychotherapy group; despite the suggestions made by the therapist that this is the time she actually needed it the most. At that time she had no close friends to confide in and she had a complicated and relatively cold relationship with her mother, who was rigid and very authoritative. So she felt completely alone in the world. During these times of stress she developed psychotic-like symptoms, her illness exacerbated to the extent of transient stress-related paranoid ideation. She had severe dissociate symptoms, im-

paired judgement, psychomotor agitation and she became extremely restless and hyperactive. The basic dysphoric mood of patients with borderline personality disorder is often disrupted by periods of anger, panic, or despair. These episodes may reflect the person's extreme reactivity to interpersonal stress. She was under this acute emotional stress for a few months when she started to lose her hair. She lost over 90% of her hair in only two months. The dermatological diagnosis, based on the clinical picture, trichogram, and histology was alopecia areata multilocularis, a psychosomatic dermatological disease that most probably occurred after stress. She had no cavities, no chronic inflammation stimulus (foci), no cats, no allergies, and no fungal infections. Her blood test results were normal as well as ASTO, ALTO, and LPT+++. Her family medical history was negative. The loss of hair was instant, painless, and in forms of circular skin areas without hair, some of them in size of a small palm. The hair could be easily pulled out, especially from the corners of the inflicted areas. The patient lost her hair only on her head. There were no changes on nails. Recent studies show that psychiatric disorders are more frequent in patients with alopecia than in healthy subjects. The comorbidity of psychiatric disorders, mainly generalized anxiety disorder, depression and phobic states, is high. Acute emotional stress may precipitate alopecia areata by activation of over expressed type 2 beta-CRH receptors around the hair follicles, which leads to intense local inflammation. Hair follicle cells possess receptors for neurotransmitters, which are synthesized by neural endings sensitive for stress-induced hormones. Furthermore, according to the higher incidence of thyroid disease in alopecia areata, our patient screening on the endocrinological diseases showed slightly lower T3 hormone. Recent research suggests that personality characteristics might modulate individual susceptibility to alopecia areata and that it tends to be associated with high avoidance in attachment relationships and poor social support. However, recent studies emphasize high alexithymic characteristics in patients with alopecia areata, which was not likely the case in our patient as she could verbally express herself very well. Also, life events played an important role in triggering the disease in our patient, together with trait-anxiety and stress perception. Fortunately, our patient was aware of psychological factors in the

etiology of her disease, so she was recognized by the dermatologist as such and treated optimally. The role of the treatment of concomitant psychopathological disorders is a vital one. Dermatologically, the patient was treated with Fluacet gel and Pifud. New hair started to grow in the short period of time and up until now, a three months later, there seems to be no new hair loss. Basic psychotherapeutic support recommended in recent studies proved to be useful in our patient. During the treatment of alopecia areata, our patient went to psychiatric controls and support and has resumed attending her psychotherapy group. This type of therapy is necessary because of her identity disturbance, characterized by markedly and persistently unstable self-image or sense of self. It has positively affected the patient's adaptation to her alopecia areata and social setting as well as the quality of her life. Although she wears a wig, she does not wear it on the group sessions. Furthermore, it is known that alopecia areata is a chronic skin disease. We could expect recidivism in our patient, especially because of her psychiatric illness, constant regret for children, remorse, affective instability that is due to a markedly changeable mood (intense episodic dysphoria, irritability or anxiety) and her sensitiveness to environmental circumstances and still unresolved financial status. Her recent wish for reconciliation with her husband for the children's sake was consistent with her previous attempts of undermining herself at the moment a goal is about to be realized. Mixed with a life situation where the ex husband and the youngest son relocated 600 miles away, trait-anxiety and stress perception constitute risk factors that may influence the exacerbation of the disease. Our patient's psychological test shows borderline personality disorder with depressive episodes. The question of self-mutilating behavior always remains opened, but we assume that this was not a case in our patient's alopecia areata.

DUO-Formula Group Therapy of Patients With Psoriasis Vulgaris

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Group therapy of patients with psoriasis vulgaris using the DUO-formula is characterized by the work of an educated team consisting of a physician and a patient with a group of patients and members of their families. The educated physician-patient lead the group by discussing various aspects of psoriasis in order to motivate patients to take a more active role in the treatment of their disease. A modified DUO-method was initiated in various affiliates of the Croatian Psoriatic Society in the cities of Slavonski Brod, Sisak, and Karlovac. A total of 42 patients, 8 dermatologists, 5 psychiatrists, 4 rheumatologists, one orthopedic surgeon, one clinical psychologist, and one chief neuropsychiatric nurse were included in the DUO-method. Group therapy according to the modified DUO-method was held 2 hours per week over 4 consecutive weeks at which time various aspects of psoriasis were discussed. The results in all the centers at which the modified DUO-group therapy method was performed indicated that this type of therapy was well accepted among patients. Patients confirmed that this sort of therapy helped them with solving everyday problems they had in their daily lives as well as improving their quality of life.

Influence of Heliomarinotherapy on Psychological Status of Patients with Psoriasis

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Heliomarinotherapy is an effective, inexpensive, and accepted method in the treatment of psoriasis. If used with care, it has a few contraindications and complications. It has been shown that psychic relaxation during therapy has important impact on the treatment success. Using a questionnaire, we examined psoriatic patients to determine the impact of heliomarinotherapy on their psychic condition and skin lesions. The patients were between 7 and 78 years of age. In 97% of examined patients, we confirmed a positive impact of heliomarinotherapy on their psychic condition.

Coping With Stress and Social Support of Research Carried out on Children with Skin Disorders vs Healthy Children

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The aim of the study was to establish any differences in dealing with everyday stress and in perception of social support between children with skin disorders, such as atopic eczema, alopecia, or psoriasis, and healthy children. The study included 40 children aged between 7 and 15 years: 20 with skin disorders that had lasted for 1 to 5 years, and 20 healthy controls. They were assessed by structural diagnostic interviews and by the questionnaire Social Support Appraisals Scale (SS-A) by Vauxa and colleagues, issued in 1989. Children with skin disorders were more emotionally dependent on social support in dealing with stressful situations and that their stress was significantly higher. They had fewer opportunities to build interpersonal relationships because of the nature of the illness. To achieve optimal functioning children with skin disorders need the support from their families and friends as well as they need to accept their physical condition without it being perceived as a limitation.

Skin Expression of the Psyche

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This is a case report of a 57-year-old woman treated for symmetrical skin lesions on both forearms in the form of excoriations, erythematous infiltrates, and scar tissue. The skin lesions accompanied with pruritus appeared 2 years before the psychiatric evaluation. Biopsy of the skin did not show any skin pathology. The patient was dismissed with the diagnosis of *Dermatitis artefacta antebrachii utriusque* and a psychiatric evaluation was suggested. When she first arrived in my office, she apologetically said the visit had been recommended by her dermatologist, because her skin

problem had not been cured in spite of all the pills and lotions she was using. She complained of itching in her forearms that made her scratch and would not let her sleep at night. She used to wake up in sweat, feeling short of breath. Several months before she had a dispute with her late husband's brothers about the inherited land. Her skin itch, high blood pressure, and insomnia appeared shortly after the quarrel. In the course of individual psychotherapy, a good transfer with the patient was established. At the beginning, she used to say that it were "not her nerves, or maybe just a little." She accepted the treatment saying she enjoyed our conversations. She was confronted with her conflicts

and her insomnia was gone, her skin got better, but she was still too edgy. Soon she got into a new dispute, this time with her daughter. With time, she discovered that she was shielding herself from her emotions and tried to hide them from her children and grandchildren by reacting harshly when faced with problems in the family. In the course of the treatment she learned how to show her emotions, not hide them or be ashamed of them. She became satisfied with herself, no longer felt alone and abandoned, and realized she was loved and needed by her children and grandchildren. Her skin lesions and itching disappeared.

Standlone Meeting

ADVANCING EXPECTATIONS IN ATOPIC ECZEMA AND BEYOND

May 7th-9th, 2004, Grand Hotel Hyatt, Berlin, Germany

International Symposium was a top event hosting key opinion leaders as Prof. Thomas Bieber (Bonn), Prof. Thomas Luger (Münster), Prof. Klaus Wolff (Vienna), Prof. Michael Meurer (Dresden), Prof. Torsten Zuberbier (Berlin), Prof. Georg Stingl (Vienna), Prof. Donald Leung (USA), Dr. Teri Kahn (USA), Dr. Robin Graham-Brown (UK), Dr. Roger Allen (UK), Prof. Anton Stuetz (Vienna), Dr. Carle Paul (Switzerland), Prof. Jean-Francois Stalder (France), Dr. Michael Cork (UK), and Prof. Jean-Hilair Saurat (Switzerland).

A distinguished international faculty has been assembled to present a scientific agenda about atopic eczema and management with pimecrolimus (Elidel®). There were 300 delegates from 28 countries. The main sponsor was Novartis Pharma AG, and chairmen of the Symposium "Advancing Expectations in the Management of Atopic Eczema and Beyond" were Professors Thomas Luger and Klaus Wolff. The Symposium brought together many international experts in the field of dermatology, pediatric dermatology and allergology, to present up-to-date understanding of the pathophysiology and management of atopic eczema. In the past few years important innovations have been introduced in the management of chronic disease. The non-steroid topical therapy was introduced, pimecrolimus cream 1% (Elidel®), in the management of atopic eczema. Pimecrolimus cream 1% to modify the course of atopic eczema and influence the atopic march is currently under investigation and was addressed at the symposium.

After Chairman's welcome, the first speaker was Professor Stingl (Vienna) with "What's new in the pathophysiology of atopic eczema?" He pointed that, in the pathogenesis of atopic eczema (AE), lymphocytes play a very important role: CD₃, CD₄, CD₈, immunoglobulin E (IgE); human thymic stro-

mal lymphopoietin (TSLP) keratinocytes; and inducer Langerhans cell (Lc)/dendritic maturation. There are two populations of LS (CD_{1a} + cells = CD_{1a}, CD_{1b}) and inflammatory dendritic cells (IDEC), immature dendritic cells and mature plasmacytoid dendritic cells (pDC). IgE antibodies as well as T-cell reactions are present in the skin. Lesional skin is abundant with antigen-presenting cells, other than Langerhans cells and dermal dendritic cells, and may influence the quantity and quality of the T-cell response. IgE on the surface of dendritic cells may allow for facilitated allergen presentation *in vitro*, and *in vivo* it can be tested with genetically modified mice expressing a high-affinity IgE receptor, not only on mast cells and basophiles, but also on dendritic antigen-presenting cells. Therapy on indigenous and nonindigenous cells with pimecrolimus is effective. Professor Saurat (Geneva) discussed the concept of "accessible targets" including chronic inflammation, *Staphylococcus* colonization and xerosis, food-borne factors and air-borne triggers, for the effective treatment of AE. Oral and topical calcineurin inhibitors are useful for chronic inflammation, the main aim being long-term remission.

Systemic immunomodulatory agents may also be used in the treatment of AE (cyclosporin, rIFN, corticosteroids, mycophenolate mofetil, intravenous immunoglobulin, or azathioprine). Role of psychotherapeutic approach, diet, and house dust mite reduction is important too. Emollients and topical corticosteroids (TC) have been the mainstay of treatment for AE for decades and, when used properly, they are safe and effective. Dr. Cork (UK) pointed that topical corticosteroids have 300-fold greater penetration through the skin of the eyelids than through the sole of the foot or eczematous skin. Kao *et al* demonstrated in 2003 that the appli-

cation of high-potency topical corticosteroids to the skin results in the premature breakdown of corneodesmosoms, resulting in the development of a defective epidermis.

There is a significant medical need for a new treatment to prevent and treat flares of AE without causing cutaneous atrophy. Pimecrolimus cream 1% (Elidel®) has been shown to be an effective treatment for the prevention of flares of AE, as it does not cause cutaneous atrophy when applied to the skin, although there is a rebound when treatment is discontinued. Dr. Robin Graham-Brown (UK) said that both physicians and patients face considerable challenges in the effective management of AE, but they often differ widely in their perception of the severity and management of the disease. A recent multinational survey of 900 eczema suffers from five countries found that significant "barriers" to doctor consultation exist, including patients perception of the severity of the disease, fear of using steroids and disillusionment with avoidable treatment options.

Professor Bieber (Bonn) presented the cellular rationale for early treatment of lesions. There is evidence to suggest that the so-called normal skin of a patient with AE is not same as the skin of a subject without eczema. For example, in the peripheral immune system of patients with AE lymphocyte number is increased twofold in unaffected and fivefold in affected skin, compared with the skin in non-atopic eczema subjects. A multicenter, double-blind study is planned to identify cellular and molecular changes in the post-lesional phase of AE and to determine of intervention with pimecrolimus cream 1% in this phase offers a treatment advantage.

Dr. Teri Kahn (USA) pointed that pimecrolimus cream 1% used in over 3 million US patients over 2 years of age in daily clinical practice as a new treatment both prevented severe flares in pediatric patients and improved long-term disease control.

Professor Meurer (Dresden) presented the use of pimecrolimus cream (1%) in the treatment of all body areas of adult patients with AE based on experience in clinical trials in Germany and in daily practice. When used twice daily from the first signs of symptoms of AE, it is highly effective in preventing progression to severe flares. Pimecrolimus cream 1% offers significant therapeutic advantages over

conventional reactive treatments in the long-term management of AE in adults. Safety of pimecrolimus cream 1% based on the evidence from 5 million patient was presented by Dr Roger Allen (Nottingham). He showed that pimecrolimus cream 1% has been shown to have a favorable safety profile in clinical studies involving more than 8,000 patients, including 923 infants (3-29 months of age), children and adults treated for up to 2 years. Data from Post-Marketing Surveillance (PMS) spontaneous reports have confirmed the favorable safety profile of pimecrolimus cream 1%. Pimecrolimus permeate through the skin to a much lesser extent than corticosteroids and has negligible systemic absorption when applied topically (Fig. 1). Pimecrolimus cream 1% was not associated with a significant increase in individual types or viral or bacterial skin infections, and did not impair immune response to vaccination against tetanus, diphtheria, measles or rubeola as showed in a 2-year clinical trial in infants. The high efficacy, tolerability and safety profile of pimecrolimus cream 1% makes it a treatment of choice for the long-term management of mild to moderate AE, particularly in sensitive areas of skin. In European Union countries, pimecrolimus cream 1% is approved for use on all skin areas, including face and intertriginous areas (except mucous membranes) for patients aged 2 years and over.



Figure 1. Professor R. Allen presenting Elidel®.

The experience in patients education as a means of improving outcomes in AE was presented by Professor Jean-Francoise Stalder (Nantes). He showed the process of management of 40 moderate to severe atopic patients in Atopic Eczema School, created in Nantes. Forty patients (mean

age: 9 years) were followed up for 6 months. At the beginning of the study, the mean SCORAD was 50.5, whereas after 6 months it was 22, with improvement noted in 97% of the cases. Educational objectives were reached in 70.6 % of the cases. The therapeutic education (by teaching them how to treat themselves) of the patients represents a major breakthrough in the care of patients.



Figure 2. D. Pezelj, S. Murat-Sušić, J. Lipozenčić, D. Vujčić, and L. Kotrulja (from left).

Professor Zuberbier (Berlin) proposed Guidelines for AE similar to GINA (Global Initiative for Asthma) for diagnosis and management of asthma. A similar step-wise approach is changing the paradigm for the treatment of AE. By using "preventers", such as the non-steroid pimecrolimus cream 1% at the first signs of symptoms to stop the attacks becoming severe, moderate to potent corticosteroids can be reserved as "relievers" to treat uncontrolled severe lesions for short periods of time. A positive outcome on the control of flares and the long-term management of AE may lead to the prevention of other atopic diseases. Looking to the future: Can intervention in AE early in life halt the atopic march?, was the title of Professor Donald Leung's (Colorado, USA) lecture. He presented the hypothesis that the non-steroid pimecrolimus cream 1% (Elidel®), a selective inhibitor of inflammatory cytokines and IgE-mediated histamine release from mast cells in the skin, prevents severe flare in 68% of infants over 6 month when applied at the first signs and symptoms of AE. Effective long-term control of AE with pimecrolimus cream 1% at the earliest signs and symptoms of the disease in life might

have the potential to prevent the progression to other atopic diseases. The randomized multicentered, double-blind, 3-year study with a further 3-year open-label extension in 1,100 infants is currently underway. In this Study of the Atopic March (SAM) atopic eczema is being assessed at the 3-year time point by the number of disease-free days, objective eczema scores, the longest duration of remission and quality-of-life scores for pimecrolimus cream 1% vs vehicle cream. If the skin inflammation is under better control, it is less likely to act in atopic march.

Very important was a lecture by Professor Thomas Luger (Münster), co-chairman, about management of other inflammatory skin diseases with pimecrolimus cream 1%: psoriasis, autoimmune diseases, Netherthon syndrome, hand eczema; dyshidrotic eczema, seborrheic dermatitis, perioral dermatitis, steroid induced rosacea, chronic actinic dermatitis, lupus erythematosus dyscoides, vitiligo, pyoderma gangrenosum, granuloma annulare, necrobiosis lipoidica, oral and genital lesions by Crohn disease, lichen sclerosus et atrophicus; and Bechcet disease. Observed efficacy of pimecrolimus cream 1% in the treatment of this disease has to be further evaluated in controlled studies.

Pimecrolimus may have therapeutic potential beyond dermatology. Eye drops containing 0.5% and 1% pimecrolimus were shown to have therapeutic efficacy in dogs suffering from severe chronic immune-mediated eye disease (Professor Anton Stuetz, Vienna, Novartis Institute for Biomedical Research). Recent research studies suggest new therapeutic options for pimecrolimus, which



Figure 3. J. Lipozenčić, D. Vujčić, J. Brajac, D. Pezelj, V. Peharda, L. Kotrulja, and S. Murat-Sušić (from left)

will be evaluated in the ongoing and future clinical studies.

Dr Carle Paul (Mulhouse, France) explained that topical pimecrolimus cream 1% has been approved for the short-term and long-term treatment of atopic eczema in more than 70 countries (8,000 patients of whom approximately 1,000 are infants). The ongoing clinical program with pimecrolimus cream 1% is currently focusing on three main aspects: 1) improving the long-term management of AE with pimecrolimus cream 1%; 2) establishing the long term safety of pimecrolimus cream 1% beyond 2 years (for up to 10 years); 3) expanding the scope of treatment indications to other inflammatory skin diseases. The pimecrolimus cream 1% clinical program represents a collaborative effort of practicing physicians, pharmaceutical researches, and regulatory authorities.

In conclusion of this Meeting, Professor Luger said that Elidel® might be able to halt the atopic march. Adapt the model of success of asthma guidelines, Elidel® showed efficacy in AE and other inflammatory diseases. The future of the treatment of other skin diseases lies with Elidel®. Dermatology can be proud on prestigious industry preparation of Elidel® for pre-emptive patient's self-management; for use in all age groups, and can be safely applied to all skin surface areas, including the face, neck, and skin folds. Clinical significant improvements

can be seen in patients within 3 days of the first application.

Due to its lipophilicity, topical pimecrolimus has a high affinity to skin and selectively targets skin inflammation. Applied to the skin it is not systemically absorbed. Elidel® is highly effective in relieving the signs and symptoms of AE (erythema, pruritus, papulae formation, and infiltration) in adults, children, and infants.

In long-term studies, Elidel® has demonstrated a unique ability to prevent disease progression if applied early on, at the first signs or symptoms of disease. Elidel® reduces or eliminates the need for topical corticosteroids and was shown to significantly improve the quality of life of patients and their families.

The guest lecture by Professor Klaus Wolff (Vienna) was unforgettable.

The "Advancing Expectations in Atopic Eczema and Beyond" Standalone Meeting was very well organized. High scientific level as well as social (Welcome reception "The Adagio Club"; Lunches; Light refreshment, Gala Dinner in Fernsehstudio Berlin, and accommodation in Hyatt hotel) were very pleasant. The six Croatian delegates were very pleased to be present there (Figs. 2 and 3).

Prof. Jasna Lipozenčić, MD, PhD

Continuing Medical Education Course

UPDATE ON PSORIASIS

Zagreb, Croatia

October 15-16, 2004

The Continuing Medical Education Course is organized by
the Chair of Dermatovenereology,
Zagreb University School of Medicine and
Department of Dermatology and Venerology,
under the auspices of

Academy of Medical Sciences of Croatia.

Known experts in the field of psoriasis will also participate in the Course.

Organizers:

Prof. Jasna Lipozenčić, MD, PhD

Aida Pašić, MD, PhD

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Zagreb University Hospital Center

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Program

Friday, October 15, 2004.

| | |
|---------------|---|
| 8:00 – 8:45 | Registration |
| 8:45 – 9:00 | Opening |
| 9:00 – 9:20 | Jasna Lipozenčić Psoriasis today |
| 9:20 – 9:50 | Aida Pašić Genetics of psoriasis with focus on HLA system |
| 9:50 – 10:20 | Marija Kaštelan, Larisa Prpić-Massari Update on immunopathogenesis of psoriasis |
| 10:20 – 10:40 | Vladimira Barišić-Druško, Ivana Ručević Epidemiology of psoriasis in Croatia |
| 10:40 – 11:00 | Ivan Dobrić, Jaka Radoš Histopathology of psoriasis |
| 11:00 – 11:30 | Coffee break |
| 11:30 – 11:45 | Mihael Skerlev Psoriasis and HIV infection/AIDS |
| 11:45 – 12:00 | Aleksandra Basta-Juzbašić Psoriasis and seborrhoeic dermatitis of the face and scalp. Similarities and differences. |
| 12:00 – 12:15 | Jasna Lipozenčić, Aida Pašić, Suzana Ljubojević, Sandra Marinović-Kulišić Contact hypersensitivity in psoriasis. Köbner phenomenon? |
| 12:15 – 12:30 | Branka Marinović Coexistence of psoriasis and bullous dermatoses |
| 12:30 – 12:50 | Sarah Brenner The influence of psychological factor on psoriasis: the psychological profile of the psoriatic patient |

- 12:50 – 13:10 **Vladimira Barišić-Druško, Ivana Ručević**
Triggers in psoriasis
- 13:10 – 13:30 **Jacek Szepietowski, Joanna Salomon**
The nail changes in psoriasis and therapy
- 13:30 – 15:00 Lunch break
- 15:00 – 15:20 **Slobodna Murat-Sušić, Karmela Husar**
Characteristics of psoriasis in childhood
- 15:20 – 15:40 **Franjo Gruber**
Local therapy of psoriasis – yesterday and today
- 15:40 – 15:55 **Franco Kokelj, Elisa Martinelli, Giusto Trevisan**
Our experience with biologics
- 15:55 – 16:10 **Višnja Milavec- Puretić**
The influence of drugs in pathogenesis of psoriasis
- 16:10 – 16:35 **Krešimir Kostović, Aida Pašić**
The light in psoriasis treatment
- 16:35 – 16:50 **Romana Čeović, Slobodna Murat-Sušić**
The management of psoriasis in childhood
- 16:50 – 17:00 **Marija Kanižaj-Vlahovski**
The skin care in psoriasis of the child
- 17:00 – 18:00 Discussion

Saturday, October 16, 2004

- 9:00 – 9:20 **Đurđica Naglić-Babić**
Psoriatic arthritis – clinical picture and current possibilities
- 9:20 – 9:40 **Aida Pašić**
Systemic therapy of psoriasis
- 9:40 – 9:55 **Romana Čeović, Aida Pašić**
Retinoids in psoriasis treatment

- 9:55 – 10:10 **Pero Vržogić**
Naphthalanotherapy in psoriasis management
- 10,10 - 11,30 **Jasminka Jakić-Razumović**
Immunohistochemistry – therapeutic approach
- 10:30 – 11:00 Coffee break
- 11:00 – 11:20 **Aida Pašić**
Biologics in psoriasis treatment
- 11:20 – 11:35 **Danijel Živković**
Heliomarinotherapy in psoriasis
- 11:35 – 11:50 **Krešimir Kostović**
Methotrexate in psoriasis treatment
- 11:50 – 12:05 **Jasna Lipozenčić, Dujomir Marasović**
Cyclosporine in psoriasis management
- 12:05 – 12:35 **Aida Pašić**
Consensus statement in psoriasis therapy today
- 12:35 – 13:35 Discussion
- 13:25 – 14:30 Written exam

Photodynamic Therapy in Department of Dermatology and Venerology, Zagreb University Hospital Center, Zagreb, Croatia

In January 2004, we started applying topical photodynamic therapy in the treatment of superficial tumors of the skin (actinic keratoses, Bowen's disease and superficial basal cell carcinomas), as well as in the treatment of psoriasis. We apply 20% 5-aminolevulinic acid to the lesions 5-6 h before irradiation with an incoherent light source (Waldmann PDT 1200). So far, we have followed up first 15 patients (9 women and 6 men) who had epithelial precancerous or cancerous lesions. Most were recurrences after surgical excision and/or radiotherapy. Unexpectedly, in most cases complete or partial regression were achieved after only 1 or 2 treatments. An excellent cosmetic results were obtained.

Our team (Aida Pašić, MD, PhD; Krešimir Kostović MD; Romana Čeović MD, MS; Damir Hrsan, rad. eng.) will continue to use photodynamic therapy in oncological patients and patients with psoriasis.



Figure 1. Krešimir Kostović, MD; Aida Pašić, MD, PhD; Romana Čeović MD, MS; Damir Hrsan, rad. eng.

We hope our preliminary results will continue to be as promising as they are now.

Krešimir Kostović, MD

Report on the International Symposium "Update on Atopic Eczema/Dermatitis Syndrome" April 25-28, 2004, Cavtat/Dubrovnik, Croatia

International Symposium on atopic eczema/dermatitis was held in the beautiful Mediterranean city of Cavtat. It was organized under the auspices of the Croatian Academy of Medical Sciences, Croatian Dermatovenerological Society of the Croatian Medical Association, and the Section Dermatology of European Academy of Allergology and Clinical Immunology (EAACI), with a co-sponsorship by International League of Dermatological Societies.

There were around 250 participants from 17 countries, with many leading scientists in the field of dermatology, allergology, and clinical immunology.

Professor Jasna Lipozenčić (Fig 1) was the main organizer of the symposium, together with Professor Carsten Bindslev-Jensen (Fig 2). Honorary presidents were J. Ring, G. Stingl and B. Wüthrich. The members of International Scientific Committee were R.C. Aalberse, W. Aberer, E. Berardesca, T. Bieber, K. Blaser, J. Bos, T. Diepgen, E. Fedenko, A. Giannetti, G. Girolomoni, H. Gollnick, K. Holubar, A. Kapp, Th.A. Luger, H. Nakayama, R. Marks, H. Merk, W.J. Pichler, T. Reunala, T. Ruzicka, S. Seidenari, W. Silny, A. Taieb, K. Thøgersen-Pedersen, K. Turjanmaa, U. Wahn, R. Wolf, and T. Zuberbier.

The Symposium was divided into 8 main sessions: progression in atopic dermatitis, current approach to allergy, immunologic basis of atopic der-

matitis, diagnostic state of the art in atopic dermatitis, prevention of trigger factors in atopic dermatitis, atopic dermatitis and other diseases, management of atopic dermatitis, new drugs for atopic dermatitis.

At the beginning of the Symposium we heard three outstanding plenary lectures. Professor B.



Figure 1. Professor Jasna Lipozenčić.



Figure 2. Professor Carsten Bindslev-Jensen, president of the International Symposium.

Wüthrich spoke about new terminology on atopic eczema. His presentation was titled: "Atopic eczema/dermatitis syndrome: classification, natural course, and immunological differences between the IgE-associated ("extrinsic") and the non-IgE-associated ("intrinsic") type." Professor G. Stingl (Figs. 3,4) discussed whether IgE is a pathogenetic factor in atopic dermatitis. Professor J. Ring (Figs. 4,5) presented some facts on IgE vs. non IgE-related



Figure 3. Professor Georg Stingl.



Figure 4. Professors (from left): G. Stingl, T. Zuberbier, J. Ring, and U. Darsow.



Figure 5. Professors (from left): J. Ring, J. Lipozenčić, and G. Novelli.



Figure 6. Professors (from left): T. Werfel, T. Zuberbier, and T. Diepgen.



Figure 7. Professor H. Deleuran.



Figure 8. Professor Thomas Ruzicka.

atopic dermatitis, and professor R. Marks presented his study on the frequency and causation of atopic eczema in Australia.

Prof. A. Kapp presented the neuroimmunological interactions in atopic dermatitis. He stated that the influx of activated CD4+ T-lymphocytes and eosinophils are increased in antigen-presenting Langerhans cells, which are important for inflammatory actions, and represent a hallmark of lesional skin in atopic dermatitis (AD). Professor Zuberbier (Figs. 4,6) talked about the role of mast cells in atopic dermatitis. He compared several studies on the importance of mast cells in pathogenesis of AD dermatitis, and concluded that new evidence suggested mast cells might play a significant role as one of the pathogenetic factors in atopic eczema. On the other hand, Professor Deleuran (Fig. 7) talked about the role of T cells in atopic dermatitis. Professor Diepgen (Fig. 6) gave an outstanding review on the natural history of atopic dermatitis. Professor Ruzicka (Fig. 8) presented review on the new developments in atopic eczema, means of treatment of AD, and he shared his experience of AD treatment with tacrolimus. Professor Werfel gave a lecture on antigen-specificities and functions of T-lymphocytes in atopic eczema/dermatitis syndrome. He concluded that autoallergens, bacterial cell-wall components, and exotoxins are leading to the activation of T-cells at the site of inflammation. Professor Novelli (Fig. 5) gave a lecture on genetic and environmental factors in the twin studies indicating that the genetic contribution is substantial in AD. He pointed out that three loci are closely coincident with psoriasis although AD is quite distinct from psoriasis and that the two diseases rarely occur together in the same patient. Professor Turjanmaa (Fig. 9) presented her study on the infant group with AD and the allergy to multiple food items. A strong association has been shown between atopic eczema and IgE-mediated allergy to milk, egg, or peanut. She compared the results of atopy patch test and skin prick test together with total and specific IgE, and she got the highest positive reactions to food allergens in atopy patch test. Professor Nakayama (Figs. 10,11) pointed out the importance of house dust mite in causation of AD. The result of his study strongly suggests that house dust mites are the most important causation of AD, although AD itself is essentially a



Figure 9. Professors (from left): F. Gruber, V. Milavec-Puretić, K. Turjanmaa, and R. Wolf.



Figure 10. Professor Hideo Nakayama.



Figure 11. From left: J. Lipozenčić, H. Nakayama, A. Pašić, V. Milavec-Puretić and Š. Puretić.

multifactorial disease. Professor Szepletowski (Fig. 12), Assist. Professor Darsow (Figs. 4,13), and Professor Gruber (Fig. 9) gave us a detailed review of pathogenesis and treatment of pruritus, particularly one that is connected with AD. Professor Behrendt



Figure 12. Professor Jacek Szepletowski.



Figure 14. Professor Heidrun Behrendt.



Figure 13. From left: S. Murat-Sušić, E. Fedenko, G. A. Vena, and U. Darsow.

(Fig. 14) presented an interesting study on the impact of airborne pollen, temperature, and humidity on severity of AD in children. Assist. Professor Czarnecka-Operacz showed a double-blind placebo-controlled trial of specific immunotherapy in the treatment of AD patients. Professor Fedenko (Fig. 13) and her coauthors presented Russian experience in managing patients with AD. Their national AD Position Paper consisted of guidelines for practitioners, atlas of topical treatment and skin care, diet therapy and pharmaceutical guide. Pro-



Figure 15. Professor Kurt Blaser.

fessor Berardesca talked about treatment of AD, the mechanism of action and inflammation as well as of gene expression in AD patients and Professor Blaser too (Fig. 15).

Among many domestic presenters, Professor Lipozenčić presented immunologic basis of atopic

dermatitis. She also gave us a short review on the new approach to a patient with AD, and a new management procedure. Head Doctor Pašić (Fig. 16) stressed out the importance of phototherapy with UVA and UVB (narrow-band) irradiation. Doctor Murat-Sušić (Fig. 13) presented a paper on the role of serum eosinophil cationic protein in children with AD dermatitis. She also gave us the review of the management of AD in infancy. Professor Basta-Juzbašić (Fig. 16) stressed out some clinical differences and resemblance of AD with other face skin dermatoses. Group of authors from Osijek, with Doctor Šustić, presented their experience of the association between psoriasis and atopic disorders. Doctor Bukvić Mokos presented her results on the significance of *Malassezia furfur* in the etiopathogenesis of atopic dermatitis. The experience in outpatient Allergology Clinic, Department of Dermatology and Venerology, Zagreb University Hospital Center, with specific immunotherapy in AD patients was presented by Assist. Professor Milavec-Puretić.



Figure 16. Professors: A. Pašić and A. Basta-Juzbašić.

An interesting sponsored lecture by Novartis on the efficacy of pimecrolimus 1% cream (Elidel®) was presented by Professor Luger (Fig. 17).

Professor B. Wüthrich, legend in AE was active presenter (Fig 18.)

In a Poster section, 11 posters were presented. There were four Satellite Symposia sponsored by



Figure 17. Professors: T. Luger and W. Silny.



Figure 18. Professor Brunello Wüthrich and his wife.

Vichy, Uriage-Formasana Ltd., A-Derma, and Beiersdorf.

Social program was as well organized and outstanding as the scientific program. The whole Symposium was a great scientific and social event!

Congratulations to Prof. Jasna Lipozenčić from all the participants for excellent organization!

Assist. Prof. Višnja Milavec-Puretić, MD, PhD

Suzana Ljubojević, MD, MS

**I would like - on behalf of the European Academy of Allergology
and Clinical Immunology - to express my sincere
thanks to the organizers and especially to
Professor Lipozenčić for the great work done!**

Thank you Jasna!

Professor Carsten Bindslev-Jensen
President of Section Dermatology of European
Academy of Allergology and Clinical Immunology
(EAACI) and Symposium President.



Fig 1. Prof. C. Bindslev-Jensen

Report from EADV 2004

2nd Spring Symposium, Budapest, April 29th – May 1st, 2004

Second EADV Spring Symposium held in Budapest Novotel Congress Center, April 29 to May 1, 2004, was attended by approximately 1,000 physicians. There were 126 oral presentations, 296 posters, and 17 lunch sessions. The main sponsors were Serono International and Fujisawa GmbH among a total of 32 exhibitors. Scientific program was held in Room Patria and Bartok and 12 smaller satellite rooms. There were 6 main sessions, 4 plenary lectures, many case presentations, 17 lunch sessions, and 11 workshops.



Figure 1. Professor J. Lipozenčić.

On the first day of Symposium, a Memorial hour for the medical victims of Holocaust was organized by the European Society for History of Dermatology and Venerology within the contribution of the Hungarian Society of Dermatological History Department of Dermato-Venerology and Skin Oncology of the Semmelweis University.

Meeting of the attendees was held at the entrance of the Old Synagogue and in the National Jewish Museum. At a walking distance from the

Synagogue, Memorial hours for the medical victims of Holocaust was held in Spinoza House, chaired by Prof. Karl Holubar, past president of the European Society for History of Dermatology and Venerology. After a short introduction by Prof. Holubar, Michael Hubenstorf talked about "Dermatology and shadow of Nazism: victims and perpetrators". Discussion under the title "Dermatology and Holocaust in Hungary" was contribution by Gabor Veres. Workshop "History of the Hungarian Dermatology" was chaired by Miklos Simon (Hungary) and Stella Fatović-Ferenčić (Croatia). There were lectures on Morbus Kaposi, David Gruby, the Hungarian father of mycology; Sam Cornelius (Samuel) Beck (1872-1930), a great Hungarian dermatopathologist; Karl and Julius Heitzmann and their link to Hungarian dermatology; Istvan Rothman, Hungarian master of the investigative dermatology and Lajos Szodoray, great Hungarian dermatopathologist.

There were two Symposia: Serono – Shaping the Management of psoriasis and Achieving long-term psoriasis control (on April 30, 2004), and Fujisawa – Protopic in clinical practice. Serono



Figure 2. J. Lipozenčić and S. Murat-Sušić as presenters.



Figure 3. J. Lipozenčić, S. Murat-Sušić and I. Lakoš-Jukić.

Symposium was dedicated to a long-term control in psoriasis; review of current systemic therapies; impact of psoriasis (more than skin deep); challenges of assessing psoriasis control; and Raptiva, whose effectiveness in long-term control of psoriasis was clearly demonstrated.

Fujisawa symposium offered lectures on Protopic and its values in optimizing the long-term treatment of patients. Main session list of titles included sexually transmitted diseases; photodermatology; inflammatory skin diseases; autoimmune blistering diseases; inherited skin diseases; presi-

dent's forum; human immunodeficiency virus infection; and laser therapy.

Workshops were given on photoageing and photocarcinogenesis; pediatric dermatology; urticaria; dermatoscopy; dermatopathology; the skin and systemic disease; pearls of dermatosurgery; and new therapies.

During the lunch time, there were sessions on vitiligo; porphyrins; overlap syndromes in connective tissue; whether patients follow their treatments; phlebology; hair and nail disorders; acne; why and when the treatment of acne fails and what to do; contact dermatitis; mycology; new trends in mycological therapy; occupational dermatoses; photoprotection; digital cameras in dermatology; ethical questions in sexually transmitted infections; lyme diseases; new therapy for atopic dermatitis, and tropical skin diseases.

There was a plethora of very instructive scientific news.

Active participants were Prof. M. Skerlev, Dr. S. Murat-Sušić, and Prof. J. Lipozenčić (Figs. 1-3).

The 3rd Spring Symposium of EADV will be held in Sofia, Bulgaria in May, 2005.

Prof. Jasna Lipozenčić, MD, PhD

Advancing Expectations in the Management of Atopic Eczema and Beyond

Novartis Pharma AG, one of the world's leading pharmaceutical companies sponsored a state-of-the-art symposium entitled "Advancing Expectations in the Management of Atopic Eczema and Beyond" that took place in Berlin, Germany, May 7-9, 2004. Novartis Pharma Services Inc., Representative Office Croatia, invited 6 Croatian dermatologists particularly interested in atopic dermatitis management, to participate in the Symposium. Novartis' distinguished guests were Prof. Jasna Lipozenčić, Slobodna Murat Sušić, MD, MS, Asst. Prof. Ines Brajac, Lena Kotrulja, MD, Vesna Peharda, MD, and Damir Pezelj, MD (Fig. 1).

Pimecrolimus cream 1% (Elidel®) is soon going to be registered in Croatia, which is the reason why it was important for Croatian dermatovenerologists to participate in the Symposium.

The symposium brought together a panel of international leaders in the fields of dermatology, pediatric dermatology and allergology, to present the most up-to-date understanding of the pathophysiology and management of atopic eczema, including approaches to long-term prevention of severe flares.



Figure 1. From left: J. Lipozenčić, L. Kotrulja, D. Pezelj, D. Vujčić, I. Brajac, V. Peharda.

The past two years have seen the most important innovation in over half a century in the management of this chronic disease, with the introduction of non-steroid topical therapy. This symposium included practical advice for clinicians with long-term experience in the use of pimecrolimus cream 1% (Elidel®) in the management of atopic eczema, and reviewed its use in the treatment of other skin conditions. The potential of pimecrolimus cream 1% to modify the course of atopic eczema and influence the atopic march has also been addressed during the Symposium.



Figure 2. Invitation to the Symposium.

A distinguished international faculty has been assembled to present a strong scientific agenda, creating a unique platform. Twenty-eight countries have sent more than 300 delegates, among them the most respected dermatologists in the world. This international symposium was a top event attended by key opinion leaders like Prof. Wolff (Vienna), Prof. Bieber (Bonn), Prof. Luger (Münster), Prof. Meurer (Dresden), Prof. Zuberbier (Berlin), Prof. Saurat (Geneva), and Prof. Leung (Denver).

Denis Vujčić, MD
Brand Manager, Novartis Pharma Services Inc.
Representative Office Zagreb, Croatia



Marko Polo's Diary

Stella Fatović-Ferenčić, ESHDV representative of Croatia

Royal Society of Medicine, London, March 26, 2004

The fear of terrorism felt is ever stronger in the media and in the busy avenues of London. Fortunately, my hotel was situated at Welbeck Street, just around the corner from Wimpole Street, meaning that public transport was superfluous. The Royal Society of Medicine was my destination this time and I was both nervous and honored to be invited to give the presentation at this prestigious place. The history of the Royal Society of Medicine goes back to the 18th century when, throughout Europe and in Great Britain, medical societies began to be founded with the intention of bringing together physicians and surgeons and facilitate scientific and professional communication. The first general medical society of note in England was the Medical Society of London, founded in 1773. In 1805, a new medical society, the Medical and Chirurgical Society of London, was established, destined to be the progenitor of the Royal Society of Medicine. In 1834, the Society received its Royal Charter from William IV and its title became the Royal Medical and Chirurgical Society of London. Members were then designated Fellows. Among Honorary Fellows there were Darwin, Pasteur, Jenner, and Freud, as well as many other distinguished figures, such as Max Neuburger, medico-historian from Vienna. Invited by the Chairman of History Special Interest Group of the British Association Sexual Health and HIV, I gave a presentation on the development of art in the field of genitourinary medicine. Quite a number of people gathered and I was impressed by their interest and warm hospitality. The next day I paid a

visit to Amersham, to Darrell Sheldon Wilkinson, the living legend of dermatology in Britain. To know about his textbook of dermatology in several editions or dermatosis pustulosa subcornalis eponymously, also called Sneddon-Wilkinson disease, is one thing, but to meet him in person is certainly a privilege. Our conversation took place in a warm although professional atmosphere. He asked me about Croatia and our language. Sitting on a large veranda and having a lovely conversation, my eyes wandered around the romantic scenery of his garden. Soft colors of grass, flowers and bushes glittered delicately in the sunny but still chilly and grey day. Dr. Wilkinson and his wife remembered their visit to Croatia, and mentioned good relations with Professor Kogoj, of whom both were very fond. I left their home pervaded with warmth and cordiality of my hosts.

Budapest: II Spring Symposium

April 29 - May 1, 2004. From Holocaust to the European Union

Tradition and science in clinical practice was the motto for the II EADV Spring symposium held in Budapest. How suitable for the land of David Gruby, Mór Kaposi and István Rothman that hosted XI World Congress of Dermatology organized by Lajos Nékám in 1935! The Budapest Spring Meeting program consisted of workshops, symposia, free communications, poster sessions, wake up sessions and - history. This time the History day was organized as a memorial hour for the medical victims of the Holocaust. After a guided tour around the biggest European synagogue and the National

Jewish Museum, we were taken to the Spinoza House where the M&M Wolff lecture took place chaired by professors Karl Holubar and László Nebenführer. The M&M Wolff lecture was given by Professor Michael Hubensdorf, head of the History of Medicine Institute in Vienna. His topic, Dermatology and the Shadow of Nazism: Refugees, Victims and Perpetrators, was followed by a discussion on dermatology and the holocaust in Hungary. The memorial was well-attended and moving. However, thousands of lights of the impressive synagogue could not lighten up the dark shadow of history enlivened in our memory. The next day the history of Hungarian dermatology was on the program, with presentations on Mór Kaposi, Soma Cornelius Beck, Karl and Julius Heitzmann, István Rothman, and Lajos Szodoray. It was also the day when Hungary was entering the European Union. Once part of the Austro-Hungarian Empire and always at the crossroads of East and West, this country looks

westward today while remaining defiantly proud of its Magyar heritage. It's Parliament, when finished, was the grandest in the world, and at the height of the Austro-Hungarian Empire, Hungary was a major player in international affairs. For this fiercely independent country may take some time to get used to membership in an enlarged Europe with collective decision-making. But, today Hungary has entered a union of a different kind. The question how much influence it will have this time we leave to history to answer and wish our neighbors a prosperous future.

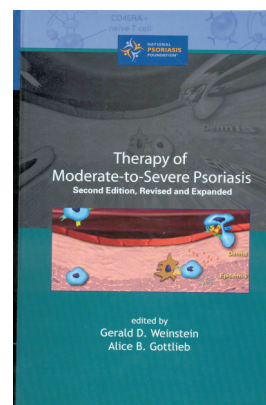
The world is waiting, sretan vam put !

stella@hazu.hr

Weinstein GD, Gottlieb AB, editors. Therapy of Moderate-to-Severe Psoriasis, 2nd Edition, Revised and Expanded. New York-Basel: Marcel Dekker, Inc; 2003. ISBN 0-8247-4116-1. Format: hard cover, one volume, 358 pages, 15 chapters.

This is the second, revised and expanded edition of the book that was first published in 1993. Like the first edition of the book, this one was also sponsored by the US National Psoriasis Foundation. Along with the editors, 21 other authors have contributed to this edition. The introductory section, written by G.D. Weinstein and M.A. Menter, provides a concise but very comprehensive survey of the current state-of-the-art in the field of psoriasis, from clinical picture, genetic advances in the study of psoriasis, pathophysiology, factors influencing the occurrence and course of psoriasis, to current therapeutic strategies. The chapter also presents the classification of psoriasis according to the disease severity, which has been followed by the authors of other chapters. Thus, moderate psoriasis is defined as a clinical form of the disease which exerts no major impact on the patient quality of life and involves 2-20% of skin surface. Topical therapy used for moderate psoriasis is associated with only minimal side effects. The term *severe psoriasis* defines a form of the disease involving >10% of skin surface, which fails to respond favorably to the treatment associated with minor side effects. The patients have to accept the life-altering side effects of therapy, with substantial impact on their quality of life. The authors emphasize that the patient's attitude toward the disease, localization of psoriatic lesions (face, genital region, and hands), symptoms of the disease (especially pruritus), and articular involvement should be taken in consideration on the disease severity evaluation.

The chapter on topical therapy for moderate and severe psoriasis highlights the crucial role of this therapy, and describes the methods of examination, mechanisms of action, pharmacologic profile, mode of application, contraindications, and side effects as well as the combined therapy options with local corticosteroids, vitamin D derivatives (calcipotriol), topical retinoids (tazaroten), anthralin, and some other immunomodulators (tacrolimus).



Special chapters are dedicated to the use of UV light in the management of psoriasis. The use of broad band and narrow band UVB therapy is presented in separate sections, emphasizing the great importance of the latter. This chapter also includes presentation of the use of lasers in the treatment of psoriasis. The information on the use of lasers for this indication mostly derives from the studies with excimer laser. The 308 nm peak provides a very narrow band (far narrower than narrow band UVB) near the peak of the psoriasis improvement spectrum. This, and perhaps the coherence of laser light, may provide some benefit over other forms of UV phototherapy. At the relatively low fluences laser does not destroy tissue but rather acts as a form of localized UVB phototherapy.

In the chapter on photochemotherapy (PUVA), written by W.L. Morison, a renowned authority in the field, the mechanism of action and various options for the use of psoralen and UVA light, indications and contraindications, and side effects of PUVA therapy are concisely and precisely presented, with particular reference to the need of careful patient monitoring.

Chapter 5, written by G.D. Weinstein, deals with the use of methotrexate in the management of psoriasis. In the introductory section, a historical account of the use of methotrexate in the treatment of psoriasis is presented. Then the author points to the

need of careful patient selection and close pretherapeutic patient evaluation for methotrexate therapy, contraindications for methotrexate therapy, mechanism of action, route of administration and patient monitoring, side effects and possible complications associated with methotrexate therapy. Liver biopsy should be performed in patients without risk factors who have received a cumulative dose of 1.0-1.5 g methotrexate. In patients with some of the risk factors, liver biopsy should be repeated at 2-4 months, and then following each cumulative dose of 10 g methotrexate.

The chapter on the use of retinoids in the treatment of psoriasis has been written by a group of authors headed by P.S. Yamauchi. The introductory section provides data on the retinoids used to date, primarily acitretin, as well as on the new generation of retinoids, bexarotene being best known among them. Bexarotene is primarily used in advanced stages of T cell lymphomas, however, there are reports on its use in the management of psoriasis. Attention is especially drawn to the options of combined treatment with acitretin and UV light (PUVA and UVB), posology, side effects, and teratogenic effects of retinoids.

Chapter 7 deals with the use of cyclosporine in the management of psoriasis, with special reference to cyclosporine interaction with other drugs. A thorough survey is presented of the drugs associated with an increase in the blood concentration of cyclosporine and those that cause synergistic nephrotoxicity. Also, the drugs that can suppress the blood concentration of cyclosporine and influence immunosuppression are mentioned. Although cyclosporine has not been approved for the treatment of psoriasis in the USA, the maximal recommended dose for this indication is 5 mg/kg.

The principles of combination, rotational and sequential therapy for psoriasis have now been almost generally accepted, thus they are discussed in a separate chapter of the book.

Psoriasis in childhood has some specific clinical characteristics, which are described in a separate chapter, emphasizing that some 4% of children aged <16 years suffer from psoriasis. In this age, psoriasis may occasionally be even more difficult to diagnose than in adults, therefore a table is provided containing 20 dermatoses that should be con-

sidered as a differential diagnosis. The great importance of appropriate choice of therapy and the psychosocial aspect of childhood psoriasis are highlighted.

Chapter 11, written by A. Gottlieb, one of the book editors and renowned expert in the field of biologic agents for psoriasis, is dedicated to targeted immunotherapies. The roles of activated T cells, memory T cells, costimulation molecules, and cytokines are emphasized. Experimental treatment of patients with moderate to severe psoriasis with biologicals has successfully targeted: 1) T cell activation; 2) memory T cells; 3) T cell migration into skin; 4) cytokines (e.g., TNF); and 5) induction of immune deviation from type 1 to type 2 cytokine predominance in plaques.

Separate chapters are dedicated to the use of etanercept (Enbrel, Amgen) acting as a competitive tumor necrosis factor (TNF) inhibitor, which has been registered in the USA for the treatment of inflammatory diseases such as psoriasis, psoriatic arthritis and juvenile rheumatoid arthritis. Alefacept is another biological discussed in the book. Alefacept inhibits T cell activation and proliferation by binding to CD2 on T cells and blocking the LFA-3/CD2 interaction.

A separate chapter of the book deals with the use of infliximab in the treatment of psoriasis. Infliximab interferes with the action of TNF α by directly binding to soluble and transmembrane TNF α both in plasma and in diseased tissue. Infliximab is in clinical development for the treatment of psoriasis. Efalizumab (Raptiva) is a humanized anti-CD11a monoclonal IgG1 antibody, which has been shown to inhibit effectively various T cell functions including target cell lysis, T cell adhesion, T cell activation, and T cell proliferation. All sections on the use of biologicals stress their favorable effects in improving the patient quality of life and their role in opening a new era in the management of psoriasis.

This book is a valuable textbook and an excellent handbook to be used in dermatologist daily routine. It offers a number of new concepts on the drugs and methods used in the treatment of moderate to severe psoriasis.

Aida Pašić, MD, PhD

ANNOUNCEMENTS

7th Dresden Symposium on Autoantibodies, Dresden, Germany, September 1-4, 2004. Contact: k_conrad@rcs.urz.tu-dresden.de

3rd Congress of the Dermatovenerologists, Struga, Macedonia, September 15-18, 2004.; Contact: Congress Secretariat, Clinic of Dermatovenerology, Vodnjanska 17, 91000 Skopje, Macedonia; makderm@unet.com.mk

Allergie Kongress 2004, Aachen, Germany, September 15-19, 2004. Contact: Gerhard.Schultze-Werninghaus@ruhr-uni-bochum.de; www.allergie-kongress-2004.de

1st Croatian Congress of Psychodermatology, Cavtat, Croatia, September 23-26, 2004. Contact: Prof. Mirna Šitum, Department of Dermatology and Venerology, Clinical Hospital "Sestre milosrdnice", Vinogradska 29, 10000 Zagreb, Croatia; msitum@kbsm.hr

7th International Congress of Dermatology, Teheran, Iran, September 29-October 2, 2004. Contact: info@iranderm.org; www.iranderm.org

25th Annual Meeting of the International Society of Dermatologic Surgery, Barcelona, Spain, October 6-9, 2004. Contact: isds2004@mccann.es; www.isds2004.com

Update on Psoriasis, Continuing Medical Education Course organized by Chair of Dermatovenerology of the University School of Medicine Zagreb, Šalata 4, 10000 Zagreb, Croatia, October 15-16, 2004. Contact: Prof. Jasna Lipozenčić, Šalata 4, 10000 Zagreb, Croatia. Phone/Fax: +385-1-4920-014; jasna.lipozencic@zg.htnet.hr

Psoriasis 2004, European Congress on Psoriasis, Paris, France, October 21-24, 2004. Contact: Psoriasis 2004, c/o MCI France, cem.unal@mci-gruop.com; psoriasis2004@mci-group.com; www.pso2004.com

Therapeutic Innovation in Dermatology and Dermatocosmetology, Bangkok, Thailand, October 23-25, 2004. Contact: thadapiaru.@thaicosderm.org

4th International Congress on Autoimmunity, Budapest, Hungary, November 3-7, 2004. Contact: fax:0041 22 732 2850; phone 0041 22 908 0488

1st Italian-Croatian Symposium on Psoriasis and 4th Congress on the Lyme Disease, Grado, Italy, November 12-13, 2004.

13th Congress of the European Academy of Dermatology and Venerology, Florence, Italy, November 17-21, 2004. Contact: *president@eadv2004.org*; *registration@eadv2004.org*; *www.eadv2004.org*

63rd Annual Meeting of American Academy of Dermatology, New Orleans, USA, February 18-23, 2005.

10th World Congress on Cancers of the Skin, Vienna, Austria, March 19-23, 2005. Contact: Elfriede Pomp, Department of Dermatology, University of Vienna, Vienna General Hospital, Waehringer Guertel 18-20, A-1090 Vienna; *info@wccs.at*; *www.wccs.at*

Spring Symposium of the European Academy of Dermatology and Venerology, Sofia, Bulgaria, May 19-22, 2005. Contact: Bulgarian Dermatological Society; *eadvsofia2005@mail.bg*; *www.eadv.org/sofia2005*

8th Congress of the European Society for Pediatric Dermatology, Budapest, Hungary, May 5-7, 2005. Contact: *www.convention.hu*; *www.espd2005.com*

28th Annual Meeting of the Israel Society of Dermatology and Venereology, Eilat, Israel, June 16-17, 2004. Contact: Prof. Sarah Brenner, The Tel Aviv Sourasky Medical Center, Weizman Street, Tel Aviv 64239, Israel; tel: 972 3 6974287; fax: 972 3 6974810

World Allergy Congress – 19th International Congress of Allergology and Clinical Immunology and 24th Congress of the European Academy of Allergology and Clinical Immunology, Munich, Germany, June 26-July 1, 2005. Contact: *wac2005@congrex.se*; *www.congrex.com/wac2005*

16th Biennial Meeting of the International Society for Sexually Transmitted Diseases Research (ISSTD), Amsterdam, Netherlands, July 10-13, 2005. Contact: *isstdr@aidsfonds.nl*; *www.isstdr.org*

14th IACD (International Academy of Cosmetic Dermatology) World Congress, Paris, France, July 3-5, 2005. Contact: IACD 2005, c/o MCI France, 11 Rue de Solferino, 75007 Paris, France; *iacd2005@mci-group.com*; *www.iacd-paris2005.com*

6th World Congress on Melanoma, Vancouver, B.C., Canada, September 2-9, 2005. Contact: Venue West Conference Services Ltd., Vancouver, B.C., Canada; *congress@venuewest.com*

15th World Congress of the International Union of Phlebology, Rio de Janeiro, October 2-7, 2005; Contact: RIO UIP 2005 - Secretary, Rua Santa Clara, 494 - Sorocaba - 108030-421 SP - Brasil; *inspemoc@dglnet.com.br*; *angelo.scuderi@flebologiabrasil.com.br*; web site: *www.flebologiabrasil.com.br*

6th Dermatology and Dermatopathology Meeting of the Turkish Society of Dermatopathology, Istanbul, Turkey October 7, 2004. Contact: Rana Yavuzer Anadolu, M.D., Ankara Uni Koza sok. 114-86, 00670 Ankara Turkey; *ranaadolu@hotmail.com*

14th Congress of the European Academy of Dermatology and Venerology, London, October 12-15, 2004. Contact: Prof. Martin Black, Congress President; British Association of Dermatologists Conference Services; *eadv@bad.org.uk*; *president@eadv2005.org*; website: *www.eadv2005.org*

2nd Trends in Medical Mycology, Berlin, Germany, October 23-26, 2005. Contact: Congress Secretariat, Congress Care, Muntelbolwerk 1, P.O. Box 440; 5201 AK 's-Hertogenbosch, The Netherlands; tel. +31-73 683 1238; Fax: +31-73 690 1417; e-mail: *info@congresscare.com*

4th EADV Spring Symposium, Saariselka, Lapland, Finland, February 9-12, 2006.

15th EADV Congress, Rhodes, Greece, October 4-7, 2006.

21st World Congress of Dermatology, Buenos Aires, Argentina, October 1-5, 2007. Contact: *info@dermato2007.org*

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Type the complete manuscript double-spaced, on one side of A4 bond paper, with a left side margin of at least 4 cm.

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The title page should carry (a) the title of the paper, which should be concise but informative; (b) full name of each author, with institutional affiliation; (c) name(s) of department(s) and institution(s) to which the work should be attributed; (d) name and address (with telephone and fax numbers as well as the e-mail address) of the author to whom requests for reprints should be addressed; (f) source(s) of support in the form of grants, equipment, drugs, or all of these; and (g) a short running head of not more than 40 characters (count letters and spaces) at the foot of the title page.

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The second page should carry a summary of not more than 250 words, followed by three to six key words from the Medical Subject Headings (MeSH) list of Index Medicus.

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Journal article

Standard journal article (list all authors, but if their number exceeds six, give six followed by *et al.*)

You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. *Gastroenterology* 1989;79:311-4.

Chapter in a book

Weinstein L, Swartz MN. Pathologic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, editors. *Pathologic physiology: mechanisms of disease*. Philadelphia: Saunders; 1974. p. 457-72.

Article not in English

Massone L, Borghi S, Pestarino A, Piccini R, Gambini C. Localisations palmaires purpuriques de la dermatite herpétiforme. *Ann Dermatol Venerol* 1987;114:1545-7.

Conference paper

Harley NH. Comparing radon daughter dosimetric and risk models. In: Gammage RB, Kaye SV, editors. *Indoor air and human health. Proceedings of the Seventh Life Sciences Symposium*; 1984 Oct 29-31; Knoxville (TN). Chelsea (MI):Lewis, 1985:69-78.

Dissertation

Youssef NM. School adjustment of children with congenital heart diseases (dissertation). Pittsburgh (PA): University of Pittsburgh; 1988.

Submission of Manuscripts

Manuscripts should be printed on paper and submitted in triplicate, with one copy on a floppy disk, and sent to:

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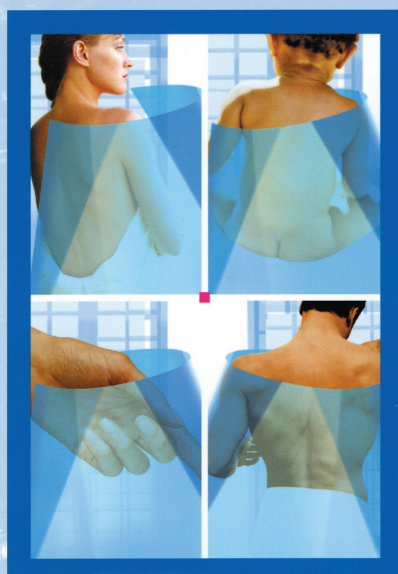
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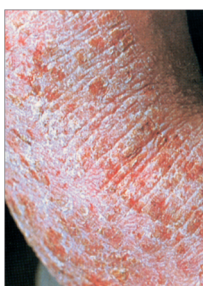
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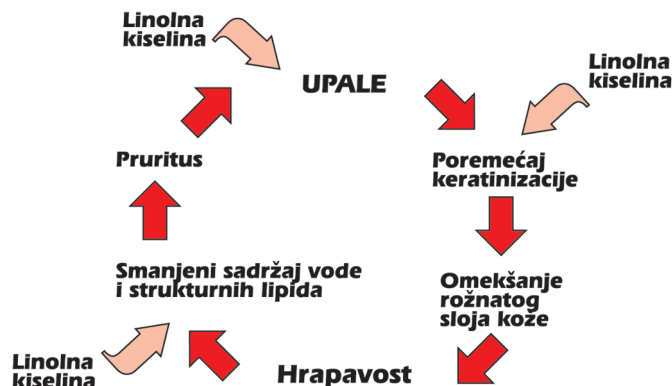
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