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Editorial Office

Acta Dermatovenerologica Croatica
Department of Dermatology and Venerology
Zagreb University Hospital Center
Šalata 4, 10000 Zagreb, Croatia
Phone/Fax: +385-1-4920 014
E-mail: *jasna.lipozencic@zg.tel.hr*

Business correspondence

Medicinska naklada, Vlaška 69, 10000 Zagreb, Croatia;
www.medicinska.naklada.hr

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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.

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E-mail: *jasna.lipozencic@zg.tel.hr.*

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Acta Dermatovenerol Croat 2003;11(3):145-152 ORIGINAL SCIENTIFIC ARTICLE

THE PRESENCE OF SURFACE CD30 ON T CELLS IN ATOPIC DERMATITIS

Jasna Lipozenčić, Dubravka Bobek, Jasminka Jakić-Razumović[1]

Department of Dermatology and Venerology, and
[1]Department of Pathology, Zagreb University Hospital Center, Zagreb, Croatia

Corresponding author:

Prof. Jasna Lipozenčić, M.D., Ph.D.

Department of Dermatology and Venerology

Zagreb University Hospital Center

Šalata 4

10000 Zagreb, Croatia

jasna.lipozencic@zg.tel.hr

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SUMMARY Atopic dermatitis (AD) has cellular immunohistochemical features similar to those of allergic contact dermatitis (ACD) and there is plenty of evidence for T-cell activation in this disease. The involvement of CD30+ T cells in acute stages of atopic dermatitis might establish CD30 as a helpful marker in differentiating those two diseases. Tissue sections from the skin of 12 patients with active atopic dermatitis and 13 with allergic contact (nickel-induced) dermatitis were immunohistochemically analyzed for cell-surface antigens, including CD30, CD3, CD4, and CD45RO. The severity of the disease was graded by the SCORAD clinical scoring system. The analysis of CD30+, CD45RO+, CD3+, and CD4+ cells in the dermis and epidermis showed a much wider range of values and statistically higher median ($p<0.01$) in the inflammatory infiltrate of acute atopic dermatitis compared with that of allergic contact dermatitis. Our results showed an association of CD30 expression with atopic dermatitis, but not allergic contact dermatitis. CD30 expression in AD might be helpful in histologic differentiation of these disorders and further characterization of atopy patch testing. The results suggested a specific regulatory function of CD30+ T cells in acute AD. Abundant CD45R0+ cells were detected in both AD and ACD lesions.

KEY WORDS CD30 expression; dermatitis, allergic contact; dermatitis, atopic; immunohistochemistry

INTRODUCTION

Atopic dermatitis is a chronic pruritic inflammatory skin disorder that frequently occurs in patients with personal and family histories of allergic disease. Increased concentrations of serum IgE (1,2) and impaired T cell function (3,4) have been reported in up to 80% of patients with atopic dermatitis. The disease is characterized by several clinical, immunological, and biochemical alterations. We investigated the role of immunological mechanisms in the pathogenesis of this disorder by comparing the patients with the “extrinsic” and “intrinsic” types of atopic dermatitis.

A dysregulated, cytokine-mediated response of the immune system to environmental, particularly inhalant, allergens is thought to be an important pathogenic factor. Atopic dermatitis lesions contain

TH2-like cells (5), and TH2-like cytokines may be pathogenically relevant in this disease (6). Spontaneous release of TH2-type cytokines, such as interleukin (IL)-4 and IL-5, has been demonstrated in supernatants of both peripheral blood lymphocytes and skin biopsies of patients with atopic dermatitis (7), and IL-4 producing CD4+ T cells have been found in cellular infiltrates in lesional skin (8). It has been recently reported that CD30, a 120-kDa membrane-bound glycoprotein belonging to the tumor necrosis factor/nerve growth factor receptor superfamily (9), is an activation marker of T-cell clones, showing a TH2-related cytokine pattern of production (9,10).

We investigated the presence of CD30+ cells in the lesional skin of patients with atopic dermatitis, and the possible relationship between CD30+ cells and clinical score.

MATERIAL AND METHODS

We obtained 25 biopsy specimens (3-4 mm punch biopsy) from various skin regions of patients with atopic dermatitis and those with allergic contact dermatitis. Punch biopsies were taken from acute erythematous lesions of 12 patients (6 women and 6 men; age range: 19-36 years) and from lesional skin of 13 non-atopic patients with nickel-induced allergic contact dermatitis (11 women and 2 men; age range: 18-35 years).

Atopic dermatitis was diagnosed according to the criteria of Hanifin and Rajka (11). These patients presented with typical clinical appearance and had positive personal and/or family history for atopic disorders, multiply positive skin prick test results, and facultatively increased IgE concentrations. Patients did not receive anti-inflammatory systemic medication before biopsy.

Patients suffering from allergic contact dermatitis had a negative history for atopy, normal IgE concentrations, and confirmed type IV (delayed) hypersensitivity.

Informed consent was obtained from all patients before biopsy.

The severity of atopic dermatitis was assessed according to the SCORAD system (12) range, from 21 to 62. According to SCORAD index, patients were subdivided into three groups: mild (0 to 30), moderate (31 to 65), and severe atopic dermatitis (66 to 100).

Skin Processing and Immunohistochemistry

Skin biopsy specimens were fixed in formalin, embedded in paraffin (4-5 m sections), and then prepared on glass slides. Immunohistochemistry peroxidase-antiperoxydase method with monoclonal antibodies was used for the analysis of paraffin-embedded skin section biopsies, as well as anti-CD30, anti-CD45RO, anti-CD3, and anti-CD4 dilutions of antibody sera (Multi-link Swine anti Goat-Mouse-Rabbit Immunoglobulins biotinylated, Dako Copenhagen, Denmark).

Sections were incubated with non-immune horse serum for 20 minutes, washed, and then incubated with primary antibodies. After that, sections were washed three times for 5 minutes in phosphate buffer (PBS) and secondary antibodies were applied. Sections were then incubated for 30 minutes, washed in PBS, and incubated with conjugate of biotin-avidin peroxidase (ABC/HRP kit, Dako) for 30 minutes.

After being washed in PBS, the product vas visualized with 3,3-2 diaminobenzidine (DAB; Dako, Copenhagen, Denmark) in PBS containing 0.01% H2O2. The whole section was colored by hemalun-eosin for 3 minutes.

The number of CD30+ cells in the whole biopsy tissue (x40) was counted by an observer in a blind fashion. After tissue sections were stained with hematoxylin-eosin, the whole section was examined at x40 magnification by an observer in blind manner.

A semiquantitative grading was used, as follows: 0 = none, 1 = a few scattered cells (mild inflammation), or 2 = a moderate or large number of cells (moderate to severe inflammation).

Data were statistically analyzed with Kolmogorov-Smirnov and Mann-Whitney tests.

RESULTS

Twelve patients (6 women and 6 men) with acute atopic dermatitis and 13 patients (11 women and 2 men) with allergic contact dermatitis (as

Table 1. Patients with acute atopic dermatitis

Patient	Sex*	Age (years)	Skin involvement	Subjective symptoms	SCORAD index
V1	m	24	28	8	35
V2	f	25	48	7	55
V3	f	29	23	3	50
V4	f	28	58	12	62
V5	m	35	23	4	37
V6	m	37	13	7	24
V7	f	36	36	14	42
V8	f	22	25	14	37
V9	f	19	78	3	43
V10	m	28	38	7	32
V11	m	26	10	12	21
V12	m	19	56	17	49

*m = male; f = female.

control group) were consecutively included in the study. Skin biopsies were performed in all 25 adult subjects. Eczematous lesions were clinically scored according to SCORAD index. Most patients (n=10) were in the mild group, with SCORAD index 0 to 30, and moderate group (n=2), with SCORAD index 31 to 65 (Table 1).

In all paraffin-embedded specimens of acute atopic dermatitis, most infiltrating cells were CD3+ T cells (Figs. 1-4).

In patients with atopic dermatitis, high CD30 expression was observed in a remarkable proportion of infiltrating cells, with a prevalent perivascular distribution in the superficial dermis (Fig 5). In the skin of patients with allergic contact dermatitis, CD30+ cells were very rare.

Table 2 shows the number of membrane CD30, CD4, CD3, and CD45RO in dermis and epidermis from skin infiltrates of patients with atopic dermatitis, compared with CD30, CD3, CD4, and CD45RO expression in patients with allergic contact dermatitis.

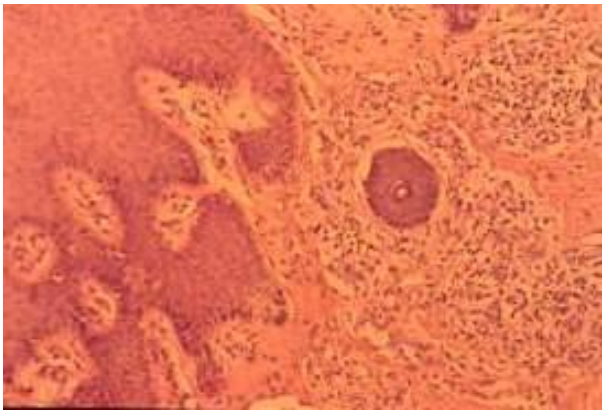

Figure 1. Atopic dermatitis. Under slight epidermal thickening, there are abundant inflammatory infiltrates of little lymphocytes (hematoxylin-eosin, x200).

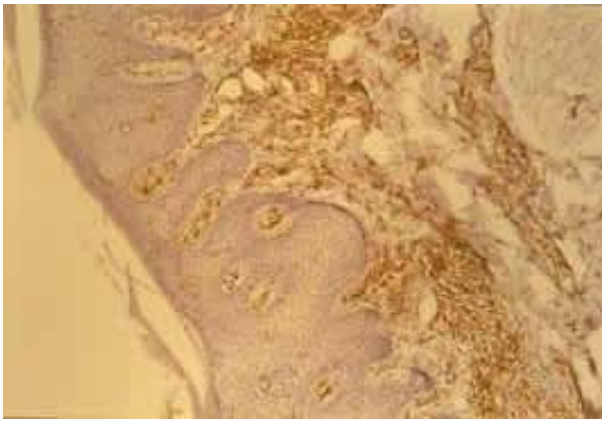

Figure 2. Atopic dermatitis. Immunohistochemical staining with anti-CD45RO antibody. There are abundant T lymphocytes infiltrates in dermis and epidermis (hematoxylin-eosin, x200).

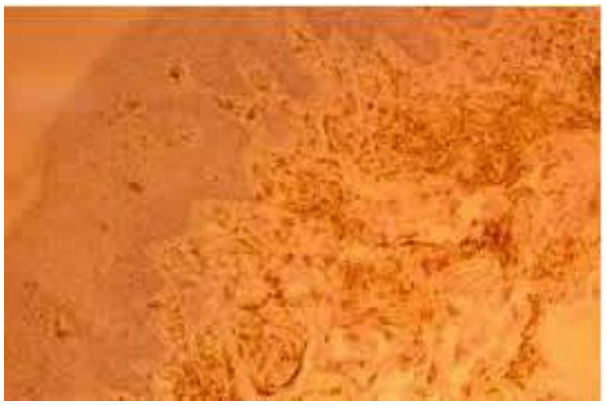

Figure 3. Atopic dermatitis. Immunohistochemical staining with anti-CD3 antibody CD3+ T lymphocytes form majority cells in dermis (hematoxylin-eosin, x200).

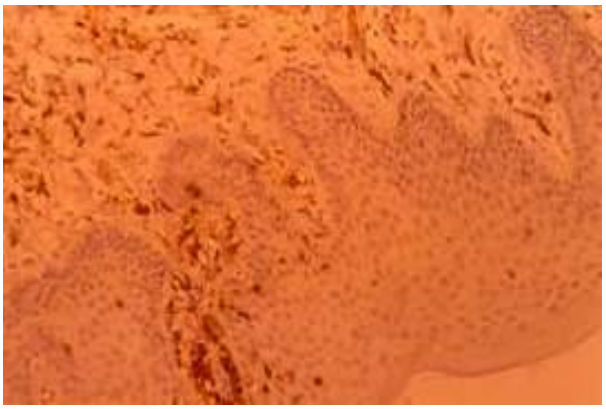

Figure 4. Atopic dermatitis. Immunohistochemical staining with anti-CD4 antibody. In the skin specimen, there are lots of CD4+ T-lymphocytes in dermis and sparse in epidermis (hematoxylin-eosin, x200).

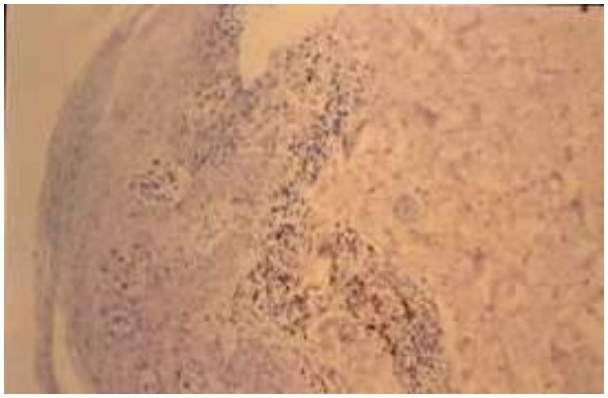

Figure 5. Atopic dermatitis. Immunohistochemical staining with anti-CD30 antibody with sparse but existing reaction on some lymphocytes (hematoxylin-eosin, x200).

The analysis of CD30+, CD45RO+, CD3+, and CD4+ cells in dermis and epidermis showed a much wider range of values and significantly higher median ($p<0.01$) in the inflammatory infiltrate of acute atopic dermatitis than in the infiltrate of allergic contact dermatitis (Tables 3 and 4; Fig. 6). The number of CD30+ ranged from 3 to 21 per mm2 of dermis in patients with atopic dermatitis, and from 0 to 3 in patients with allergic contact dermatitis (Fig. 6).

Average CD30 expression was significantly higher in patients with atopic dermatitis than in patients with allergic contact dermatitis ($p<0.01$; Fig. 6). The analysis of CD45RO+ cells in the dermis also showed a much wider range of values and significantly higher median ($p<0.01$) in the inflammatory infiltrate of acute atopic dermatitis than in that of allergic contact dermatitis (Fig. 6).

We found positive correlation between the number of CD30 and clinical score according SCORAD index (r=0,402; p=0,113, r2=23,2%; Figs. 2 and 7). The same was found for the correlation between CD30 expression and intensity of skin changes ($p=0.050$), extent of skin lesions ($p=0.294$), and subjective symptoms ($p=0.458$), which were all positive but statistically non-significant.

DISCUSSION

Our results showed an association of CD30 expression with atopic dermatitis, but not with allergic contact dermatitis. This suggested a specific regulatory function of CD30+ T cells in acute atopic dermatitis and confirmed the importance of CD30 as T cell activation marker, which is useful to reveal a TH2 immune response occurring in vivo. Abundant CD45RO+ cells were detected in both atopic dermatitis and allergic contact dermatitis lesions. The correlation of SCORAD index and CD30 expression were positive but statistically non-significant. The same was found for the correlation of CD30 expression and intensity of skin changes, extent of skin lesions, and subjective symptoms, which were all positive but statistically non-significant. Our results seem to confirm that the correlation with the SCORAD method is probably due to the relevance given by this scoring system to subjective symptoms, such as pruritus or sleep loss, which are not easy to evaluate.

The relationship between allergy and the pathogenesis of the skin lesions in atopic dermatitis is not clear. In atopic dermatitis, a large proportion

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of skin infiltrating TH cells express a TH-2 like phenotype (8,13,14). The production of TH2-type cytokines is associated with membrane expression of the glycoprotein CD30 in both CD4+ and CD8+ cell clones (9), and CD30 expression is regulated by IL-4 (15). Based on these findings, expression of the CD30 molecule has been considered a marker for TH2 cells (16).

According to a recent hypothesis by Del Prete et al (17), the analysis of CD30 expression would be helpful in discerning TH2-from TH-1 type cells. They based this notion on the following observations: 1) TH2-type clones expressed higher amounts of CD30 than either TH0- or TH1-type cells; 2) antigens that elicited TH2-type responses up-regulated CD30 on in vitro activated T cells, whereas TH1-inducing antigens did not; and 3) the CD30+ T cell fraction from atopic patients primed in vivo by allergen was highly enriched for allergen-specific T cells. Contrary to that, Hamann et al (18) demonstrated that CD30 expression could not be used as a

Table 2. The number of membrane CD30, CD4, CD3, AND CD45RO in dermis (D) and epidermis (E) from skin infiltrates of patients with atopic dermatitis (AD), compared with CD30, CD3, CD4, AND CD45RO expression in patients with allergic contact dermatitis (ACD)

	Number of positive cells							
	CD30		CD45 RO		CD3		CD4	
Diagnosis	D	E	D	E	D	E	D	E
AD:								
V1	15	2	324	38	218	21	112	9
V2	6	1	91	8	85	6	25	1
V3	11	2	93	6	72	4	59	2
V4	21	4	131	28	116	32	75	10
V5	10	2	185	21	154	16	20	5
V6	5	1	72	6	65	5	38	2
V7	9	3	92	15	78	12	52	6
V8	3	2	68	15	52	12	36	7
V9	5	2	172	28	158	25	49	6
V10	10	6	132	22	112	15	92	10
V11	5	1	52	6	48	3	39	2
V12	7	2	62	6	52	4	31	2
ACD:								
V1	0	0	15	1	12	0	4	0
V2	1	0	28	2	15	1	11	1
V3	0	0	14	0	10	0	9	0
V4	0	0	45	3	38	0	20	0
V5	0	1	26	2	25	0	20	1
V6	3	0	38	3	28	2	22	0
V7	2	0	19	2	14	0	10	0
V8	0	0	22	5	19	3	15	0
V9	0	0	16	0	13	0	11	0
V10	2	0	34	6	32	3	18	0
V11	0	0	44	8	28	3	24	2
V12	0	0	32	5	35	4	10	0
V13	1	0	41	3	25	4	10	0

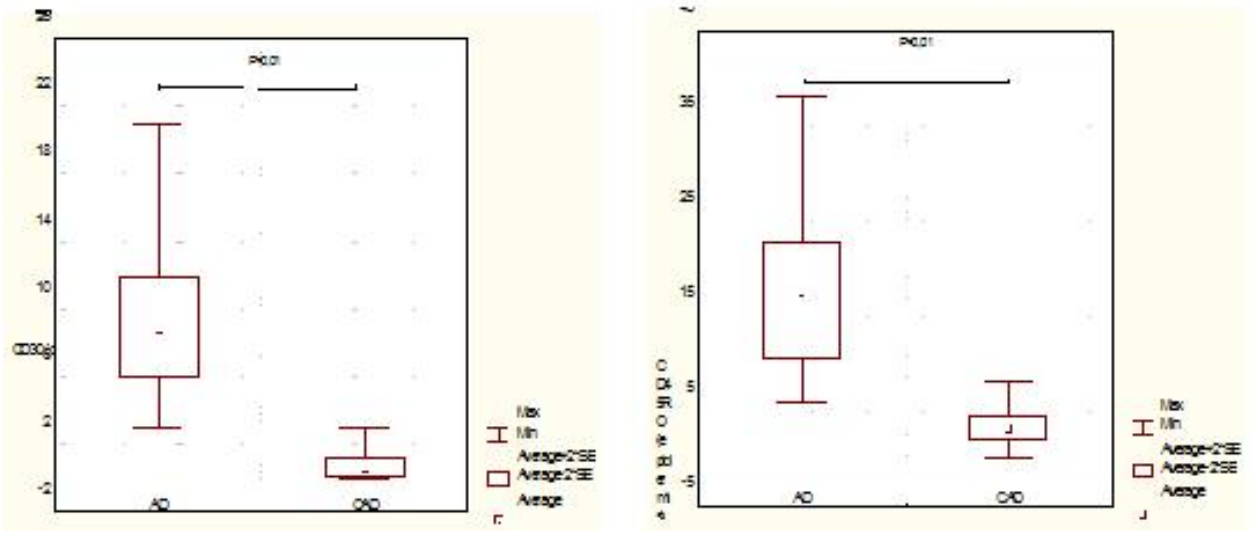

Figure 6. Membrane CD30 and CD45RO expression in dermis derived from skin infiltrates of patients with atopic dermatitis compared with membrane CD30 and CD45RO expression patients with allergic contact dermatitis.

Table 3. Value ranges of CD30, CD4, CD4, and CD45 in dermis (D) and epidermis (E) of patients with atopic dermatitis (AD) and allergic contact dermatitis (ACD)

		Value ranges	
		AD	ACD
CD 30	D (mm^2)	3-21	0-3
	E (mm)	1-6	0-1
CD 3	D (mm^2)	48-218	10-38
	E (mm)	3-32	0-4
CD 4	D (mm^2)	20-112	4-24
	E (mm)	1-10	0-2
CD 45RO	D (mm^2)	52-324	14-45
	E (mm)	6-38	0-8

marer for individual T cell secreting TH2-type cytokines, because CD30 could be found on TH2-, TH0-, and TH1-type T cell clones. Thus, they concluded that CD30 was present on activated T cells independently of the nature of the antigens and therefore could not discriminate between TH1- and TH2-like T cells.

In addition, most T cells infiltrating atopic dermatitis lesions as well as contact dermatitis lesions express high levels of cutaneous lymphocyte-associated antigen (CLA), which functions as a skin homing receptor for T lymphocytes (19).

Contact dermatitis is a delayed-type hypersensitivity reaction and depends on a cell-mediated immune response. Data about the frequency of

Table 4. Results of analysis CD30, CD45RO, CD3, and CD4 expression by skin-infiltrating T cells in patients with atopic dermatitis (AD) and allergic contact dermatitis (ACD)

		AD					ACD				
		x	s.d.*	min.	med.	max.	x	s.d.	min.	med.	max.
CD30	D	8.92	5.07	3	8	21	0.69	1.03	0	0	3
	E	2.33	1.44	1	2	6			0	0	1
CD45-RO	D	122.8	76.31	52	92.5	324	28.54	11.05	14	28	45
	E	16.58	10.85	6	15	38	3.08	2.36	0	3	8
CD3	D	100.8	52.77	48	81.5	218	22.62	3.39	10	25	38
	E	12.92	9.34	3	12	32	1.54	1.66	0	1	4
CD4	D	52.33	27.96	20	44	122	14.15	6.08	4	11	24
	E	5.17	3.35	1	5.5	10			0	0	2

*s.d. = standard deviation.

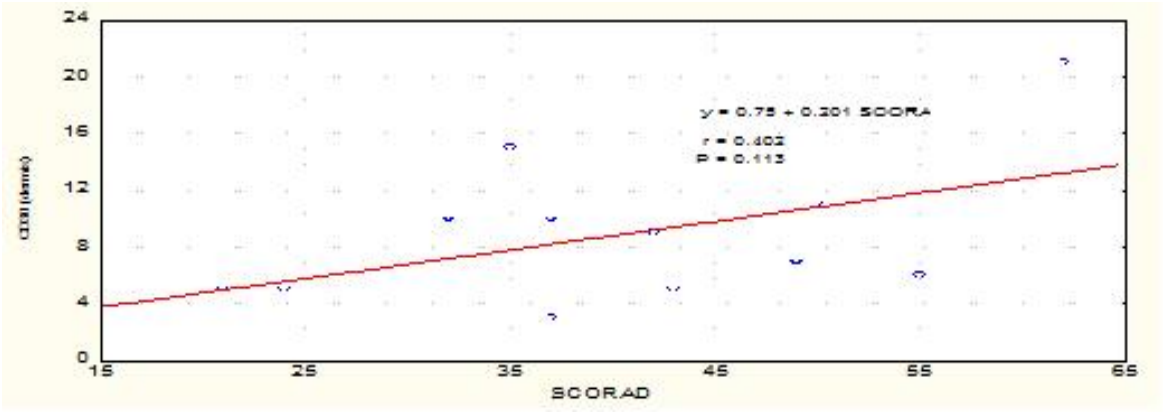

Figure 7. Correlation between presence of CD30+ cells in the lesional skin adults with atopic dermatitis and clinical score (SCORAD index).

contact allergy in atopic patients are controversial (20).

For years it has been accepted that contact dermatitis is mediated by a TH1 response, whereas atopic dermatitis occurs as a result of sustained activation of the TH2 subset, or even TH0 cells (21).

Our analysis of CD30+, CD45RO+, CD3+ and CD4+ cells in the dermis and epidermis showed a much wider range of values and significantly higher median in the inflammatory infiltrate of acute atopic dermatitis than that of allergic contact dermatitis. These data are in accordance with the results obtained by Caproni et al (22) and Dummer et al (23). Thus, CD30 expression in atopic dermatitis might be helpful in histologic differentiation of these disorders and in further characterization of atopy patch test.

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Acta Dermatovenerol Croat 2003;11(3):153-157 CLINICAL ARTICLE

HEAD AND NECK SQUAMOUS CELL CARCINOMA SKIN METASTASES BELOW OF THE DIAPHRAGM

Davorin Đanić, Ana Đanić[1]

Department of Otorhinolaryngology and Cervicofacial Surgery, Slavonski Brod General Hospital, Slavonski Brod, and Osijek University School of Medicine, Osijek;
[1]Zagreb University School of Medicine, Zagreb, Croatia

Corresponding author:

Prof. Davorin Đanić, M.D., Ph.D.

Department of Otorhinolaryngology and Cervicofacial Surgery

Dr. Josip Benčević General Hospital

35000 Slavonski Brod, Croatia

davorin.djanic@sb.tel.hr

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SUMMARY Cutaneous metastases from carcinoma are relatively uncommon in clinical practice. Metastasis to skin sites from squamous cell carcinoma of the mucosa of the head and neck are also very rare. However, skin metastases may be the first clinical evidence of the malignant disease or its loco-regional recurrence. Early recognition of skin metastasis can lead to an accurate and prompt diagnosis and timely treatment. Patients with skin metastases have very poor prognosis. We report on four such patients, one of them with multiple skin metastases from the squamous cell carcinoma in the cervical part of the esophagus above and below the level of the diaphragm. In reviewing the literature, only two cases of solitary skin metastases below the diaphragm from laryngeal squamous cell carcinomas have been reported.

KEY WORDS carcinoma, squamous cell; neoplasm metastasis; skin

INTRODUCTION

Metastasis is one of the most critical prognostic factors of malignances arising in the head and neck (1,2). In general, prognoses for patients with distant metastases are poor, with many patients surviving only a few months (1,3). Distant metastases from squamous cell carcinoma of the mucosa of the head and neck have a complex biologic nature. The incidence of distant metastases of the head and neck squamous cell carcinoma is relatively small in comparison with other malignancies. In 1923, Crile (4) was the first to report that the incidence of metastases in patients with head and neck carcinoma was approximately 1%. During the past years, better local control of the malignant disease have caused distant metastases to become a common occurrence. Recent clinical data have shown increased incidence of distant metastases, up to 30% or even 50% at autopsy, most commonly involving the lung, bone, and liver (5-7). The incidence of distant metastases is influenced by the location of the primary tumor, initial T and N stage of the neoplasm, and presence or absence of regional involvement above clavicula (8). Skin metastases are a form of distant metastases. They are defined as an isolated or multiple intradermal collection of tumor cells remote from the primary tumor or

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loco-regional disease. Skin metastases in patients with metastatic disease, including melanoma, from internal malignant tumors are not uncommon; we previously found that they accounted for <10% of all distant metastatic lesions (9). In patients with squamous cell carcinoma of the head and neck, skin metastases are rare, with incidence ranging from 0.76% to 2.4%. Most are sporadic cases, with the exception of two studies reporting a significant number of the cases (1,2). The site and the number of metastases vary, with the neck and chest being the most common sites. Yoskovich et al (2) reported on watershed characteristics of metastases distribution; however, they did not report any occurring below the level of the diaphragm (2). The development of skin metastases may be a consequence of aggressive nature of the tumor or may indicate patient's local resistance at typical distant metastatic sites.

We present three cases of the skin metastases of the squamous cell carcinoma from the head and neck as well as a patient with multiple nodular skin metastases above and below the level of the diaphragm. To the best of our knowledge, the latter is the first such case ever described.

SUBJECTS AND METHOD

There were 372 consecutive patients with squamous cell carcinoma hospitalized at the Department of Otorhinolaryngology and Cervicofacial Surgery, Slavonski Brod General Hospital, in the 1992-2002 period. Data collected from their medical records for the needs of analysis were the following: age, sex, tumor site and size, nodal status and stage, histologic grading, time of presentation of skin and distant metastases, and localization of metastases (Table 1). Skin metastases were differentiated clinically and histopathologically from other forms of skin involvement. Lesions of the epidermis, dermis, and immediate subcutaneous tissue were morphologically and histochemically compared with the primary squamous cell carcinoma.

RESULTS

Out of 372 patients with squamous cell carcinoma of the head and neck, four (0.93%, three men and a woman) developed skin metastases. At the time of presentation of the primary tumor, the average age of the patients was 56 years. Two of the patients who developed skin metastases had poorly differentiated invasive squamous cell carcinoma (G3) and the other two patients had moderately differentiated carcinoma (G3) with respect to their primary tumor. All of them had stage IV of the disease. They presented with skin metastases in the period between 0 and 40 months. None of them were alive a year after the development of skin metastases. The sites of development of the skin metastases included the neck, chest, face, back, and arm, above the level of the diaphragm; and abdomen, pelvis, and legs below the level of the diaphragm. The patient with poorly differentiated squamous cell carcinoma (G3) in the cervical part of the esophagus developed multiple skin metastases above and below the diaphragm (Figs. 1 and 2). In this patient, no other tumors but esophageal carcinoma were found on additional clinical examination. He had no clinically evident local or regional metastasis, but developed distant metastases in liver. His general condition was very poor because he had very serious associated illnesses. The patient did not receive any kind of therapy and

Table 1. Clinical features of the primary carcinoma and skin metastases*

Gender	Site	HG	TNM	Stage	APP	TPSM	Site SM	Site DM	RLM
F	oral cavity	G2	T1N3a	IV	69	3	neck, chest		neck
M	oral cavity	G3	T3N2c	IV	48	40	neck, chest	axilla, mediastinum	neck
M	oesophagus	G3	T3N0	IV	50	0	face, chest, back, arm, abdomen, pelvis, leg	liver	M
M	laryngo-pharynx	G2	T4N1	IV	58	10	neck, chest		neck

*Abbreviations: HG = histologic grade; APP = age at presentation of primary lesion (years); TPSM = time of presentation of skin metastasis after the presentation of primary lesion (months); site SM = site of the skin metastases; site DM = site of the distant metastases; site RLM = site of the regional lymph node metastases.

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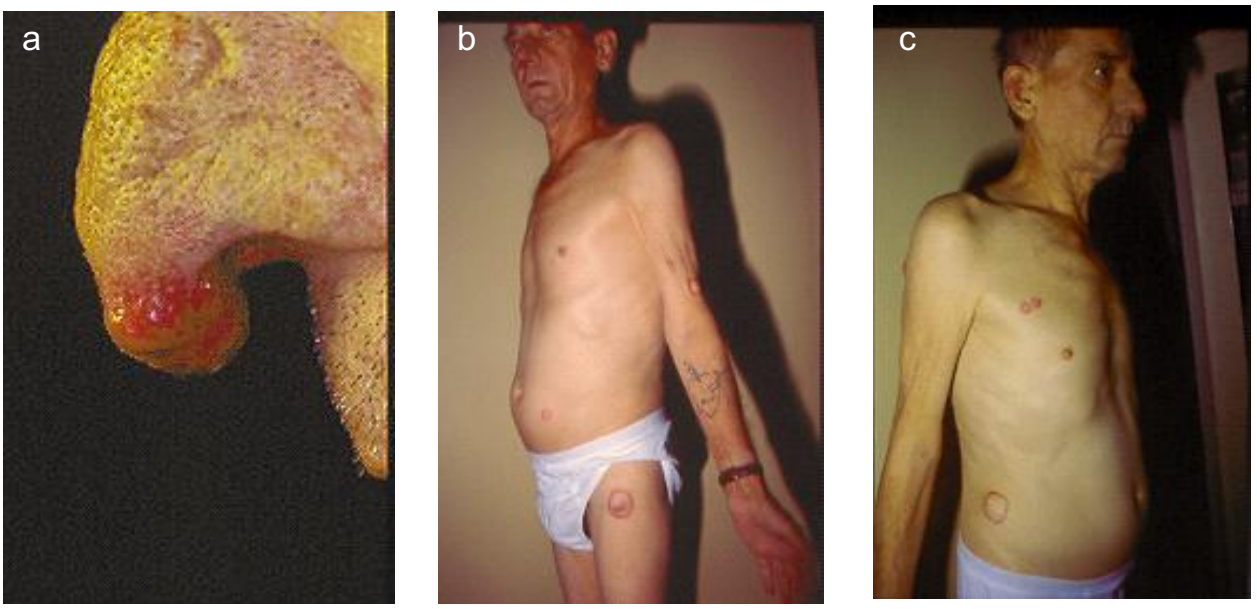

Figure 1. Tumor (skin metastasis) on the apex of the nose (a) is the first presentation of the esophageal carcinoma and skin metastases above (b) and below (c) the level of the diaphragm.

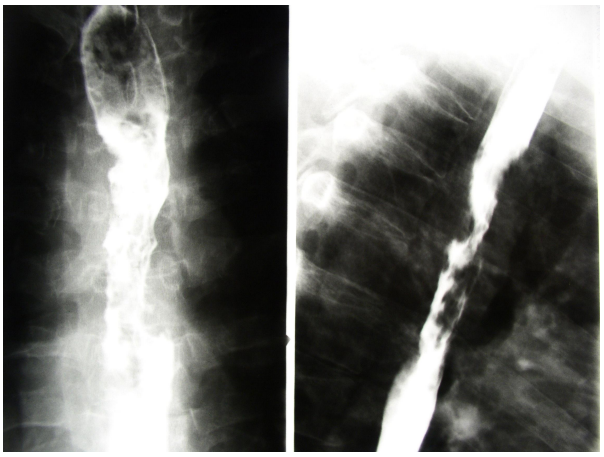

Figure 2. X-ray finding of primary squamous cell carcinoma of the esophagus.

died 4 months later. Two patients with the primary carcinoma of oral cavity had neck metastases in the time of the presentation of primary tumor. They were first treated with radiotherapy and chemotherapy. One of them died after 6 months due to the progression of the metastatic disease, and the other developed metastasis in the neck and distant metastases in the axilla 23 months later. He underwent radical dissection of the neck and lymphadenectomy of the axilla and received another round of radiotherapy with chemotherapy. After 17 months, the patient developed distant metastases in the mediastinum and skin metastases on the neck and chest, and died 3 months later. Patient with laryngeal carcinoma died 10 months after laryngectomy and radiotherapy because of local tumor progression and regional metastases in the neck and distant in the chest.

DISCUSSION

The mechanism of the development and appearance of skin metastases is not completely understood. Prior retrospective clinical study suggested that skin metastases might evolve by different mechanism. When metastases arise in the head and neck region, the spread of tumor cells can occur through local dermal lymphatic network. Distant metastases are thought to spread by blood. Perineurial spread can also be a possible route for metastases to the skin (2,10). «Metastasis from metastasis» presumes aggressive nature of tumor and high frequency of associated distant metastatic lesions (11). New and highly sensitive immunohistochemical methods, molecular analyses, and techniques of cell culture may improve the detection of distant micrometastases in head and neck cancer (12,13).

Skin metastases may occur in local, regional, and distant sites, but most frequently they occur in the vicinity of the primary tumor and some tumors metastasize with predilection to specific areas (14).

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Local skin metastases may develop in scars at a surgical incision site (9). Skin metastases from squamous cell carcinoma of the head and neck appear to have watershed characteristics; extremely rare cases have been reported with skin metastases below the level of the diaphragm. Reviewing the literature, we found two such cases (9,15). In both reports, primary tumors were squamous cell carcinoma of the larynx and skin metastases occurred in the anterior wall of the abdomen like solitary subcutaneous nodule. Our patient with the carcinoma of the cervical part of the esophagus developed multiple skin metastases that presented as subcutaneous nodules above the level of the diaphragm (on the face, chest, and arms) and below the level of the diaphragm (on the abdomen, pelvis, and leg). No other tumors, except for the carcinoma of the cervical esophagus, were found in this case. There was no evidence of loco-regional spread of tumor, but the patient developed distant metastases in liver. Skin metastases were the first clinical indicator of disease in apparently disease-free patient, leading to the earlier discovery of the local malignant disease. Multiple skin metastases above and below the level of the diaphragm may develop due to aggressive nature of the tumor or indicate patient's local resistance at typical distant metastatic sites, such as the lung and liver. In a very small percentage of cases, metastases may be discovered at the some time or prior to the diagnosis of a primary tumor. Lookingbill et al (9) found that 0.6% patients developed skin metastases as the first sign of internal carcinoma. The development and appearance of skin metastases is similar in severity to the development of other distant metastases in other cases. The histology of the metastases is similar to the primary tumor, although metastases may be more anaplastic and less differentiated.

The true skin metastases from squamous cell carcinoma from the head and neck must be differentiated from other skin malignancies or malignancies associated with or affecting the skin, because they have different prognosis. These malignancies included tumors with direct spread in skin or metastasis from cutaneous squamous cell carcinoma. Recurrence in previously operated neck portends a poor prognosis (15). Inadequate clearance of lymph-bearing tissue from dissected levels in the neck may also account for tumor recurrence. One possible complication of the aspiration biopsy of malignant tumor is dissemination of tumor cells along the needle track or tumor implantation into the incision site at the time of surgery. As the use of endoscopic surgical technique for the management of malignances has increased over the last years, metastases developing at the troacar insertion site became an emerging problem (16,17).

In conclusion, skin metastases from squamous cell carcinoma of the head and neck are uncommon and in some cases, the first sign of the cancer disease. They can occur above and below the level of the diaphragm and early recognition can lead to timely treatment. The treatment is palliative, it must be individualized, and prognosis for patients with skin metastases is poor. A better understanding of the biology of tumor invasion and metastasis occurrence may lead to the development of new, more effective strategies in prevention of secondary tumors.

Acknowledgments

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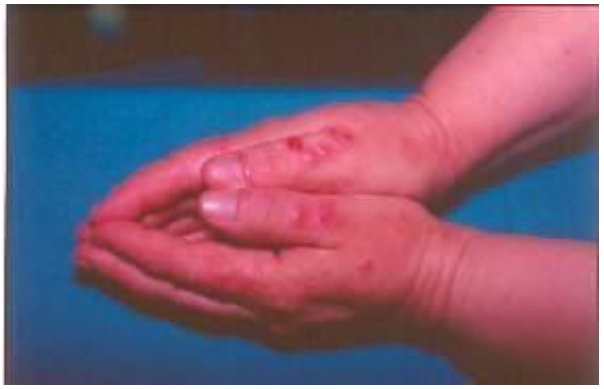
ERRATUM ADC 2003;11(2):76

In the paper “Frequency of standard and occucpational contact allergens in Tuzla area, Bosnia and Hercegovina: retrospective study” bypublished in Vol 11, No. 2 of Acta Dermatovenerologica Croatica, Figure 1 was incorrectlys printed. For the reader’s convenience, the correct picture is provided below.



Acta Dermatovenerol Croat 2003;11(3):158-162 REVIEW

SUNSCREENS – THE ULTIMATE COSMETIC

Ronni Wolf[1], Hagit Matz[1,2], Edith Orion[1], Jasna Lipozenčić[3]

[1]Dermatology Unit, Kaplan Medical Center, Rechovot, Israel;
[2]Department of Dermatology, Tel-Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel;
[3]Department of Dermatology and Venerology, Zagreb University Hospital Center, Zagreb, Croatia

Corresponding author:

Prof. Ronni Wolf, M.D., Ph.D.

Head of Dermatology Unit

Kaplan Medical Center

76100 Rechovot, Israel

wolf_r@netvision.net.il

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SUMMARY One decade ago, a sun protection factor (SPF) of 15 was considered a complete blocker of ultraviolet radiation (UV). The logic behind that cutoff point was that sunscreens with this SPF number would always prevent erythema and that preventing erythema would prevent all the ill effects of UV exposure. Today, we know that both of these assumptions were wrong and we tend to recommend higher SPF. Consumers apply only about one-quarter to one-half thickness of the layer of sunscreen material used to measure the SPF in the laboratory. That means that less than 50% of the SPF number claimed on the label is spread on the consumer's skin, meaning that a sunscreen with an SPF 30 will give the real protection of an SPF of 15. Therefore, recommend 60 when you want a real protection of 30! Significant injury, DNA damage, mutations, and carcinogenesis can and do occur also with cumulative suberythemal UV exposure. Thus, erythema induction, a criterion that defines SPF, is not a good indicator of UV damage. We also need higher SPF values to prevent the damage caused by suberythemal doses of UV. The value of the SPF claimed on the label is diminished by environmental factors that are not taken into account during SPF measurements in the laboratory, such as sweating, water immersion, rubbing off, and photodegradation. There are some misunderstandings and confusion about the mode of action of physical sunscreens. It was originally considered that, in contrast to organic sunscreens, the inorganic metal oxides (zinc oxide and titanium dioxide) acted as scatterers or reflectors of UV light, as a mirror. This is not the case with modern micronized forms of metal oxides. It has been shown that both zinc oxide and titanium dioxide mobilize electrons within their atomic structure while absorbing UV radiation. Thus, although metallic oxides are not inert per se, in their coated form they are stable, non-toxic, and safe and they act as highly efficient UV attenuators. Therefore, we recommend our patients to use this type of sunscreens. We should exert all our influence upon our patients not to expose themselves to excessive sunlight, to routinely use generous layers of sunscreen agents, and to wear protective clothing. To wait for the dust to settle around the issue of the effectiveness of sunscreens in preventing melanoma, while the ideal sunscreens - topical, systemic, whatever - are at our disposal, is a luxury we cannot afford.

KEY WORDS sunlight; sunscreening agents; skin; ultraviolet rays

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INTRODUCTION

Our paper will be brief, but it will touch upon one of the hottest subjects in the universe, the sun, and how to shield the protective covering and most extensive organ of the human body, the skin, against the damaging effects of sunlight.

For hundreds of years, it was social snobbery – not sunscreens – that protected the rich from having their skin damaged by sun. A bronzed face and hands were the telltale signs of poor, of those who labored beneath the sun. Then one day in the 1920s, the doyen of fashion, Coco Chanel, returned from a Palm Beach vacation with a suntan, and the bronzed look suddenly ceased to be lower class stigma and became upper class chic. It was another French Revolution!

The parasols were put away and the beaches and poolsides packed with sun worshippers. The bathing suits became skimpier and skimpier, and the bikini, let alone the topless, exposed more and more flesh to be baked and fried under the sun. As economic conditions improved, even "ordinary" people had more leisure time, took longer holidays, and became involved in outdoor activities. Such newly defined signs of success, appeal, and beauty turned out to be a lethal combination too often when it came to health.

Then, around two decades ago, the men in the laboratories who were apparently insensitive to social pressures had the temerity to cast shadows on "healthy" sunshine and even went so far as to emphasize its damaging, harmful, and carcinogenic effects. The golden tan not only paled, but became an enemy. The data were so irrefutable that the public had no other choice but either to give up their long-cherished solar rituals and protect themselves or risk major health problems. The overwhelming majority finally became convinced that there was no "healthy" tan, and no "healthy sunshine", and accepted the verdict of medical research that it was a matter of "fry now and pay later".

For most of us who made outdoor activities an integral part of a normal, healthy lifestyle, the change has been easier said than done. Count Dracula had to go to great lengths to manage his schedule and escape the sun, but few of us ordinary mortals could, or would even want to, do anything similar. This created an urgent need for effective photoprotective measures. To our good luck, the promise of enormous profits from photoprotective agents galvanized the sunscreen manufacturers. The discovery of the solutions, however, is no less a real testimony to the use of chemistry for improving the quality of life of millions of people all over the world.

Although sunscreen formulation and production are guided by well-based and proven scientific and theoretical considerations for the sake of the users and their well-being, the process is also vigorously motivated by economic, commercial, and business interests that form the backbone of a worldwide, multibillion-dollar industry. The shelves offer such a wide range of choices that recommending a sunscreen is like finding one's way alone through a minefield in no-man's land. We will try to help you to navigate through this minefield and we will highlight the essential points of the rational use of sunscreens.

HOW HIGH SPF SHOULD WE RECOMMEND TO OUR PATIENTS?

One decade ago, an SPF of 15 was considered a complete UV blocker. The logic behind that cutoff point was that these sunscreens would always prevent erythema and that preventing erythema would prevent all the ill effects of UV exposure (1). Today we know that both of these assumptions were wrong and we tend to recommend higher factors. Most currently popular sunscreens have an SPF between 15 to 35, and it is not uncommon to find products claiming to have a factor of 50 or 70, or even higher.

The Food and Drug Administration has recently set a limit of 30 as the optimally recommended SPF value and the upper limit for approved SPF labeling. Products with the SPF above 30 will be labeled as having SPF "30 plus" (2), because the additional benefit derived from using sunscreen formulations with an SPF above 30 is outweighed by the potential risks of exposing the skin to a higher concentration of sunscreen ingredients as well as the increase in the costs of the products. The mathematics here are actually very deceptive: increasing the SPF of a product over 15 theoretically adds very little to its blocking capacity! For example, increa-

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sing the SPF from 30 to 40 will increase its capacity to block UV by only 1%, i.e., from 96.7% to 97.5%. But that difference in 10 points and increased benefit of 1% means far more chemicals on the skin and much higher prices.

These numbers are theoretical extrapolations and it would be careless not to defend the belief that sunscreens with the SPF 15 are optimal blockers and the ones we should recommend. This reasoning is based on the following considerations:

1. A number of studies have shown that consumers apply only about one-quarter to one-half thickness of the layer of sunscreen material used to measure the SPF in the laboratory (3). This means that the actual SPF spread on the consumer's skin is less than 50% of the SPF number appearing on the label, meaning that a sunscreen with an SPF 30 will give the real protection of an SPF 15. So, recommend 30 when you want a real protection of 15!

2. We now know that significant injury, DNA damage, mutations, and carcinogenesis can and do occur with cumulative suberythemal UV exposure. Thus, erythema induction, a criterion that defines the SPF, is not a good indicator of UV damage. We need higher SPF values to prevent the damage caused also by suberythemal doses of UV (1).

3. The value of the SPF number stated on the label is diminished by environmental factors not taken into consideration during SPF measurements in the laboratory, such as sweating, water immersion, rubbing off, and photodegradation of the active ingredients that is not related to their fading from the skin (4,5).

CHEMICAL *VS.* PHYSICAL INGREDIENTS – WHICH TO ADVOCATE?

Sunscreen chemicals contain conjugate double bonds. This configuration permits electron delocalization to occur throughout the molecule. This process absorbs light at comparatively low energies in the UV wavelength range. At this point, the electromagnetic energy is converted into chemical energy, which is stored in the molecule. The molecule is now in an excited and chemically unstable state and might react with other ingredients of the sunscreen or with organic tissue compounds, and cause damage. As the molecule in the excited state returns to the ground state, energy is emitted in lower magnitude, for example, in the infrared region.

There are some misunderstandings and confusion about the mode of action of physical sunscreens. It was originally considered that, in contrast to organic sunscreens, the inorganic metal oxides (zinc oxide and titanium dioxide) acted as mere scatterers or reflectors of UV light, as a mirror. This is not the case with modern micronized forms of metal oxides. Another and more far-reaching misconception is that they are inert materials that do not undergo any chemical change while attenuating UV light. Things go so far that some of these products bear the claim of being "chemical-free", which is absurd.

Both zinc oxide and titanium dioxide mobilize electrons within their atomic structure while absorbing UV radiation. The absorbed energy results in mobilization and transition of electrons from one part of the molecule (creating a "hole") to the other (creating excited electrons), both of which are chemically unstable and active. When the electron returns to its lower energy band, it emits energy in a lower frequency than the excitation energy, and this is exactly what happens with organic sunscreens. Although more than 90% of these electrons return back to their original band within nanoseconds, some do not, and these might react with water and organic compounds, forming free radicals. Again, it is similar to what happens with organic sunscreens (6-8).

So if the physical or particulate sunscreens absorb light by the same mechanism as the chemical ones and are not inert materials that just reflect and scatter light, what is the difference between the two and do the physical sunscreens have any advantage? The answer is – there is a difference in favor of the physical sunscreens!

The reason is that the metallic oxides in sunscreens are always coated with silicone or other materials. In this form, their photoreactivity and their ability to react with living tissues is nearly nonexistent. Furthermore, it has been shown that metallic oxides do not penetrate the stratum corneum and thus do not cause any harm to living cells

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of the epidermis. So, although metallic oxides are not inert per se, they are stable, non-toxic, and safe in their coated form as well as they are highly efficient UV attenuators. Although they are "newcomers" to the market, they have already become considerably popular and will most probably continue to enjoy the fine reputation they deserve in future.

THE QUESTION OF REAPPLICATION

Sunscreen performance is often tested in air-conditioned laboratories under artificial light. It is inevitable, then, that the most frequently used models have only limited ability to incorporate behavioral and environmental variables. Therefore, they have limited reliability and predictive value. There are few studies on the efficacy of sunscreen reapplication, and even fewer involved in comparing the effect of various regimens and their reapplication (9).

While it is quite clear that one cannot gain extra or additional SPF values from reapplication of a sunscreen, the reapplication might well assure the presence of a given SPF on the skin for a longer period of time, since the SPF of sunscreens decreases due to environmental factors and photodegradation (4,10).

The use of sunscreens, however, carries risks that could be explained by the theory on human behavior and risk management, called "risk compensation" or "risk homeostasis"(11). This means that the use of seat belts would be compensated by riskier driving; the use of condoms would increase the number of different sexual partners; the improvement in the treatment of human immunodeficiency virus (HIV) infection would lead to the higher exposure to unsafe sex (11); and the morning after pill would allow carelessness the night before. Several convincing studies have shown that the use of sunscreens was associated with an increase in the duration of recreational sun exposure (12). It was suggested that sunscreen use might even encourage prolonged sun exposure because it delays sunburn. This tendency might also explain why there are a so many epidemiological studies showing that the use of sunscreens did not reduce the incidence of melanoma, but even increased it.

There is a clear and urgent need for a wise and appropriate education policy to avoid the scenario in which behavioral adaptation may decrease the influence and benefits of sunscreen-promotion policy. Also, the authorities should prohibit the appearance of gorgeous suntanned models in sunscreen advertisements and replace them with gorgeous pale models...

CONCLUSION

Sunscreens are and will remain the ultimate cosmetic and we should not reverse a decade-long policy or stop recommending sunscreens on the basis of some epidemiological studies whose results indicated that sunscreen use may not protect against melanoma, or may even increase its risk. We should instruct our patients not to expose themselves to excessive sunlight, to routinely use generous layers of sunscreen agents, and to wear protective clothing.

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Advertisement for KRAMER thermometers, from 1937.
From the collection of Stella Ferenčić-Fatović, M.D., Ph.D.

Acta Dermatovenerol Croat 2003;11(3):163-170 REVIEW

TREATMENT OF VITILIGO: CURRENT METHODS AND NEW APPROACHES

Krešimir Kostović, Ivana Nola, Željana Bučan, Mirna Šitum

Department of Dermatology and Venerology, Sisters of Mercy University Hospital, Zagreb, Croatia

Corresponding author:

Krešimir Kostović, M.D.

Department of Dermatology and Venerology

Sisters of Mercy University Hospital

Vinogradska cesta 29

HR-10000 Zagreb, Croatia

kreso.kostovic@zg.hinet.hr

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SUMMARY Vitiligo is an acquired idiopathic hypomelanotic disorder characterized by circumscribed depigmented maculae. It can be treated in many ways. The choice of therapy is individually adjusted depending on various factors, such as the patient age, type and stage of disease, and affected body site. Current treatment modalities include psoralen with exposure to ultraviolet A (PUVA) radiation therapy, narrow-band UVB therapy, topical corticosteroids, depigmentation therapy with monobenzylether of hydroquinone, and surgical treatments (minigrafting, thin split-thickness grafting, suction blister grafting, micropigmentation). There are also some new treatment modalities, such as 308-nm excimer laser, vitamin D analogues, tacrolimus, depigmentation with Q-switched ruby laser, and grafting of cultured melanocytes.

KEY WORDS immunosuppressive agents; lasers; photochemotherapy; phototherapy; vitiligo

INTRODUCTION

Vitiligo is an acquired idiopathic hypomelanotic disorder characterized by circumscribed depigmented macules. Histologically, involved skin shows a loss of functional melanocytes and melanin within the epidermis (1). Vitiligo affects people of all races, with the incidence of 1-2% without sexual predilection (2).

There are several hypotheses on the pathogenesis of the disease, but not a single one is fully explanatory. The autoimmune hypothesis stems from the association of vitiligo with autoimmune disorders and the finding of antimelanocyte autoantibodies in some individuals (3-5). The neuronal theory suggests that a neurochemical mediator is responsible for destroying the melanocytes (6,7). In the self-destruction theory, it is proposed that melanocytes destroy themselves due to a defect in the natural protective mechanism that removes toxic melanin precursors (8,9).

The disease is categorized according to the extent of involvement and the distribution of depigmentation. Generalized vitiligo is the most common presentation, with bilateral, symmetric depigmentation of the face (especially periorificial

areas); neck; torso; extensor surfaces or bony prominences of the hands, wrists, and legs; axillae; and orifices or mucosal surfaces. Acrofacial vitiligo encompasses depigmentation of the distal fingers and facial orifices. Focal vitiligo describes depigmented maculae in a localized, non-dermatomal distribution. Segmental vitiligo occurs in a dermatomal, asymmetric distribution. Because of its earlier onset, recalcitrant course, and decreased association with autoimmune disease, segmental vitiligo is considered a special type of the disease. Universal vitiligo implies loss of pigment over the entire body surface area (10).

PHOTOTHERAPY

PUVA

Photochemotherapy is a therapeutic method that uses psoralen and exposure to ultraviolet (UV) A radiation (PUVA). Psoralens can be applied either topically ("topical PUVA") or orally ("oral PUVA"), followed by exposure to artificial UVA radiation. The most widely used photosensitizers for oral PUVA therapy are 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP). 8-MOP (0.6 mg/kg bodyweight) should be given two hours and 5-MOP (1.2 mg/kg bodyweight) one hour prior to UVA radiation exposure. 5-MOP is a less phototoxic agent. This reduced phototoxicity is important when treating a disease like vitiligo. The incidence and severity of adverse events, such as nausea, vomiting, pruritus, and erythema, is 2 to 11 times more frequent with 8-MOP than with 5-MOP (11). Both treatments are administered two to three times per week. An initial dose of UVA radiation is approximately 0.5 J/cm2 (2). Alternatively, the initial dose can also be based on minimal phototoxic dose (MPD) and it is about 75% of the MPD. PUVA is the most useful for extensive vitiligo, and the areas that respond most favorably are the face and trunk (10,12).

Although 70-80% of patients will experience the induction of pigment with oral psoralen treatments, less than 20% of patients have total repigmentation, and 30-40% of patients can expect to have only a partial treatment response (13-16).

Topical PUVA can be used in patients with less than 20% total body surface area depigmentation and has to be done very carefully because of phototoxicity (17). The preparation, which is usually in a form of solution or cream, is applied directly to the lesions typically 20 minutes before exposure to UVA. Initial UVA doses are about 0.25 J/cm2, with the same increments until mild erythema of the lesions is achieved (18). The advantages of topical PUVA are lack of gastrointestinal (nausea, vomiting) and hepatic (increased liver transaminases) side effects and no need for post-treatment eye photoprotection because there is no systemic photosensitization.

PUVASOL, which is commonly used in countries with abundance of sunlight and lack of the facilities for artificial sources of light, works on the same principle except that natural sunlight is used instead of UVA. The same types of oral and topical preparations are used. PUVASOL should be prescribed only to very conscientious patients who comply with dermatologist's instructions (2).

For all types of PUVA the recommended upper limit for the total number of treatments is 100-150, with a cumulative dose of 1,000-1,500 J/cm2 for white-skinned individuals (1).

Stimulation of melanocytes in the outer root sheath of the hair follicle in areas affected by vitiligo is the mechanism by which PUVA acts in repigmenting the white areas (19,20). It has been determined that this repigmentation occurs through the action of immune cytokines and inflammatory mediators released in the skin by keratinocytes in particular, as a consequence of PUVA therapy (20-25). These cytokines and mediators act as signals for melanocyte migration from the hair follicles.

Narrow-Band UVB

Narrow-band UVB is a more recent form of phototherapy. Narrow-band UVB lamp delivers almost exclusively 311-nm radiation. Treatments are given two to three times every week. The start dose is 0.10-0.25 J/cm2, with increments of 20% in each subsequent exposure until satisfactory erythema in the lesions is achieved (2, 26).

The advantages of narrow-band UVB over oral PUVA therapy include the following: shorter treatment time; no systemic effects since oral drugs are not required; less burning incidents; less contrast formation between depigmented and normal pigmented skin; no need for post-treatment eye photo-

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protection; and allowed use in children and pregnant and lactating women (27).

Westerhof and Nieuweboer-Krobotova (28) compared narrow-band UVB with topical PUVA. Repigmentation showed after 4 months in 46% of their patients in the group treated with topical PUVA and 67% of their patients in the 311-nm UVB treatment group. Two recent studies also showed favourable results with narrow-band UVB as a monotherapy (29,30). Scherschun et al (29) treated 7 patients with narrow-band UVB three times per week. Five of the seven patients achieved more than 75% repigmentation after a mean of 19 treatments. The remaining two patients had 50% and 40% repigmentation after 46 and 48 treatments, respectively. Njoo et al (30) treated 51 children with generalized vitiligo twice a week with narrow-band UVB for the maximum period of one year. The treatment resulted in more than 75% overall repigmentation in 53% of their patients.

Nowadays, narrow-band is considered as a first choice therapy for adults and children with generalized vitiligo (26).

308-nm Excimer Laser

The most recent form of phototherapy is 308-nm xenon chloride excimer laser, which emits coherent, monochromatic UV-B light in short pulses and delivers high doses of light to localized area (31). It allows treatment of hard-to-reach lesions, and unnecessary exposure of the surrounding, uninvolved, normal skin can be avoided. Baltas et al (31) treated four patients twice a week with excimer laser during six months, achieving 50-95% repigmentation in all four patients. In the most recent study, 18 patients with vitiligo were treated with 308-nm excimer laser three times per week for a maximum of 12 treatments (32). Twenty-three vitiligo patches from 12 patients received at least 6 treatments, which resulted in some degree of repigmentation in 57% of the treated patches. Eleven vitiligo patches from 6 patients received all 12 treatments and resulted in some degree of repigmentation in 82% of the treated patches. The degree of repigmentation in the period of two (57%) to four (82%) weeks was much higher than that achieved with any other present vitiligo therapy (32).

PAUVA

Phenylalanine, which is not phototoxic, has been tried for the treatment of vitiligo along with UVA (PAUVA). Camacho and Mazuecos (33) reported in their retrospective study on 193 patients treated with a combination of topical phenylalanine gel and oral phenylalanine an overall improvement rate of 83.1% with the maximum response on the face. Other reports reported lower success rates ranging from 14-44% (34,35).

IMMUNOMODULATING AGENTS

Corticosteroids

Topical corticosteroids are useful for the treatment of small, localized vitiliginous patches of recent onset. The best results are achieved on face and neck (26,36). High-potency steroids are used for the treatment of localized, depigmented areas for the period of 1 to 2 months, during which the therapy is slowly tapered to a lower-strength preparation (37). Several investigators reported that 32-58% of patients experienced full repigmentation of the vitiliginous areas and that an additional 16-40% of patients experienced partial repigmentation (38- 41).

Systemic corticosteroids can be helpful in arresting rapidly spreading disease, but they are less effective in inducing repigmentation (42,43). They are used in high-dose pulsed therapy. The role of systemic corticosteroids in the treatment of vitiligo remains controversial given the potential of causing serious adverse effects (2).

The mechanism of action of corticosteroids in vitiligo is unclear. It is often assumed that corticosteroids suppress inflammatory processes frequently observed in active progressive lesions (44).

The use of oral corticosteroids was associated with decreased serum levels of antimelanocyte antibodies among patients with active vitiligo (45,46).

Levamisole

Levamisole is an immunomodulating agent used for controlling slowly progressive disease. The mechanism of its action remains unknown, but it seems to be a safe mode of treatment. It is administered at doses of 150 mg on two consecutive days per week during 2-4 months. In an uncon-

trolled study on Indian patients (who overall respond better than lighter skinned patients to vitiligo remedies), the disease progression was arrested in 34 of 36 (94%) patients with active disease. A variable degree of repigmentation was seen in 64% of patients treated with levamisole (47).

Tacrolimus

Tacrolimus (FK 506) is the first topical immunomodulator to be approved for the therapy of atopic dermatitis. In a recent uncontrolled study, 6 patients with generalized vitiligo were treated with tacrolimus ointment. Excellent repigmentation was achieved only in a single patient, whereas moderate repigmentation of 50-75% was observed in other four patients after a treatment period of 1-5 months (48). In their case report, Smith et al (49) described a man with atopic dermatitis and vitiligo treated with tacrolimus ointment. Over 90% repigmentation of face and scalp was noted after 18 month of therapy, although the truncal areas showed no discernible improvement.

This treatment requires further confirmation, and control studies are needed to determine the efficacy and safety of topical tacrolimus in the treatment of vitiligo.

VITAMIN D ANALOUGES

Two recent studies have shown that topical calcipotriol potentiates efficacy of PUVA in the treatment of vitiligo (50,51). In another study, 17 our of 22 patients treated twice daily with calcipotriol as monotherapy showed 30-100% improvement after 3-9 months of therapy (52). However, Chiaverini et al (53) concluded on the basis of their results that topical calcipotriol in monotherapy was not an effective treatment of vitiligo.

It should be emphasized that most studies performed so far were small and poorly designed. Thus, the use of vitamin D analogues in vitiligo treatment remains a highly controversial issue.

COMBINATION TREATMENTS

Topical Corticosteroids With UVA

A combination therapy using a potent corticosteroid (fluticasone propionate) applied once daily and UVA irradiation performed twice weekly is an effective and well-tolerated method for repigmentation of localized vitiligo lesions (54). The combination therapy can lead to a higher percentage of repigmentation than either fluticasone propionate or UVA alone.

Pseudocatalase With Narrow-Band UVB

It was found that the concentration of catalase in the epidermis of patients with vitiligo is decreased (55,56). This finding led to the use of an interesting molecule, pseudocatalase, in vitiligo therapy, as pseudocatalase removes hydrogen peroxide from the depigmented epidermis.

Topical pseudocatalase, used in combination with UVB and a topical calcium preparation, has been reported in an open study to lead to complete repigmentation in 90% of treated patients (57). However, these results have not been confirmed in controlled studies. In an open single-center trial, Patel et al (58) found no clear evidence of the efficacy of the topical pseudocatalase (applied twice daily) with narrow-band UVB (twice weekly), but a slight tendency of worsening of vitiligo in almost all patients (58).

DEPIGMENTATION THERAPY

For patients with extensive areas of depigmentation (more than 80%) and/or disfiguring lesions on the face, who do not respond to repigmentation therapies, depigmentation of the residual melanin should be considered (26).

Monobenzylether of Hydroquinone

Monobenzylether of hydroquinone (MBEH) is the most commonly used agent to remove residual melanin in patients with vitiligo universalis. MBEH is a potent melanocytotoxic agent (59-62). It is used at 20% concentration and applied twice daily. Depending on the percentage of the residual pigmentation, 6 months to 2 years may be required to complete the therapy (26). There is a risk of depigmentation at distance sites and 15% of patients develop contact dermatitis (1,2,63); ochronosis is a rare complication (64).

Q-Switched Ruby Laser

Another form of depigmentation therapy for vitiligo uses a Q-switched ruby (QSR) laser apparatus. The QSR laser is capable of selectively dest-

roying melanin and melanin-containing structures in the skin (26). Depigmentation by laser therapy is reported to achieve faster depigmentation than depigmentation with a bleaching agent (65,66).

SURGICAL TREATMENTS

Surgical treatments are undertaken only for small, localized, recalcitrant lesions in vitiligo that bas been stable for many months. All procedures can be performed under local anesthesia. The general selection criteria for surgical treatments are non-responsiveness to medical therapy; stable vitiligo; absence of the Koebner phenomenon; positive minigrafting test; no tendency for scar or keloid formation; and age over 12 years (67,68).

Minigrafting

Multiple, small-punch biopsy specimens (1-2 mm) are obtained from a pigmented donor site (buttocks or hip) close together to minimize scarring and at the recipient treatment site, where the biopsy specimens are separated by 4 to 5 mm of vitiliginous skin (69-71). Erbium YAG laser can be used to prepare the recipient site (72). Subsequently, grafted areas are irradiated with PUVA to promote the outgrowth of pigment cells from the minigrafts (2,73). Complications at donor site may include light scarring, postinflammatory hyper- or hypopigmentation, and infection. At the recipient site, cobblestone effect (wrinkles in graft) and infection have been observed as adverse effects (71).

Thin Split-Thickness Grafting

This technique allows the grafting of large areas in a relatively short time, with a minimum scarring in treated areas. It involves obtaining superficial normally pigmented skin by using a dermatome (74,75). The tissue obtained is then placed on vitiliginous patches, which have been prepared in a similar way or by dermabrasion. The success rate of this technique is >80% (2).

Suction Blister Grafting

In this technique, a blister is made on normally pigmented donor skin by the application of negative pressure. To produce a negative pressure of 200 mm for 2-3 h, special apparatus is required (76). The depigmented areas are denuded with liquid nitrogen or dermabrasion (12,77). Erbium YAG laser or CO2 laser can be used to prepare the recipient site (72-79). The roof of the blister, which contains the melanocytes, is snipped off with fine scissors and the harvested skin is simply placed on the recipient site and covered with non-adherent dressings. This technique is non-scarring since only the epidermis is used, whereas the dermis is left untouched (2,26). The mean success rate of this procedure is 87% (80).

Grafting of Cultured Melanocytes

During this procedure, autologous melanocytes are expanded by in vitro culturing techniques and transplanted into a previously denuded achromic skin area. It may represent an adequate method to repigment larger vitiliginous skin areas in the future. The major disadvantage of melanocyte transplantation lies in the complexity and cost of the culture systems and equipment needed to obtain the culture (12,26). Also, there is a concern about the possible effects the chemicals (tetradecanoylphorbol acetate, or TPA) used in culturing the cells might have on a post-transplantation transformation of normal melanocytes into malignant ones (81). Therefore, culturing of melanocytes in physiologic reagents is highly recommended, although it is very expensive (82,83).

Micropigmentation

This technique is an adaptation of the technique of permanent tattooing and may be helpful for very stable, recalcitrant, small lesions, especially on the lips, areolae, and hands (84). Pigments based on iron oxides are mixed to obtain a match as close as possible with the normal skin color (2,12).

CONCLUSION

Vitiligo can be treated in many ways. Unfortunately, not all patients respond to current treatment methods. The choice of therapy depends of individual characteristics of the patient: age, type and stage of disease, and affected body site. According to a recent meta-analysis, the guidelines for vitiligo should include topical corticosteroids for localized disease (excimer laser is a potential new therapy); narrow-band UVB (alternatively PUVA) for generalized vitiligo; surgical interventions for segmental, stable, and lip-tip vitiligo (around the

lips); and depigmentation with monobenzylether of hydroquinone or Q-switched ruby laser for residual pigmented maculae in vitiligo universalis (2,85).

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CANDIDA INFECTIONS TODAY – HOW BIG IS THE PROBLEM?

Ivana Nola, Lenka Oremović, Krešimir Kostović, Antica Soldo-Belić, Liborija Lugović

Department of Dermatology and Venerology, Sisters of Mercy University Hospital, Zagreb, Croatia

Corresponding author:

Ivana Nola, M.D., M.S.

Department of Dermatology and Venerology

Sisters of Mercy University Hospital

Vinogradska cesta 29

10000 Zagreb, Croatia

ivana_nola@hotmail.com

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SUMMARY Thirty years ago, superficial fungal infections were common, but systemic fungal infections were not as frequent as today. Since that time incidence in both superficial and systemic fungal infection has been increasing. The reasons are many. Due to advances in medicine, human life span is extended and many people suffer from various immunodeficiencies. Transplantation of organs and tissues, wide application of parenteral feeding and parenteral administration of drugs, infection with human immunodeficiency virus (HIV), and long-term peroral administration of antibiotics are the main reasons for appearance of many immunologic dysfunctions and thereby systemic fungal infections. The most usual predisposing factors for systemic fungal infection are skin and mucosal damage, hypofunction of T-cell-mediated immunity, decreased function of neutrophiles, long-term administration of corticosteroids, as well as dysfunction of microbial flora. Systemic fungal infections are a great problem, because they are very difficult to prove and to treat. This is why prevention of systemic infections is extremely important today, including the removal of predisposing factors as well as rational drug administration.

KEY WORDS antifungal agents; *Candida*; *Candida albicans*; candidiasis; causality

INTRODUCTION

Eighty percent of normal individuals harbor yeasts as commensals in the oropharynx, gastrointestinal tract, or vagina. Yeasts are rarely found on the normal skin, except in occluded intertriginous areas (subaxillary, groins, submammary, and intergluteal region) (1-5).

About thirty years ago, systemic fungal infections were extremely rare. Nowadays, the incidence of local and systemic fungal infections increases and the reasons for this are many (6). Due to advances in medicine human life span has extended. Many individuals suffer from immunodeficiencies. Administration of chemotherapeutical drugs, transplantation of organs, parenteral feeding, and parenteral drugs administration, infections with human immunodeficiency virus (HIV), and wide administration of antibiotics are the main reasons of immunological disorders and systemic fungal infections today. The most common predisposing factors for developing fungal infections are skin and mucosal damages, dysfunction of T-cells and

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neutrophiles, long-term administration of corticosteroids, and disturbance of microbial flora. Systemic fungal infections represent a great problem in the clinical practice as they are very severe diseases, sometimes very hard to prove, and often difficult to treat (3,5).

DEFINITION OF CANDIDOSIS

Candidosis (or candidiasis) is an infection, with protean clinical manifestations, caused by the yeast *Candida (C.) albicans* or occasionally by other species of the genus *Candida*. The infections are usually confined to the skin, nails, mucous membranes, and gastrointestinal tract but can also be systemic and involve multiple internal organs (1-6).

ETIOLOGY OF CANDIDOSIS

Among various species of the genus *Candida, C. albicans* is the most common cause of superficial and systemic candidiasis. *C. albicans* and *C. tropicalis* together make about 80% of the species isolated from medical specimens (7,8). The species of *Candida* have been graded by descending degree of pathogenicity as follows: *C. albicans, C. stellatoidea, C. tropicalis, C. parapsilosis, C. pseudotropicalis, C. glabrata, C. dubliniensis, C. guilliermondii, and C. krusei* (1,9).

C. albicans lives in the human digestive system. *Candida* is kept at low levels by “friendly” bacteria that feed on *Candida*, thus a balance in the body is maintained. Once the “friendly” bacteria have been destroyed, the yeast begins to overgrow and takes over the digestive system. It may break through the intestinal walls and spread to other areas of the body, such as sinuses, throat, reproductive organs, lungs, and skin. *Candida* also becomes a pathogen when, depending on its virulence and the state of the host’s immune system, it multiplies greatly and converts from the saprophytic form to the parasitic “mycelium phase”. Then it causes diseases of the skin, mucous membranes, and internal organs (1,8).

PATHOGENESIS OF CANDIDOSIS

The development of the diseases due to *Candida* species depends on the complex interaction between the innate pathogenicity of the yeast and the defense mechanisms of the host. Other important factors in the initiation of infection with *Candida* include adherence of the yeast to epithelial cells and subsequent invasion (10). Normal intact skin with its constant sloughing and regeneration provides an effective barrier against *Candida*. Skin surface lipids are also partly inhibitory. The damage of this barrier by mechanical means or occlusion facilitates infection. The mechanism of invasion is unclear but may involve elaboration of keratinolytic enzymes – phospholipases, or strain-specific proteolytic enzymes (11,12). Ultrastructurally, pseudohyphae can be seen penetrating intracellularly into corneocytes in clinical lesions consistent with candidiasis. Around the organisms a prominent clear space can be seen, suggesting an ongoing process of epithelial tissue lysis (13,14). It seems that mycelial growth predominates in invasive disease states, while the blastospore growth phase predominates in saprophytic states. Highly antigenic or toxic products of *Candida* are able to induce vigorous host response mechanisms that limit infection and produce the typical cutaneous manifestations of the disease at the same time. Such a mechanism may explain certain findings in systemic candidiasis (1-4).

The main part of host defense is prevention of adherence. Furthermore, in healthy people neutrophiles, eozinophiles, and monocytes that phagocytose and kill hyphe also have an important role in defense. Therefore, in host defense against Candida infection, cellular immunity is considered more important than humoral immunity (15,16). Recently, it has been found that neutrophiles excrete candidacide factors, e.g. myeloperoxidase. In the field of the humoral immunity great interest is dedicated to specific secretory immunoglobulin-A (anti-candida s-IgA) in saliva and serum (16).

Progress in medicine has also brought about immunological and systemic disorders related to very early or very advanced age. Certain systemic disorders (diabetes mellitus, Cushing’s disease, uremia), chemotherapy of malignant diseases, organ transplantation, wide application of parenteral feeding and parenteral therapy, HIV infections, and administration of antibiotics are the main reasons of increased incidence of systemic fungal infections (3,4).

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Main Pathogenetic Factors of Candidosis

Some people develop candidosis due to a combination of causes. Factors that favor candidosis are numerous. The most common are skin and mucosal damages, immunosuppression, neutropenia, endocrinopathies, malignant diseases, advanced age, pregnancy, and iatrogenic factors (Table 1.)(1-6,17).

Table 1. Most common factors that favor candidosis

Occlusion
Damage to the stratum corneum
Immunosuppression
Neutropenia
Endocrinopathies (diabetes mellitus and Cushing's disease)
Uremia and malignant diseases
Extremes of age, menstruation, and pregnancy
Iatrogenic factors (antibiotics, oral contraceptives, steroids, X – irradiation, indwelling catheters, and i.v. drug abuse) (4).

Skin damages and locally reduced microbial resistance of the skin and mucous membranes due to maceration and erosive intertrigo, napkin rash, damage to the acid mantle of the skin (particularly in obese people), and mechanical irritation of the mucous membranes by, for example, ill-fitting dentures facilitate *Candida* infection (1-4).

Any condition that weakens immune system can facilitate the onset of candidosis (e.g., intrinsic immunodeficiency states, such as DiGeorge syndrome, myeloperoxidase deficiency, Chadiak-Higashi syndrome, hyperimmunoglobulinemia E syndrome, chronic granulomatous diseases, AIDS) (18). Immunodeficiency, humoral and especially cell-mediated (which is the major fault in the rare disease of chronic mucocutaneous candidosis), is a frequent pathogenetic cause (4).

Although *Candida* is known to induce Th-1 clones that suppress IgE synthesis (19), serum concentration of IgE antibodies against *Candida* is often increased in atopic patients (20). IgE synthesis may be precipitated not only by enhancing interleukin 4 production, but also by reducing interferon gamma secretion (20). Thus, attention has recently been focused on fungi as aggravating factors in atopic dermatitis due to the frequent detection of IgE antibodies to fungi in these patients. In patients with atopic dermatitis, the rate of positive skin prick tests for *Candida* is high, like in other fungal infections, e.g., in *Malassezia* infection anti-Malassezia IgE antibodies are also high (21,22). Antifungal drugs improved the skin manifestations in patients with atopic dermatitis who had IgE antibodies against *Candida*; the serum IgE levels against *Candida* in these patients also decreased (23,24).

Neutropenic patients are particularly vulnerable because phagocytosis of the yeast depends on functioning of polymorphonuclear leukocytes and macrophages (4).

Endocrinological factors can be predisposing factors for *Candida* infections, which occur more often in patients with diabetes mellitus and Cushing's disease (1-4). The mechanism by which diabetes mellitus is believed to increase infection rates is through increased tissue glucose, altered yeast adhesion, and decreased phagocytosis (25).

Lack of proper digestive secretions can cause reduction in "friendly" bacteria. Constipation is also common in hypothyroidism. A drop in body temperature stops many different chemical reactions, some of which prevent *Candida* overgrowth (1-4).

Malignant diseases (lymphoma, leukemia, and malignant tumors) predispose patients to *Candida* infections.

In old age, infancy or during pregnancy candidosis often indicates a diminished state of defense of the host (1-3).

The *copper intrauterine device* (IUD) is another possible yeast promoter. Copper IUD users often develop excessive levels of copper in their tissues. Excess copper can depress the adrenal, thyroid, and immune systems of the body, making it more difficult for the body to resist yeast (8).

Nowadays *iatrogenic* factors are common causes of candidosis, such as long-term administration of antibiotics, oral birth control pills, cytostatics, and glucocorticoids (1-3).

Antibiotics are a common cause of *Candida* infections, because they destroy "friendly" as well as harmful bacteria. When antibiotics destroy "friendly" bacteria, *Candida* has a chance to begin to multiply. Anyone who has been treated with antibiotics for

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acne, major dental work, or any condition where antibiotic use has been frequent, i.e., for more than 7-10 days, is a candidate for *Candida* infection (1-3).

Cytostatics and *glucocorticoids* are also a common cause of candidosis today due to their immunosuppressive effect (2).

Oral birth control pills mostly contain the hormone estrogen. Supplemental estrogen in the synthetic form has been found to promote the growth of yeast (8).

Estrogen also plays role in women's susceptibility to *Candida* infections. *Candida* colonization of vaginal mucosa is estrogen-dependent and decreases sharply after menopause. In contrast, the likelihood of colonization increases during pregnancy by 25-33% (25). The widespread use of hormone replacement for reduction of osteoporosis and heart disease may cause an increasing trend in vulvovaginitis caused by *Candida* among older women (25).

Other causes of *Candida* infections are common tap water consumption, parasites and intestine worms, constipation, alcohol and excessive bowel cleansing as well as generalized malnutrition (Table 2.)(1-6,8).

Table 2. Other factors that favor candidosis

Copper intrauterine device (IUD)
Tap water consumption
Parasites and intestinal worms
Constipation
Drugs and alcohol
Excessive bowel cleansing
Occupation
Hyperhidrosis
Maceration
Heat
Iron deficiency
Generalized malnutrition
Acrodermatitis enteropathica
Intrinsic immunodeficiency states (DiGeorge syndrome, myeloperoxidase deficiency, Chëdiak-Higashi syndrome, hyperimmunoglobulinemia E syndrome, chronic granulomatous disease, and acquired immunodeficiency syndrome) (1-6,8).

Common tap water is rich in chlorine, which has been found to destroy "friendly" intestinal bacteria, leaving space for *Candida* to grow (8).

Parasites and intestinal worms destroy "friendly" bacteria in the intestines, making yeast overgrowth possible (8).

Constipation can lead to *Candida* infection, because a slow moving digestive tract becomes very alkaline and an alkaline environment is perfect for *Candida* overgrowth (8).

*Excessive use of alcoho*l can directly destroy "friendly" bacteria and allow yeast to grow. Beer, for example, can be a particular problem not because of it destructive effect on the intestinal bacteria, but primarily because of its maltose content. Yeast cells feed on maltose extremely well and grow very quickly (1-3).

CLINICAL MANIFESTATIONS OF CANDIDA INFECTIONS

Candida infections may be superficial but also may involve internal organs or cause candidemia (1-3).

Superficial Candidosis

Superficial candidosis is restricted to skin and mucosa. Symptoms are multifarious, but in most cases characteristic (2).

Cutaneous candidiasis occurs on moist cutaneous sites as localized infection (intertrigo, folliculitis, diaper dermatitis, pustular folliculitis, or paronychia) (1-3).

Mucosal candidiasis occurs in the oral cavity and/or oropharynx as acute pseudomembranous *candidiasis* or thrush, acute atrophic *candidiasis*, chronic atrophic candidiasis, cheilosis, chronic hyperplastic *candidiasis*, black hairy tongue, or median rhomboid glossitis; or in genital region as vulvovaginitis or balanitis (1-6,26-28). Thrush may present early in life, as *Candida*, presumably originating from the maternal birth canal, colonizes the mouth of the newborn. Thrush is the most common form of oral *candidiasis* and may affect up to 5% of newborns and 10% of hospitalized elderly patients, as well as patients with diabetes mellitus, malignan-

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cies, and immune deficiency states (2,18). It affects over 90% of patients with AIDS (29,30).

Acute atrophic candidiasis (antibiotic candidiasis) may occur *de novo* or after sloughing of pseudomembrane of thrush (1,2,4). It is commonly associated with broad-spectrum antibiotic administration, but can be also seen with the use of topical, inhaled, or systemic corticosteroids. The most common location is the dorsal surface of the tongue that presents with patchy depapillated areas with minimal pseudomembrane formation (2).

Chronic atrophic candidiasis (denture stomatitis) is a common form of oral candidiasis among denture wearers. The condition is characterized by chronic erythema and edema of the palatal mucosa in contact with the dentures. Angular cheilitis is commonly present as well (2,3,27).

Chronic mucocutaneous candidiasis (CMC) includes a heterogeneous group of clinical symptoms characterized by chronic, treatment-resistant, superficial *Candida* infections of the skin, nails, and oropharynx. In patients with this form of candidiasis, numerous immunologic defects have been described usually involving abnormalities in cell-mediated immunity, while humoral immunity is largely intact (1-4).

Cutaneous candidods are allergic cutaneous reactions ("id" reactions) to localized infections with *C. albicans* (1,2).

Candidosis of Internal Organs

Candidosis of internal organs is found more frequently in patients with immunodeficiencies and malignant tumors, as well as in the patients receiving chemotherapeutics.

The first symptom of candidosis of *esophagus* is pain behind sternum during swallowing, and the most common changes are aphthous lesions in the lower third of esophagus. The diagnosis can be made by esophagoscopy and microbiologic examination of the biopsy material. Candidosis can involve the whole gastrointestinal mucosa, from stomach to colon, and by further spreading it can cause systemic candidosis.

Candida peritonitis can develop in patients with lien transplantation, perforation of duodenal ulcer, and in patients on peritoneal dialysis. It is characterized by fever, pain in the abdomen, and clinical signs of peritoneal reaction.

Cystitis caused by *Candida* is very common in patients with urinary catheters, especially if they have been receiving antibiotics for a long time. If there is a high number of *Candida* in the urine, the infection can ascend and cause obstructive nephropathy or nephritis.

Candida can be found in sputum or in bronchial secrets in patients with *immunodeficiencies*, but without the signs of pneumonia. The most reliable method of diagnosis is biopsy (3).

Disseminated Candidiasis

Disseminated candidiasis is usually fatal and can develop in patients with neutropenia or in patients in terminal phase of malignant diseases. It usually involves kidneys, lungs, brain, meninges, liver, and adrenal glands (30). Characteristic clinical signs are fever, weakness, hypotension, tachycardia, dyspnea, hepatomegaly, and splenomegaly (3,29,30).

Candidemia

The clinical signs of candidemia are fever, weakness, hypotension, and signs of shock. It can be transient during disseminated candidosis or can occur in attacks and be complicated by sight disturbances, arthritis, osteomyelitis, or endocarditis. Diagnosis is made by finding Candida or its antibodies in the blood (1-3).

Other Manifestations of Candidosis

Candida infections may have over hundred symptoms, such as athlete's foot, jock itch, fungal infections on the skin or nails, prostatitis or vaginitis, diarrhea, constipation, abdominal distension, gas or flatulence, rectal itching or rash, colic, diaper rash, vaginal itch, kidney and bladder infections, sinus infections, itching skin, eczema, fatigue, flu-like symptoms, headaches, mucus in the stools, dry mouth, sore or blister in the mouth, bad breath, nasal congestion, nasal discharge, nasal itching, cough, burning or itching eyes, burning on urination, ear pain, food allergies or food reactions, general allergies, and hair loss (1-4,8).

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HISTOPATHOLOGY OF CANDIDOSIS

Common superficial candidiasis of the skin has as primary lesion a subcorneal pustule resembling that of impetigo. The fungal organisms are present in small amounts in the stratum corneum. They consist of mycelia and ovoid spores, some in a budding stage.

Candida granuloma is characterized by pronounced papillomatosis and hyperkeratosis, and a dense infiltrate of lymphocytes, plasma cells, neutrophiles, and foreign-body giant cells in the dermis (1-3).

DIAGNOSIS OF CANDIDOSIS

Diagnosis of superficial cutaneous *Candida* infection can be made on the basis of typical appearance of the clinical lesions and the presence of satellite vesicopustules, and confirmed by KOH examination and culture of skin scrapings (1,2).

Diagnosis of disseminated infections is not easy and can be made only in 10-40% of the patients. The identification of the pathogen by hemoculture and/or tissue biopsy is the most relevant method. Other option is by serological methods, by which antibodies, antigens, or metabolic products of fungi are traced in blood. Serological methods include indirect immunofluorescent method (IgG and IgM) of determination of *Candida* antigens (antigen of cell membrane, cytoplasmatic antigen), determination of metabolites of fungus (arabinitol), and determination of mitochondrial and chromosomal DNA of fungi (3).

TREATMENT OF CANDIDOSIS

Drugs used in management of cutaneous candidiasis include polyene antibiotics (nystatin cream, solution, or powder) and imidazoles (miconazole, clotrimazole or econazole, ketoconazole, itraconazole, and fluconazole). For local treatment, very convenient is 0.1% gentian violet, especially for mucosal infection in children and adults (25,34-36). Gentian violet is not used for newborns because it may irritate the infant's mouth (25).

Systemic *Candida* infections require parenteral administration of amphotericin, administration of ketoconazole *per os* or fluconazole *per os* or intravenously (3).

Amphotericin (fungizone) is a polyene antibiotic preparation derived from *Streptomyces nodosus* (1-3). It is insignificantly resorbed from the gut and therefore administered orally only in the treatment of fungal diseases of the gut. Whether administered intravenously or by infusion, amphotericin can reach the necessary concentration and spread in all tissues. It passes blood-brain barrier poorly, except in case of meningitis. Amphotericin is excreted very slowly, mainly by the kidneys. It is administered intravenously in infusion form and its administration is indicated in all forms of deep mycosis. In the treatment of mycotic meningitis it should be administered intrathecally. Treatment usually takes several weeks (3).

PREVENTION OF CANDIDOSIS

Prevention of candidosis consists of the removal of all predisposing factors. In superficial candidosis it consists of wearing suitable clothes, maintaining intertriginous regions dry, cleaning mouth and dentures properly, changing diapers frequently, and so on (1-3).

In prevention of systemic *Candida* infection, it is important to rationalize antibiotic administration, decrease application of corticosteroids (as much as possible), control diabetes mellitus, and reduce the use of intravenous and urinary catheters (3).

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NAPHTHALAN – A NATURAL MEDICINAL PRODUCT

Pero Vržogić, Želimir Ostrogović, Anđa Alajbeg

Naftalan Special Hospital for Medical Rehabilitation, Ivanić Grad, Croatia

Corresponding author:

Pero Vržogić, M.D.

Naftalan Special Hospital for

Medical Rehabilitation

Omladinska 23

10310 Ivanić Grad, Croatia

pero.vrzogic@zg.htnet.hr

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SUMMARY Naphthalan has long been known for its medicinal properties and beneficial effect in inflammatory diseases such as psoriasis, atopic dermatitis, and psoriatic dermatitis. Physicochemical analyses of the naphthalan found at the Križ oil field near Ivanić Grad in Croatia have shown it to be identical to the naphthalan from Baku, Azerbaijan, which has been used in the treatment of vulgar psoriasis since the beginning of the 20th century. At Naftalan Special Hospital for Medical Rehabilitation, naphthalan therapy has been used for 14 years. Experience acquired to date in the use of naphthalan in the management of squamous dermatoses and atopic dermatitis as well as inflammatory rheumatic diseases has shown favorable results that have been scientifically and professionally verified. Naphthalan is definitely a potent natural medicinal agent, which should be further investigated to confirm its usage in the treatment of these diseases as fully justified.

KEY WORDS naphthalanotherapy; baths; dermatologic agent; psoriasis; tars

INTRODUCTION

Everything springing from the earth is termed water or oil. According to this classification, naphthalan belongs to oils, or more precisely to naphthene-based oils. Today, the term “oil” reminds us of a power source, a fuel in our car tanks, and seems to be less conceivable as a medicinal agent. Therefore, it should be emphasized that oil was first recognized as a medicinal product, and only much later as a power source.

As early as the 1930’s, academician T. G. Pašaev tried to isolate naphthalan from industrial paraffin and naphthene oils and proposed the term ”naphthalan oil” for the product (1). According to current concepts, however, the term “earth mineral oil” seems most appropriate (1,2).

Naphthalan – Ancient Cure

The use of oil as a medicinal agent dates back to ancient Egyptians, Assyrians, and Babylonians (2). There are historical records on a number of oils that were used as medicinal agents (2). For example, on the Apsheron Peninsula, wandering surgeons used the “white or red Surahan oil”; the oil obtained from the Tagern Lake Bogem monks named “St. Quirinus oil”; North American Indians also used oil as a medicinal agent in wound healing and management of skin diseases (2). Pliny, a Roman naturalist and historian, provided initial information on the medicinal properties of oil in his book *Naturalis historia*, writing about the mineral oil used by the citizens of Agrigento (Sicily) in the management of

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skin lesions (1); the heavy Pennsylvanian oil, known as "Seneca oil", was successfully used in the treatment of skin diseases not so long ago; and the "light Parmesan oil", *oleum petroleum Italicum*, from Amian near Parma was used in the Middle Ages not only in Italy but throughout Europe (2,3).

A number of written documents dating from the Middle Ages deal with the results, indications, and contraindications of oil treatment, e.g., "Tafta" and "Mehzan – Uol Aravie" (1-3). Naphthalan wells were found between the Large and Small Caucasus Mountains, along the Kuru River in Azerbaijan. Naphthalan was also mentioned in a 700 years old document describing the great Hindus' ritual of offering sacrifice "for cure from awful diseases" (3).

There are many legends on the medicinal properties of naphthalan, the rumor on its curative effects having spread far and wide. Sick people frequented naphthalan wells to take naphthalan baths or simply apply it all over the body. Camel caravans passing naphthalan wells on their Silk Road, filled the goatskins with naphthalan and carried it on their way back to the Far East to sell it at fairs. That is why naphthalan first appeared as a medicinal product in the Oriental medicine. The term "naphthalan" has been postulated to derive from '*naft o lan*', which in the Orient means 'there where oil is" (2,3).

In the 13th century, the world traveler Marco Polo ran across naphthalan wells on his way to China and described them in his travel-book *Million, or Libre des merveilles du monde*, as large wells filled with oil that is not edible but is useful in the treatment of skin and joint diseases (4).

Beginnings of Naphthalan Products

Engineer Jeger, who stayed in Baku during the oil boom in 1895, learned about the medicinal properties of naphthalan by word of mouth, and went to see the wells (2). He decided to take them on lease and soon organized a tub treatment, also arranging for initial drills to provide adequate supply with naphthalan. In this way he ensured higher naphthalan supplies than those provided at the natural wells and soon started transporting it to Dresden, where he built a small plant for naphthalan processing and manufacture of naphthalan ointments and other products. At the same time, Professor List from Magdeburg embarked upon similar activities (1-8).

Thus, there were two naphthalan companies in Germany at the beginning of the 20th century: Naphthalan in Dresden and Naphthalan in Magdeburg, both manufacturing various standardized naphthalan-based products, such as well known Dresden ointment "skinlan", cosmetic creams, ointments for the treatment of burns, suntan oils, toothpaste, and so on. These products soon became very popular all over Europe, America, and Japan.

The Naphthalan Company from Dresden contributed greatly to wide knowledge about naphthalan by issuing a handbook on the use of naphthalan. Beside Jeger's commercial papers, this book brought more than 600 brief reports by the renowned physicians of the time on their experience with naphthalan. Professor Unna, a famous German dermatologist, said: "The one who has naphthalan has everything" (2).

At that time, naphthalan was introduced in the pharmacopoeia of many countries under the terms *Naphthalanum, Naphthalanum liquidum, Vaseline oduste saponifice*, and others (2). It was almost regularly available in pharmacies, mostly formulated as ointment, oil, or some other preparation. In the anthological pharmacology books by Martindale and Haagar, it is found under the terms "naphthalan" and "naphalan", referring to the same earth oil from the same well, only one of them was a product from Dresden, and the other from Magdeburg. Kottmaier's *Handbook of Practical Medicine*, published in 1967, recommends a magistral product containing 20% of naphthalan (9).

After the October Revolution in 1917, the borders between the USSR and the rest of the world were closed, and naphthalan fell into oblivion. However, it should be noted that dermatologists from the Zagreb University Department of Dermatology (Kogoj, Čajkovac, and others) continued prescribing magistral naphthalan-containing products that some pharmacies still used to prepare (10,12).

And what happened to naphthalan in Azerbaijan after the October Revolution?

Scientific elaboration of the use of naphthalan oil was launched as early as 1920, a health resort with 33 beds was opened in 1933, and Institute for the Study of Naphthalan Action and Utilization was founded at the Department of Balneology and Physical Medicine, School of Medicine in Baku in

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1938. Until 1982, Naftalan Health Resort had 5,600 beds, whereas 1,672 professional papers had been published and 49 doctoral dissertations defended on the topic of naphthalan (4-7). During the Second World War the solders were supplied with naphthalan ointment as medical remedy against frostbites, burns, dermatological diseases, and inflamed wounds.

Investigations in Naphthalan

The Institute of Balneology, Zagreb School of Medicine, and INA Laboratory of Chemistry, Zagreb, Croatia, confirmed the high conformity between the oils in Baku and Križ. An expert group was formed to visit the Department of Balneology in Baku, where they were provided with professional information, relevant literature, and the required amount of naphthalan. Then, a comparative study of naphthalan and Križ oil was designed consisting of the following:

a) clinical studies in the efficacy of local application of naphthalan performed at Department of Rehabilitation and Orthopedic Aids (Professor V. Mandić) and Department of Rheumatologic Diseases and Rehabilitation (Professor T. Dürrigl), Zagreb University Hospital Center; Department of Dermatovenereology, Dr. Kučić Rijeka University Hospital (Professor A. Vukas); and Department of Physical Medicine and Rehabilitation, Ivanić Grad Health Center; (Ž. Ostrogović, MD).

b) comparative chemical analyses at INA laboratories; and

c) testing for carcinogenicity at Ruđer Bošković Institute in Zagreb performed in three systems: cell cultures of human and animal origin (Hela and BHK cell lines), bacterial cultures (*Escherichia coli* C 600, *Escherichia coli* C-600 lambda), and laboratory animals (cross-bred mice).

The required answers were obtained in two years. Clinical results obtained by the follow-up of 770 patients with rheumatologic diseases and locomotor system impairment as well as skin diseases confirmed the data on Azerbaijan naphthalan efficacy. Chemical analysis showed significant similarity of Križ oil and the well-known naphthalan from Azerbaijan in all tested parameters. Two microbial systems and the expertise performed on animal cell cultures and laboratory animals showed that neither naphthalan nor Križ oil was carcinogenic. Thus, in 1978, we could finally state that we had the second source of the naphthalan medicinal oil in the world.

Naphthalan in Ivanić Grad

Naphthalan, an earth mineral oil, is a very rare and specific balneologic agent, which, along with thermomineral water, was an impetus to construct the Health Resort in Ivanić Grad. Thus, the Health Resort for Skin and Rheumatic Diseases and Rehabilitation opened in 1989 and accommodated first patients for naphthalan-based treatment (Fig. 1 and 2). Having a relatively modest capacity of 111 beds, but offering great therapeutic opportunities,

Figure 1. Naphthalan earth mineral oil in Ivanić Grad.

Figure 2. Naftalan Special Hospital for Medical Rehabilitation.

the Resort has made a breakthrough as a trustworthy and successful medical institution.

However, the mode of naphthalan application was not an easy issue to decide upon. The experi-

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ence from the Naphthalan Health Resort in Azerbaijan could not be used because, according to European criteria, application of native oil was not acceptable. Therefore, we have adopted Professor Pašaev's instructions from the literature. Pašaev ascribed naphthalan bioactive component to polycyclic naphthene carbohydrates and suggested removal of tar and aromatic content. Naphthalan therapy practiced at the Naphthalan Resort in Ivanić Grad is based on this principle. The refined naphthalan oil distillate of 283-432 °C is free from tar and other undesired substances, while the concentration of medicinal components is increased, because 4 liters of native naphthalan yield 1 liter of the purified agent. The use of this medicinal product is associated with a minimal rate of contraindications and possible side effects, whereas the application meets the required cosmetic and hygienic conditions. We use naphthalan tubs intended for sitting and lying posture (Fig. 3), where naphthalan is being regenerated, rinsed, and thermally "sterilized" during the session; therefore, the process of naphthalan application is automated (10,12,15-17).

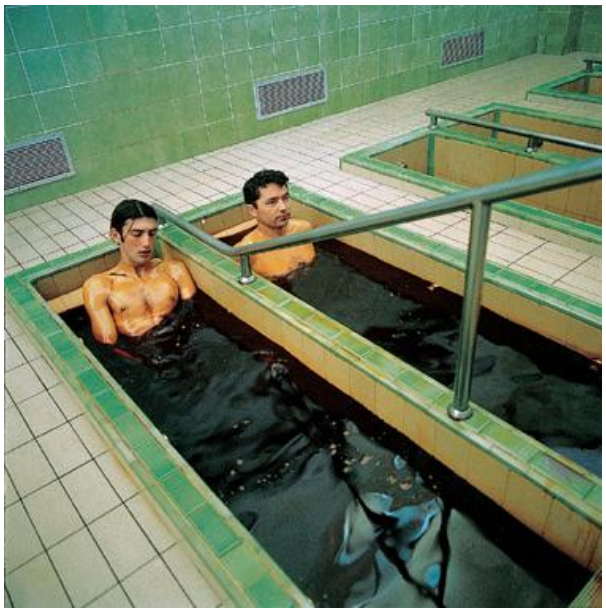

Figure 3. Naphthalan tub application in psoriatic patients.

PHYSICOCHEMICAL PROPERTIES OF NAPHTHALAN

Petroleum (oil) and its derivatives are rather complex mixtures of organic compounds, predominantly composed of carbon and hydrogen, and some heteroatoms (mostly nitrogen, sulfur, and oxygen) (18,19). Oil constituents belong to different compound classes: saturates (composed of acyclic and cyclic naphthene moieties), aromatics (compounds containing at least one aromatic ring), and polars (containing at least one heteroatom besides carbon and hydrogen). Oil components with high molecular mass, which precipitate in n-alkanes, are classified as asphaltenes.

Today, there are plenty of published data on the composition of oil (18-20). As analytical tools become ever more sophisticated regarding separation and sensitivity, the number of components thought to compose petroleum increases. Some classes of oligocyclicity, which belong to the so-called biological markers, are extensively investigated (21-24). These are complex organic compounds, which, during the process of petroleum generation in nature, have retained the chemical skeleton characteristics of the parent organic molecules (of biologic origin). They often occur among the variety of stereoisomers, which sensitively indicate the different stresses they had suffered (24).

For centuries petroleum has been considered to have curative properties, to accelerate skin and mucous membrane cell regeneration. Baths and preparations as ointments, pastes, liniments, and creams have been applied. Azerbaijani petroleum called "naphthalan" was used as antimicrobial and healing preparation for burns and injuries, for the treatment of eczema, arthritis, neurodermitis, skin fungi, and parasites (25). Therapeutic effects of naphthalan oil and its preparations have been intensively studied (26-30). Naphthalan baths are used for rheumatism and gout treatment and have also been reported effective in the treatment of some gynecologic diseases. Saturated petroleum oligocycles (naphthenes) were considered to be the main active ingredients in disease treatment.

Some encouraging results with preparations derived from the Croatian naphthalene oil have been reported in the treatment of psoriasis vulgaris and atopic eczema (24). The necessity of precaution in health service makes intensive research obligatory in order to enjoy the natural advantages and to minimize predictive hazards. To evaluate the Croatian naphthalene oil, a realistically based interdisciplin-

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ary study has been launched to bring, hopefully, some elucidation to the subject complexity.

Naphthalan oil belongs to "younger" oils than the industrial oil; it is of plant origin and is found in superficial layers of the earth (100-700 m depth). Native naphthalan springs as a thick, dark-brown liquid of a specific aromatic odor. It is classified among heavy oils for its high specific weight (0.93-0.98 at 15 °C). Naphthalan contains negligible concentrations of light benzine, ligroine and kerosine fractions, whereas condensed paraffins are only found in traces or not at all. It is characterized by high viscosity, 6.45 °E at 50 °C according to Engler, and contains 0.46% of sulfur and 0.11% of nitrogen, according to Kjeldal. Native oil contains 28% of tars, with condensation point at 21 °C and inflammable point at 110 °C. Naphthalan contains a relatively high concentration of naphthene acids (3%), among them a biostimulant cyclopentane acid and 1.32% of organic acids, which is why it is characterized by acidic reaction.

Naphthalan also contains a high percentage of naphthene carbohydrates (55%), 15% of aromatic carbohydrates, and no methane carbohydrates. Naphthene oil is characterized by high polycyclicity of naphthene carbohydrates, with a small number of carbon atoms in lateral chains constituting three-, tetra-, and pentacyclic compounds of the cyclopentanoperhydrophenanthrene structure, the most important being isoprenanes, steranes, and triterpanes. By their chemical structure, they closely resemble hormones, vitamins, and bioactive substances. The medicinal properties have just been ascribed to these polycyclic naphthene carbohydrates. Finally, naphthalan is neither skin irritant nor carcinogenic.

THERAPEUTIC EFFECTS OF NAPHTHALAN

In addition to mechanical and thermal effects, naphthalan has a very pronounced bioactive effect on the human body. The main bioactive components of naphthalan are polycyclic naphthene carbohydrates, consisting of 4, 5, or more rings of a characteristic cyclopentanoperhydrophenanthrene nucleus. This structure is very similar to some endocrine compounds, e.g., vitamins, hormones, and bioactive substances. Thus, it is postulated that naphthalan enters the body by the principle of substitution only to be involved in various physiologic and pathologic processes, i.e. in the humoral-hormone chains of the pathogenesis of various diseases.

Based on the 10-year clinical follow-up and observation of 10,000 patients, literature data, and laboratory and experimental studies, a number of naphthalan effects have been identified and described.

Anti-inflammatory Effect

The active substances from naphthalan penetrate through the skin to form compounds similar to the suprarenal gland mediators, which stimulate the function of the glands and act on corticosteroid synthesis. Laboratory findings confirm this activity, point to normalization of the inflammatory activity parameters, and suggest an effect on immune function. Clinically, suppression of inflammatory activity, reduction of edema and rubor, pain alleviation, general state improvement, and reduced severity and duration of "morning stiffness" are recorded in patients with inflammatory rheumatism who were treated with naphthalan. In skin diseases, reduction of infiltration and erythema is observed (29).

Antiproliferative Effect

Naphthalan exerts antiproliferative activity and decreases the immunocompetent cell counts in psoriatic lesions (30).

Stimulation of Terminal Keratinocyte Differentiation

Studies of the effects of naphthalan on in vitro proliferation and differentiation of keratinocytes were carried out at Department of Dermatology and Venereology, J. W. Goethe University Hospital in Frankfurt, Germany. The results pointed to the inhibition of keratinocyte proliferation, with a tendency to normalization in the psoriatic skin. These two facts suggest the naphthalan therapy to be a promising contribution in the management of psoriasis and atopic dermatitis (31).

No Toxic Effects

The experience from several-year follow-up of patients undergoing naphthalan therapy showed no

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therapy-related impairment of hematological and biochemical parameters (32).

METHODS OF NAPHTHALAN UTILIZATION

Naphthalan Bath

The patient is immersed up to the shoulders in the oil medium, at the temperature of 34-38 °C, for 8-14 minutes. Also, only parts of the body can be immersed in the bath or, instead of bath, naphthalan can be applied all over body surface.

Occlusive Naphthalan Dressing

This method is usually applied overnight on the psoriatic body areas with severe inflammation, infiltration, and thick scaling patches.

Iontophoresis with Naphthalan

The medicinal agent is introduced from the cathode into the affected area by galvanic current.

Sonophoresis

Naphthalan is applied as a contact medium between the ultrasonic head and target body area. Sonophoresis for small joints of the hand and foot is performed in naphthalan bath into which the ultrasound head is immersed.

Mastic Therapy

Mastic is a solid preparation of 30% naphthalan, which is applied in the form of compress or soaking in dissolved medium, as in the application of paraffin. This thermotherapeutic procedure produces hyperemia, considerably prolonged thermal effect, and pronounced consensual reaction. The measurements of skin temperature on the palm and dorsum of both hands before, during, and 20 and 60 minutes after therapy revealed that the temperature increased during therapy by 5.5 °C, exceeding initial temperature by 4.3 °C immediately upon therapy, by 2.5 °C at 20 minutes, and by 1.5 °C at 60 minutes. Upon the application of mastic, patients feel pleasant warmth, less warm than paraffin of the same temperature, which allows for the use of higher temperatures for therapeutic purpose.

Specific effects in rehabilitation in inflammatory rheumatism should also be emphasized, as this therapy results in pain alleviation, edema reduction, relaxation of musculature tension, and increase in previously restricted movements. The rate of solidification, i.e. lower or higher progressive resistance during rehabilitation treatment, is adjusted by modifying the volume ratio of the mastic product constituents.

INDICATIONS FOR THE USE OF NAPHTHALAN THERAPY

Naphthalan therapy can be used in the treatment of various diseases affecting different organs and organ systems. Skin diseases that respond well to the naphthalan therapy are atopic dermatitis, psoriasis, prurigo, ichthyosis, and scleroderma. Among musculoskeletal diseases, there are some inflammatory rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, and Bechterew's disease), degenerative diseases of joints and spine (arthrosis and vertebrogenous syndromes), and extra-articular rheumatism that can be treated with naphthalan. Naphthalan can also be applied in the treatment of peripheral nervous system diseases, such as neuritis, radiculitis, neuropathies, and paresis, and in the posttraumatic and postoperative rehabilitation of the locomotor system (contractures, postoperative infiltrates, circulatory disturbances, Sudeck syndrome, burns, and frostbites).

CONCLUSION

Naphthalan has long been known for its medicinal properties. Physicochemical analyses of the naphthalan found at the Križ oil field near Ivanić Grad have shown it to be identical to the naphthalan from Baku, Azerbaijan, which has been used in the treatment of vulgar psoriasis since the beginning of the 20th century.

At Naftalan Special Hospital for Medical Rehabilitation, naphthalan therapy has been used for 14 years, during which period numerous professional and scientific studies were performed. The experiences acquired to date in the use of naphthalan in the management of squamous dermatoses and atopic dermatitis as well as of inflammatory rheumatic diseases have shown favorable results that have been scientifically and professionally verified.

Naphthalan is definitely a potent natural medicinal agent calling for additional studies to confirm its

further usage in the treatment of these diseases as fully justified.

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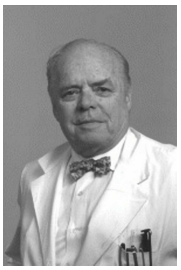

In Memoriam

THOMAS BERNHARD FITZPATRICK
(1919-2003)

E-mails from the ADA, sadly but necessarily, may be harbingers of bad news. When I opened my mailbox in the wee hours last night, I learned about the demise of Professor Thomas B. Fitzpatrick last Saturday. I was aware of Tom's suffering but the immutable finality of death commands awe. This is when history places a full stop in its narrative. TBF, as he was frequently referred to, is no more.

I knew Tom for 35 years, almost to the day, and it is just over thirty years that I stayed with the Fitzes while en route from Buffalo back to Vienna, about to pay my first visit to Harvard. My family and I could experience the fine hospitality and charm of the Fitzes' wonderful old home and the warmth Bea radiates at all times. And not much later we had the Fitzes in our home outside Vienna, with Franz Greiter, when the women went shopping for some very Central-Eastern European item, namely, a plumeau. The decades passed, the century ended, and ever so many personal encounters had followed.

Tom was a frugal personality, very curious and quick-witted. In conversation he did not weigh every sentence, nay, he weighed every single word and put invisible question marks behind, before he would believe it. Not too long ago, I heard Walter Shelley say that, when he was a resident, there were but four MD-PhD's in US dermatology, Tom Fitzpatrick, Aaron Lerner, Albert Kligman, and Shelley himself.

One of the Four Grand Old Men Has Gone.

I do not feel entitled to write a full obituary, others and worthier colleagues will do that. But let me elaborate for the readership of the Acta Dermatovenerologica Croatica what are some of the strong pillars to uphold his memory in the field. Tom was four decades with Harvard, twenty-seven years of which as chairman and Wigglesworth Professor of dermatology. He was a dedicated teacher, an almost omniscient dermatologist, a fine investigator and mentor to many. In tandem with Aaron Lerner, in neighboring Yale, he serendipitously formed sort of a tandem in pigment cell research. He was also active in another such trio, with Klaus Wolff and John Parrish, in the introduction of PUVA therapy with systemically administered psoralens. I well remember the Academy Meeting in December 1974 when the news about this regimen was broken on the front page of the New York Times. In this very month, TBF celebrated his 54th, and Klaus Wolff his 39th birthday. Lastly, the edition of Dermatology in General Medicine, the DIGM as it is called colloquially, is now in its 6th edition. This encyclopedic volume, two in fact per edition by now, has become a bible for investigators in, below, and beyond the skin. These achievements guarantee that his legacy will last many decades to come. Too bad that the late flower of the nineties, Fitzpatrick´s Journal of Clinical Dermatology, withered away after a short period, being so much a mirror of Tom senior and junior.

Innumerable honors have been bestowed upon Tom, which will not be detailed here. The Fitzpatrick Festschrift in the JID (Supplement 1983), is a good place to look up and most certainly now, upon his demise, other such texts will follow.

Tom's approach to problems, as much as his face and the sound of his voice, will remain before my mind as long as I can think. And so will be the image of his personality, the cabochon ruby peeking from the end of his watch chain running through the button holes of his gilet.

To Bea and the Junior Fitzes all our love and condolences go at this moment. May G-d grant them solace in these bitter days of mourning.

R.I.P.

August 19, 2003.

Karl Holubar, MD FRCP GSE
Institute for the History of Medicine
University of Vienna
Vienna, Austria

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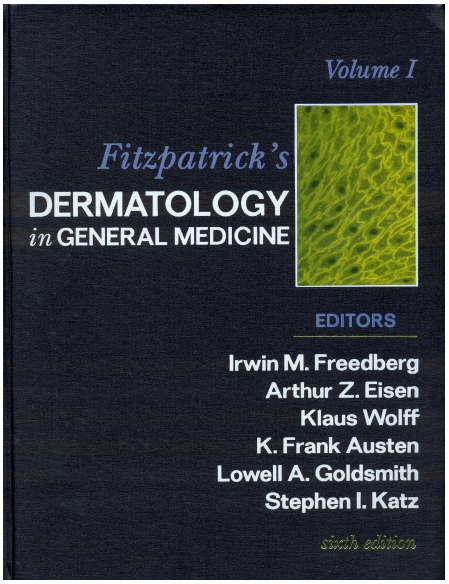
Announcement by the Editor

Just out: The Sixth Edition of Fitzpatrick's Dermatology in General Medicine (DIGM)

Every discipline has its heroes and its bibles. In dermatology, for most of us Thomas B. Fitzpatrick at Harvard was more than that. Established as one of the leading authorities in modern investigative dermatology, he became a symbol and the role model. Unfortunately, nobody is immortal. Heroes die, too. We learned about his death on August 16, 2003. The light of his work, however, remains a solace, and thus, the newest, sixth edition of DIGM in two volumes is the best way to keep his memory and ideas alive. The editors of this edition are some of the most prominent dermatologists (Irwin M. Freedberg, Arthur Z. Eisen, Klaus Wolff, K. Frank Austen, Lowell A. Goldsmith, and Stephen I. Katz), who were partly his close collaborators. For many of the contributors, it was and is both a confirmation of good reputation and an act of honor to write a chapter in this encyclopedia.

The sixth edition of DIGM covers advances in clinical dermatology as much as in basic sciences related to skin, and is also intended for physicians of other specialties for whom changes of the skin are important. The DIGM is truly encyclopedic in its width and depth, of which half a century ago nobody could even dream. It includes a new section on evidence-based dermatology, dealing with dermatologic changes through the stages of life. Notably so, illustrations are in color. The therapeutic sections have all been updated. Disorders thought to be only of historic importance, such as antrax and variola, are discussed, as well as dermatologic diseases as potential agents of mass destruction. Thus, the sixth edition of DIGM reflects the complexities of our age. There are 280 chapters, grouped into 37 sections covering all aspects of the science and care of the skin in health and disease.

Many of the chapters are completely new, and many rewritten. Part one consists of two sections – General Considerations and Introduction; part two – Biology and Development of Skin, of four sections; part three is entitled Disorders Presenting in the Skin and Mucous Membranes; part four – Dermatology and Medicine; and part five – Diseases



Due to Microbial Agents, Infestations, Bites and Stings, where Sexually transmitted diseases are included. Part six – Therapeutics, is presented in four sections divided in evidence-based dermatology, topical therapy, systemic therapy, and surgery in dermatology.

Notably, this is the second out of six editions of DIGM that carries a chapter on the history of dermatology, which is included at the beginning of volume I. It should be considered a matter of small pride to the Croatian medical community that this chapter is co-authored by Stella Fatović-Ferenčić, as another Croatian author, our colleague Mihael Skerlev, was a co-author of the chapters on viral diseases in the Fourth and Fifth edition of this great textbook.

Anyway, Fitzpartick's sixth edition, the DIGM, remains a testament to his vision of dermatology and a legacy of his activities.

A gentle reader and connoisseur of dermatology may wonder if the DIGM is to be preferred to the British encyclopedia, the Rook-Wilkinson. There is only one answer to that question: both should be on the shelves of any major dermatologic library.

Prof. Jasna Lipozenčić, MD., PhD.

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ANNUAL MEETING OF THE CROATIAN DERMATOVENEROLOGICAL SOCIETY

The Annual Meeting of the Croatian Dermatovenerological Society (CDS) was headed by its President Prof. Jasna Lipozenčić on May 31, 2003, at Plitvice Lakes. Highlights included the retrospective itinerary of congresses and symposiums organized by the Executive Board of CDS since 1999 and the decision to organize three Meetings in 2004. At the meeting on November 21, 2003, the same CDS Board will be chosen for the next four years.

The discussions were positive, such as those led by Prof. Mirna Šitum M.D., Ph.D. secretary and vice president, and Branka Marinović, M.D., Ph.D. vice president, and the future success of CSD was shared.

The meetings to be held in 2004 were proposed, as follows: **Update of Atopic Dermatitis**, April 2004, president Prof. Jasna Lipozenčić; **Psychodermatology** in September 2004, president Prof. Šitum; and **Immunosuppressants in Dermatology** in December, 2004, president Branka Marinović M.D, Ph.D., and Prof. Franjo Gruber M.D., Ph.D.

International Congress on "Topical Procedures, Innovations, and Mistreatments" held in Plitvice, May 29-31, 2003, was a big success, with over 260 in attendants from all over the world (17 countries).

Prof. Jasna Lipozenčić, M.D., Ph.D.

President of the CDS

RAVE company: Very gentle Lily soap recommended for sensitive skin of ladies and children.
From the collection of Stella Ferenčić-Fatović, M.D., Ph.D.

Under the auspices of the Croatian Academy of Medical Sciences

International Symposium

UPDATE ON ATOPIC ECZEMA/DERMATITIS SYNDROME

organized by

Section Dermatology of the European Academy of Allergy and Clinical Immunology

in cooperation with

Croatian Dermatovenerological Society of the Croatian Medical Association

Hotel Croatia, Cavtat/Dubrovnik, Croatia

www.cybermed.hr/4dermkh

April 25-28, 2004

Contact:

Jasna Lipozenčić (Zagreb)

Department of Dermatology and Venerology, Zagreb University Hospital Center, Šalata 4, 10000 Zagreb, Croatia

Phone/Fax: + 385-1-4920-014; e-mail: jasna.lipozencic@zg.tel.hr

International Symposium on

PSYCHODERMATOLOGY

Cavtat, Croatia

September 22-26, 2004

is organized by

Croatian Dermatovenerological Society of the Croatian Medical Association

Contact:

Mirna Šitum

Department of Dermatology and Venerology
Sisters of Mercy University Hospital
Vinogradska 29, 10000 Zagreb, Croatia
Tel. +385-1-3787-422; Fax. +385-1-3769-067
e-mail: mirna.situm@zg.hinet.hr; mirna.situm@htnet.hr

REPORT FROM HISTORICAL SATELLITE SYMPOSIUM VENERAL DISEASES: REALITIES AND TABOOS

Assist. Prof. Stella Fatović-Ferenčić was the main organizer of a very successful Historical Satellite Symposium – Veneral Diseases: Realities and Taboos, with international participation, which was held in Zagreb, May 28, 2003, in the Palace of Croatian Academy of Sciences and Arts, and dedicated to the memory of Academician Franjo Kogoj (1894-1983), the founder of dermatovenerology in Croatia, on the occasion of the 20th Anniversary of his death. The Symposium was held under the auspices of the Croatian Academy of Sciences and Arts, Department of Medical Sciences, Institute of History of Medical Sciences, Croatian Society for History of Medicine, and Croatian Dermatovenerological Society of the Croatian Medical Association. Academician Dragan Dekaris gave a warm welcome at the beginning of the Symposium. The president of Croatian Academy of Sciences and Arts Academician Ivo Padovan was also present. Prof. Jasna Lipozenčić, president of the Croatian Dermatovenerological Society welcomed all the attendees with the following words: “It is my pleasure to welcome you cordially on behalf of the Croatian Dermatovenerological Society of the Croatian Medical Association, here in the Palace of Croatian Academy of Sciences and Arts, Zagreb, on the occasion on 20th Anniversary of the death of Academician Franjo Kogoj, at Historical Satellite Symposium Venereal Diseases: Realities and Taboos. Croatian Dermatovenerological Society had an important and fare reaching influence on development of Croatian dermatovenerology. The Members participated enthusiastically on many levels, and some of them were internationally recognized. The most prominent of them was Franjo Kogoj. Contribution will be dedicated to the memory of Academician Franjo Kogoj. Many thanks to the Croatian Academy of Sciences and Arts and Assist. Prof. Stella Fatović-Ferenčić for the idea and organization of this Historical Symposium with International participation. It is honor for Croatian Dermatovenerological Society to be a co-organizer of this memorial Symposium.”

All lectures (nine of them) were interesting and presented by our colleagues from different medical specialties and presenters from abroad. Prof. Marcia Ramos-e-Silva (Rio de Janeiro) presented facial and oral aspects of some venereal and tropical diseases (Figs 1,2). It was a very instructive presentation. Dr. Michael Waugh (Leeds) gave an interesting lecture, “A historical study of why venereology and not dermatovenerology in Great Britain: an evolution”. Assist. Prof. Mihael Skerlev (Zagreb) held a presentation on HPV genital infections and what we really kn ow about them. Prof. Aleksandar Štulhofer (Zagreb) presented a short history of re-

Fig. 1. M. Ramos-e-Silva and J. Lipozenčić

Fig. 2. S. Fatović Ferenčić, M. Waugh, J. Lipozenčić

search in sexual risk-taking in Croatia and social impact in terms of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) prevention campaigns and sex education programs. Ana Marija Dürrigl and Stella Fatović-Ferenčić (Zagreb) shed light on some aspects of sexuall-related topics based on evidence from Croatian Glagolitic writing. Prof. Josip Begovac (Zagreb) with his presentation, "The success and failures in combating the HIV/AIDS epidemic", informed us on new advances in basic and clinical research in HIV infection. "The Skerlievo disease: between myth and reality" was presented by A. Muzur and A. Škrabonja (Rijeka).

Very impressive were lectures of two young students of history of medicine – Agata Maković (Zagreb) – "Aids in Public Journals; and M. Mišir (Osijek) – "AIDS in Biomedicine Journals in Croatia". Most Croatian medical journals were a good source of quality information about AIDS in our country long before first patients appeared in our hospitals.

In spite of multidisciplinary participation, we believe that this Historical Symposium proved his full success. Congratulations to Assist. Prof. Stella Fatović-Ferenčić for organization of the Symposium.

Prof. Jasna Lipozenčić, M.D., Ph.D.

RAVE company: cream against common cold (left) and pastilles for disinfection of the mouth (right). An advertisement from 1937.
From the collection of Stella Ferenčić-Fatović, M.D., Ph.D.

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WELCOME OF PRESIDENT OF THE CROATIAN DERMATOVENEROLOGICAL SOCIETY OF THE CROATIAN MEDICAL ASSOCIATION AND CONGRESS PRESIDENT, TOPICAL PROCEDURES, INNOVATIONS, AND MISTREATMENTS IN DERMATOVENEROLOGY, Plitvice, May 29, 2003

On behalf of the Organizing and Scientific Committees of the International Congress “Topical Procedures, Innovations, and Mistreatments in Dermatovenerology”, president cordially welcomed everyone to the Plitvice Lake National Park, in the heart of Croatia. At the beginning of the opening ceremony, Prof. Jasna Lipozenčić read the following excuses: “Because of uncertainties, I would be unable to attend the Congress. I’m very sorry that I am unable to do this in 2003. Perhaps I can try to attend it next year”, Larry C. Millikan. “I deeply regret that, due to an unfortunate crisis which has arisen, I have to cancel my trip to Plitvice. I hope for your kind understanding in this very serious situation. I sincerely wish you all the very best for a successful congress and once again apologize for this sudden change of events. I hope for another opportunity in the future and remain yours, with warmest regards”, Andreas Katsambas. “I am so sorry that unfortunately I can’t come to Plitvice because of series of administrative requirements that have made me cancel my participation. I do wish you a successful meeting and I hope to enjoy in participating at the Congress next year, wish warm regards”, Prof. Attila Horvath.

“I hope you will enjoy 16 beautiful blue-green lakes, linked by a series waterfalls and cascades forming a chain through a wooden valley. In 1979, UNESCO Office included the Plitvice Lake in the list of World Cultural and Natural Inheritance. Held on the premises of the Hotel Jezero in this lovely ambient, the International Congress ”Topical Procedures, Innovations, and Mistreatments in Dermatovenerology" is a scientific and travel experience to be treasured forever,” said Prof. Lipozenčić.

Like a year ago at the Congress in Opatija, we were proud to have again at this meeting our good old friends, Prof. Ring (Munich), Prof. Nakayama (Tokyo), Prof. Kapp (Hannover), Prof. Heghyi (Brno), Prof. Arslanagić (Sarajevo), Prof. Ramose-Silva (Rio de Janeiro), Dr. Celebi (Turkey), Prof. Stary (Vienna), Prof. Trevisan (Trieste), Dr. Kokelj (Trieste), and Head doctor Potočnik (Ljubljana). We also welcomed new friends of our Society and country, Prof. Gollnick (Magdeburg), President of UEMS, Prof. Wolf (Tel Aviv) from Kaplan Medical Center, a very important publisher in dermatology worldwide, and Dr. Lawrence, Fujisawa senior investigator from the USA. We wished them a very enjoyable stay that will make them to come to Croatia again in May 2004 on International Symposium on Atopic dermatitis.

(Figures 1-6)

Prof. Jasna Lipozenčić, M.D., Ph.D.

Fig. 1. Prof. Lipozenčić, Congress president at the Opening ceremony

Fig. 2. Professors at the Welcome dinner from left hand side: H. Behrendt-Ring, J. Ring, Mr. and Mrs. Stary, H. Gollnick and A. Kapp.

Fig. 3. Welcome dinner from right hand side: Prof. Heghy, his sun and wife, Professors F. Gruber, M. Skerlev and M. Ramos e Silva

Fig. 4. Welcome dinner from left hand side: Dr. C. Celebi, Prof. R. Wolf with his wife, Doctors M. Potočnik and M. Sirotković-Skerlev

Fig. 5. Welcome dinner, from left hand side: Prof. J. Lipozenčić, G. Trevisan, Dr. F. Kokelj, Prof. M. Šitum, Dr. A. Pašić, Assist. Prof. V. Barišić-Druško and Prof. M. Waugh

Fig. 6. Welcomce dinner, from left side hand: Assist. Prof. V. Milavec-Puretić, Prof. J. Lipozenčić, Mrs. and Dr. I. Lawrence, Prof. A. Basta-Juzbašić

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FINAL CONCLUSION
of the International Congress "Topical Procedures, Innovations, and Mistreatments" Plitvice, May 31, 2003

It's a pleasure to close such a successful meeting as it was International Congress «Topical Procedures, Innovations, and Mistreatments», said Prof. Jasna Lipozenčić.

Prominent lecturers came from 17 countries. We have successfully resolved 41 oral presentations, 6 Satellite Symposiums with 12 oral presentations, and we have awarded the best three posters presented at the Congress. Dermatology is playing an increasingly vital role in patient care. Throughout this Congress, we have concentrated on the following initiatives: educating and increasing the availability of primary skin care, providing patients with highest quality of care through direct access to dermatologic local therapy, and increasing support to basic and applied research with pharmaceutical industry. The Croatian Dermatovenerological Society (CDS) was very active in the last 5 years (16 meetings). The CDS is pursuing a full agenda in the coming year. Progress we have made thus far in each area in the field of dermatology and venereology was discussed, along with anticipation of what the future holds in dermatologic health care.

I believe the Congress program was interesting and informative, and proved to be successful and useful for all of us. (Figs 1-3)

In the six main topics of the Congress, we heard the following:

1) That the local treatment is very important in dermatology as well as inappropriate indications;

2) That optimization of topical therapy is needed;

3) That cosmetic products, sunscreens, and many new topical products are on the market and must be used appropriately;

4) An update on extemporaneous prescriptions in dermatology with quality management, presented by Prof. Gloor in Spirig Satellite Symposium;

Fig. 1. Professors from left hand side: M. Skerlev, V. Heghy, J. Lipozenčić, M. Ramos-e-Silva, J. Ring, H. Gollnick

Fig. 2. Prof. M. Gloor in Spring Sattelite Symposium

Fig. 3. Assist. Prof. I. Bartenjev in Vichy – Satellite Symposium

5) New approaches in the treatment of atopic dermatitis;

6) About new psoriasis therapy, phototherapy and photochemotherapy with own experiences from different countries;

7) Results of Sun Prevention campaign in Slovenia and Croatia, with photoprotection emphasized in Vichy Satellite Symposium;

8) Treatment of viral, bacterial, and parasitic diseases and sexually transmitted diseases (STDs) as a part of our specialization – venereology was important part on this congress;

9) The Congress was organized because of mistreatments in dermatologic cosmetology, and there were many presentations and discussions about that;

10) Topical corticosteroids (old and new) were presented and guidelines for all dermatovenerologists were very instructive;

11) Laser in dermatology was present and the future of dermatotherapy not only as innovation in Croatia. The experience from Slovenia and Croatia was very impressive;

12) Dermatosurgery is important part of local dermatotherapeutic methods and excellently performed in Sisters of Mercy University Hospital, Zagreb;

13) Appropriate treatments and mistreatments in dermatomycology are very often seen in daily praxis and often unrecognized;

14) It is necessary to educate not only general practitioners, but also dermatovenerologists;

15) Itraconazole (ITRAC3) is a novel treatment for onychomycosis and tinea capitis and was successfully presented at Belupo Satellite Symposium and exhibition;

16) Atopic dermatitis treatment and skin care was provided by Uriage-Formasana, with great palette of products in skincare of dry and atopic skin;

17) The Skin Scare Reducer therapy – Hansaplast was presented by Beiersdorf as the only product in Croatia for the treatment of new and old scars and keloids;

18) Hair and scalp problems and importance of cosmetic dermatology was presented in Satellite Symposium by Oktal-Pharma.

The Congress attended 260 participants from 17 different countries all over the world.

Prof. Jasna Lipozenčić, M.D., Ph.D.

President of the CDS

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Farewell Remarks
International Congress of Croatian Society for Dermatology and Venerology, Plitvice, May 07-14, 2003

Dear Professor Lipozenčić, Ladies and Gentlemen,

At the end of this wonderful congress I would like to speak on behalf of the foreign guests, who came from 17 countries to the 16 lakes and 100 waterfalls of beautiful Plitvice. We want to thank the organizers for this excellent congress and their wonderful hospitality.

We have heard a lot of excellent lectures, seen interesting posters, and got new and exciting information for our patients. I want to congratulate the Croatian Dermatological Society on many enthusiastic young dermatologists in this country!

At this event, I also would like to say one word on behalf of the European Academy of Dermato-Venerology (EADV). Yesterday, we had some personal discussions and I learned that many people in Eastern European countries have the feeling that EADV is restricted to the political body of the European Union. This is not true: the EADV is not a political body and comprises the whole Europe with all its richness and diversity in culture and history. So the EADV is also your academy and I would like to ask you to join it. For residents there is the possibility to become a junior member with reduced fees.

Again, let me thank Professor Jasna Lipozenčić and her splendid team for this outstanding meeting!

Prof. Johannes Ring, M.D., Ph.D.

SECTION DERMATOLOGY OF THE EUROPEAN ACADEMY OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY

Section Dermatology of the European Academy of Allergology and Clinical Immunology (EAACI) business meeting in Paris was held on Saturday, June 7, 2003, at 5.00 p.m. A new Board of Dermatology Section for the 2003-2005 period was constituted. The president chosen was Prof. Bindslev-Jensen Carsten (Denmark), and secretary Prof. Thomas Bieber (Germany). New members of the Section are Girolomoni Gianpiero (Italy), Hauser Conny (Switzerland), Lipozenčić Jasna (Croatia), Kristine Turjanmaa (Finland), and Törsten Zuberbier (Germany).

The timetable was as follows: 1) Report of activity last year (past president Prof. A. Kapp and secretary Prof. T. Reunala); 2) New board suggestion and voting – Prof. A. Kapp; 3) Future activities – new president Prof. Bindslev-Jensen, and 4) other. The next EAACI Meetings will be held in Amsterdam, 2004; in Munich, 2005; in Moscow, 2007, and in Gothenburg, 2008.

It was suggested that Postgraduate course in Pathophysiology, Diagnosis, and Therapy of Contact Allergic Dermatitis will be held by European Society of Contact Dermatitis (Diepgen). Task Forces: Dermatologic Section plus Pediatric Section: Atopy Patch Testing and Dermatology Section: Urticaria. It was proposed that International Symposium about Atopic Dermatitis under sponsorship of EAACI Dermatology Section will be organized in Croatia (by Prof. Lipozenčić) in 2004.

Prof. Jasna Lipozenčić, M.D., Ph.D.

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REPORT FROM XXII CONGRESS OF THE EUROPEAN ACADEMY OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY,

PARIS, JUNE 7-11, 2003

This was the fifth time that European Academy of Allergology and Clinical Immunology (EAACI) was held in France (1950 Paris, 1971 Marseille, 1981 Clermont Ferrand and again in Paris, 1992) in one of the most attractive cities in the world. The venue of the Congress was Palaise des Congres, one of the largest Congress centers in Europe.

On June 7, 2003 Prof. Lipozenčić was active in Dermatology Section Meeting at 5.00 p.m.

At Sunday June 8, 2003, a Company sponsored Symposium Aventis, Antihistamines Evaluation or Revolution? took place. There were lectures presenting fexofenadin as a better medication than loratadine, which has same effect as levocetirizin. In seasonal and perennial allergic rhinitis and chronic idiopathic urticaria, levocetizin 5 mg (Xyzal®) is effective. Montelukast (Singulair, tbl.) effectively treats the nighttime impact of seasonal allergic rhinitis.

Very good statement was in Symposium Drug Allergy; Food Allergy; Pediatric Allergies; New Language and Medias Allergy and Asthma and the patients. On Monday June 9, 2003, there were many presentations on asthma, whereas allergy problems in dermatology were given less attention at the EAACI, except for urticaria, angioedema, and atopic dermatitis. Very successfull presentations were the following: in Mains Symposium 1 – Allergy to Cosmetics and Perfumes: Allergenic ingredients in cosmetics and perfumes; New clinical aspects and allergy testing and How sensitizing potential is evaluated. In Main Symposium 5, the most successful presentation was on drug allergies by H. F. Merk (Germany), entitled Drug metabolism in the skin, and Diagnosis of drug-induced skin reactions by Annick Burband.

Rhinitis and asthma in children and adults, Company sponsored symposia and Main Symposia, were maybe given too much space for the profile of the audience attending the Congress.

Allergy Gene to Disease in Plenary Session 3 included the following interesting sessions: “Genes if tolerance” , “How do genes affect the response do drugs?”, and “Gene therapy is here today and is here to stay”.

Main Symposia 25, New Trends in Atopic Dermatitis was promising, with lectures titled Epidemiology and Genetics (Zuberbier); Are there new mechanisms? (Bieber), Is IgE really important in atopic dermatitis? (Werfel); New treatments (Reitamo); Hot topics in insect allergy from natural history of insect allergy in children; Interface between insect allergy and mastocytosis; Immunological mechanisms of venom immunotherapy, and Recent development in venom immunotherapy.

There were 1,405 registered posters and about 5,000 participants, 100 sessions (4 plenary sessions, 28 main symposia, 4 mini symposia, 14 oral abstract sessions, 12 poster discussion sessions, 8 company sponsored symposia and a series of satellite symposia) covering all aspects of allergy, from basic science to diagnosis, treatment, and socioeconomy.

We enjoyed in Paris during the 22nd EAACI Congress.

Prof. Jasna Lipozenčić, M.D., Ph.D.

Marko Polo´s Diary

Stella Fatović-Ferenčić, ESHDV representative of Croatia

On the Iraq War, the Munich Clinic and a Historical satellite symposium in Zagreb

It has been more then 700 years since Marko Polo passed the land between the Tigris and Euphrates Rivers on his way to China. It is hard to believe, looking at the Tigris and Euphrates today, the area where Western civilisation was rooted, that once it was the site of the biblical Garden of Eden. Instead, we witness war in the name of liberty and democracy. Tons of bombs are being dropped.

Munich April 10th: Hospital of Ludwig-Maximilian–University

Munich was my destination in April. I had an appointment with Professors Plewig and Holubar and Blackwell publishers at the Hospital of the Ludwig-Maximilian–University. We continued with preparations of our book *Skin in Water Colors*, which will hopefully be presented at the Barcelona Congress. After a work fruitful, our host took us late in the afternoon to the Asamkirche (officially known as St-Johann-Nepomuk), one of the most enchanting examples of the Bavarian Roccoco style. After a pleasant though rainy walk around Sendlinger-Tor-Platz, we finished our day at an enjoyable Bavarian restaurant. I left Germany by train. An early spring landscape with a crisp order of the fields framed my window sight. The solid mountains rising steeply away from the train tracks, hiding forests and cabins, as well as secretes and stories, which I was familiar with from Grimm's fairy tales.

Zagreb May 28th – Venereal diseases: Realities & Taboos

This historical satellite symposium within a dermatological congress was held at the Conference Hall in the Palace of the Croatian Academy of Sciences and Arts. The organizers, the Croatian Academy of Sciences and Arts (the Department for Medical Sciences as well as the Department for the History of Medical Sciences) and two societies of the Croatian Medical Association (the Dermatovenerological and the Medico-shistorical) dedicated the event to the memory of Franjo Kogoj, on occasion of the 20th anniversary of his death. By today, investigations of venereal diseases have clearly surpassed the limits of medicine and revealed the complexity of life and sickness, in biology as much as in sociology and culture. During the symposium, we learned that, regarding venereal diseases, the British Isles did not follow the continental traditions. Knowledge about syphilis came to England only in 1686, and the first who wrote on syphilis was Daniel Turner in 1717. From another corner of the world, Brazil, we heard about facial and oral aspects of venereal and tropical diseases, whereas data on HPV genital infections were presented from the Department of Dermatology and Venereology at Zagreb University School of Medicine. The symposium offered a multidisciplinary approach aiming to clarify various aspects of venereal diseases in different times. For that reason, not only dermatovenerologists, but also specialists of infectious diseases, medical historians philologists, and

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sociologists were invited to speak. Successes and failures in combating the HIV/AIDS epidemic were outlined, and risks posed by STD research and its social impact in Croatia were addressed. Causes and consequences of Skerlievo disease two hundred years ago were described by medical historians from Rijeka, and the attitudes vis-á-vis sexuality and social stigma in the medieval period were pinpointed. The lecturers Michael Waugh, Marcia Ramos-e-Silva, Mihael Skerlev, Josip Begovac, Aleksandar Štulhofer, Marija Ana Dürrigl, Amir Muzur, and Ante Škrobonja competently and clearly outlined their topics. Agata Maković and Mihael Mišir, two young physicians, participated in such a symposium for the first time. Their research concerned the appearance of AIDS as a topic in public and biomedical journals. As their mentor, I was proud of their work. In the process of globalization to which we are so strongly, and sometimes unwillingly, exposed, knowledge should become a dominant power. Young people must therefore be stimulated more and considered the most promising and important force in a knowledge-based society in the making. The following day, the Congress of dermatologists started in Plitvice. I stayed in Zagreb, making preparations for my next destination – London.

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The world is waiting, sretan vam put !

stella@hazu.hr

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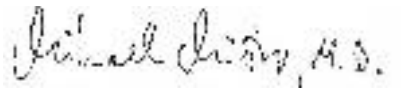
Dear Editor-in-Chief,

I would like to offer my comment on the article published in your Journal (Ljubojević S. Severe acute respiratory syndrome, Acta Dermatovenerologica Croatia 2003;11:129-30). As journals have also informative and educative purpose, I may say that Acta Dermatovenerologica Croatica undoubtfully represents such a strategy in the best possible way by publishing the information of the highest priority. I would like to congratulate you as the Editor-in-Chief of Acta Dermatovenerologica Croatica.

Cordially,

Mihael Mišir, MD



Acta Dermatovenerologica Croatica: Priority in Reporting on New Epidemic

To the editor. It is quite a while that I have been involved with an investigation on the earliest news and information associated with epidemics dealt with in biomedical journals in Croatia. Although I was mainly dealing with acquired immunodeficiency syndrome (AIDS), the new challenge, Severe Acute Respiratory Syndrome (SARS), that we became aware of in early 2003, prompted me to follow also what kind of information was presented on that topic. I checked the same selection of journals, which I used in the AIDS investigation. I was disappointed to learn that Croatian medical journals come to libraries with incredible delay. This is opposite to the policy journals should follow, i.e. reaching a high impact factor, and prevents prompt information to the readers. The editorial staff of each journal should mind that apart from internet possibilities and the priority list of journal's subscribers, there are many researchers, who just need a variety of periodicals at hand.

Since the time of the earliest journals on our territory professional information in medicine was available. The first most fascinating news, such as that on X-rays in the earliest issues of *Liječnički vjesnik*; outbreaks of certain diseases, new diagnostic tools and therapies, were thus transplanted from other journals into ours (1,2). Consequently, knowledge, therapeutic regimens and health policy was influenced favorably. *Acta Dermatovenerologica Iugoslavica,* for example, whose editorial board included numerous prominent dermatovenerologists of Croatia, brought one of the first reports, e.g., on a new entity already in 1982 – reporting on *sarcoma Kaposi* in young homosexuals in New York. *Acta Dermatovenerologica Iugoslavica* published it before *Epidemiološki vjesnik* or any similar journal of infectious diseases (3).

New diseases seem to be reported speedily in Croatian public rather than in biomedical journals. According to another line of investigation, carried out by Maković (4), it is evident that public journals were as prompt bringing the news on AIDS in Croatia as elsewhere in the world. Regarding SARS the results are quite similar. Besides, the journal of the Croatian Medical Chamber, *Liječničke novine*, which somehow bridges the information gap between public and biomedical journals, appeared to be quite informative in this aspect. Regarding

SARS, it adequately fulfilled its task bringing sufficient information on new outbreak. Three articles were thus published in its pages in April and May 2003 (5-7). The first text contained a short history of the disease, number of affected people and countries involved, and further, epidemiology, diagnostic and etiological data as well as protective measures. The second text reported that there are no SARS cases in our country but in case of appearance, no provisions for their isolation are available as well (6).

My investigation showed that there is no information on SARS within Croatian biomedical journals, until June 2003 when two articles appeared. The first one was published in *Farmaceutski glasnik,* transferring the information from *Liječničke Novine*, mentioned above (8). The second was Ljubojević's comment on SARS published in *Acta Dermatovenerologica Croatica* aiming to inform the readership on the new and puzzling outbreak and offering a list of useful web sites for those who need to know more and prefer virtual reality (9). The only detail which I would add to supplement Ljubojević's data is that according to *The Lancet*, SARS occurred in Guandong Province, in China already in November, 2001 which moves back the beginning of the outbreak one year and three months before February 1, 2003 (10).

In conclusion I may say that a dermatological journal was again the first among the Croatian biomedical journals to shed light on a new disease even though one would expect to find such an information in the pages of some general medical journal, or more likely, in an epidemiological journal. The fact that the SARS issue, although not strictly belonging to sphere of dermatology, appeared in *Acta Dermatovenerologica Croatica* demonstrates the sensitivity and openness of its editorial staff. It also leaves us hope for the future biomedical journalism not fragmented and not just targeting evidence based medicine but committed to new dangers and risks.

Mihael Mišir, M.D.

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ANNOUNCEMENTS

XVIII World Allergy Organization Congress ICACI, Vancuver, Canada, September 7-12, 2003. Contact: Sally Kolf, 611 East Wells Street, Milwaukee, WI 53202, USA; e-mail: *congress@worldallergy.org*; *www.worldallergy.org*

Current State on Psoriasis and Naphtalanotherapy, Symposium of Croatian Dermatovenerological Society of the Croatian Medical Association, Ivanić Grad, Croatia, September 19, 2003. Contact: Prof. Jasna Lipozenčić, Šalata 4, 10000 Zagreb, Croatia. Tel./Fax: +385-1-4920-014; e-mail: *jasna.lipozenčić@zg.tel.hr*

9th Congress of the European Confederation of Medical Mycology and 7th Trends in Invasive Fungal Infections, Joint Meeting, Amsterdam, The Netherlands, September 28-October 1, 2003. Contact: Congress Care, Muntelbolwerk 1, P.O. Box 440, 5201 AK's-Hertogenbosch, The Netherlands; e-mail: *info@congresscare.com* , *www.congresscare.com*

12th Congress of European Academy of Dermatology and Venerology, Barcelona, Spain, October 15-18, 2003. Contact: Unicongress, Calvet, 55, Baixos, 08021 Barcelona, Spain; e-mail: *eadv2003@unicongress.com*; *www.eadv.org*

6th Tergestinum Symposium on Psoriasis and 2nd Alpe Adria Meeting on Psoriasis, Bibione, Italy, November 7-8, 2003. Contact: Organising Secretariat, Via San Nicolo 14, 34121 Trieste, Italy. Tel +39 40 368343, Fax: +39 40 368808

Sexually Transmitted Diseases, Continuing Medical Education Course organized by the University School of Medicine Zagreb and Croatian Dermatovenerological Society of the Croatian Medical Association, Šubićeva 9, 10000 Zagreb, Croatia, November 21-22, 2003. Contact: Prof. Jasna Lipozenčić, Šalata 4, 10000 Zagreb, Croatia. Tel./Fax: +385-1-4920-014; *e-mail: jasna.lipozenčić@zg.tel.hr*

9th Alple-Adria-Danube Congress of Sexually Transmitted Diseases and Infections of the Skin, Prague, November 27-30, 2003. Contact: jana.hercogova@lfmotol.cuni.cz

8th World STI/AIDS Congress, Punta del Este, Uruguay, December 2-5, 2003

3rd World Congress of the International Academy of Cosmetic Dermatology, Beijing, China, December 7-10, 2003. Contact: IACD2003 Secretariat, Chinese Medical Meetings International, 42 Dongsi Xidajie, Beijing 100710, China; e-mail: lillian.lee@263.nrz; *www.chinamed.com.cn/IACD*

6th International Congress of the European Society for Laser Aesthetic Surgery (ESLAS), What Laser: when and why, Rome, Italy, December 12-14, 2003. Contact: itskcanf@rm.unicatt.it

International Master Course of Ageing Skin, Paris, France, January 8-10, 2004. Contact *www.web-imcas.com*

"Allergy and Eczema", Milan, Italy, January 22-24, 2004. Contact: e-mail: info@mcaevents.org, *www.mcaevents.org*

62nd Annual meeting of Academy of Dermatology, Washington DC, USA, February 6-11, 2004.

4th World Congress of IACD, Cairo, Egypt, April 12-18, 2004.

Update on Atopic Eczema/Dermatits Syndrome, Cavtat, Croatia, April 25-28, 2004. Contact: Prof. Jasna Lipozenčić, Department of Dermatology and Venerology, Zagreb University Hospital Center, Šalata 4, 10000 Zagreb; e-mail: *jasna.lipozencic@zg.tel.hr*

Second EADV International Spring Symposium, Budapest, Hungary, April 29-May 1, 2004. Contact: *www.eadvbudapest2004.com*; e-mail: *info@eadvbudapest2004.com*

9th International Congress of Dermatology, Beijing, China, May 2004. Contact: ICD2004 Secretariat, Dept. of Foreign Relations, Chinese Medical Association, 42 Dongsi Xidajie, Beijing 100710, China. e-mail: *ICD2004@chinamed.com.cn*; *www.chinamed.com.cn/dermatology*

15th Ljudevit Jurak International Symposium on Comparative Pathology; Main Topic: Head & Neck Pathology, Zagreb, Croatia, June 4-5, 2003. Contact: *www.kbsm.hr/jurak/symposium.htm*

23rd Congress of the European Academy of Allergology and Clinical Immunology, Amsterdam, Netherlands, June 12-16, 2004. Contact: Dept. Allergology, University Hospital Rotterdam, dr. Molewaterplein 40, NL-3015 GD Rotterdam, The Netherlands; e-mail: *degroot@algo.azr.nl*; *www.congrex.com/eaaci2004*

10th Congress of the European Confederation of Medical Mycology, June 17-20, 2004, Wroclaw, Poland. Contact: Congress Care, Muntelbolwerk 1, P.O. Box 440, 5201 AK's-Hertogenbosch, The Netherlands; e-mail: *info@congresscare.com* , *www.congresscare.com*

X World Congress of Pediatric Dermatology, Rome, Italy, July 7-10, 2004. Contact: Triumph Congressi, Via Lucilio, 60, 00136 Rome, Italy; e-mail: *dermo@gruppotriumph.it*; *www.gruppotriumph.it*

American Academy of Dermatology, Academy '04, New York, USA, July 28-August 1, 2004. Contact: American Academy of Dermatology, Department of Meetings & Conventions, 930 E Woodfield Road, Schaumburg, IL 60173; fax: 847 330 1090

Deutsche Gesellschaft fur Allerologogie und Klinische Immunologie e.V. Tagung, Aachen, Germany, September 15-19, 2004. Contact: *Gerhard.Schultze-Werninghaus@ruhr-uni-bochum.de*

International Symposium on Psychodermatology, Cavtat, Croatia, September 22-26, 2004. Contact: Prof. Mirna Šitum, Department of Dermatology and Venerology, Clinical Hospital "Sestre milosrdnice", Vinogradska 29, 10000 Zagreb, Croatia; e-mail *mirna.situm@zg.hinet.hr*, *mirna.situm@htnet.hr*

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

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

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, e-mail: *info@wccs.at*; *www.wccs.at*

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-June 1, 2005. Contact: e-mail: *wac2005@congrex.se www.congrex.com/wac2005*

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

INSTRUCTIONS TO AUTHORS

ACTA DERMATOVENEROLOGICA CROATICA (ADC) is a quarterly peer-reviewed journal, indexed in Index Medicus/MEDLINE and Excerpta Medica/EMBASE. It publishes original scientific articles, short scientific communications, clinical articles, case reports, reviews, reports, news and comments, and announcements in the fields of dermatology and venerology.

General Guidelines

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

The manuscripts should not exceed 12-15 typed pages in case of original scientific papers, and 6-8 pages in case of short communications, clinical articles, case reports, and reviews.

The manuscripts should be written in English. The authors are responsible for ensuring that the English used is suitable for publication. All material is assumed to be submitted exclusively to this journal.

All manuscripts are subject to peer review.

Preparation of Manuscripts for Submission

Title Page

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 adress) 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.

Second Page

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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The text of observational and experimental is usually, but not necessarily, divided into sections with the headings Introduction, Material (Patients) and Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their contents, especially Results and Discussion sections. Other types of articles, such as case reports, reviews, and editorials, are likely to need other format.

Abbreviated terms should be written in full the first time they are used in the text, with abbreviation in parentheses.

Underline the words that must be printed in italic.

References should be identified in the text by arabic numerals in parentheses, and be numbered and listed consecutively at the end of the manuscript in the order in which they are first cited in the text.

Indicate in the text where the illustrations (figures and tables) should be inserted.

Tables and figures should be provided each on a separate sheet of paper after the references. Descriptive legends to figures should be typed double-spaced on a separate sheet of paper, whereas figures should be submitted in an envelope, with the number, the name of the (first) author, and title of the manuscript on the back: each table should be typed on a separate sheet of paper, numbered in the order in which they are first cited in the text, with a title and descriptive legend. Terms used in tables should not be abbreviated.

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When reporting experiments on human subjects, indicate whether the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) or with the Helsinki Declaration from 1975 as revised in 1983. Do not use patients, names, initials or hospital numbers, especially any illustrative material.

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Describe statistical methods and provide enough data to enable a knowledgeable reader to assess the reported results him or herself. Please state the statistical package (version, manufacturer) used for statistical analysis.

Acknowledgements

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terest. Technical help should be acknowledged in a separate paragraph as well as other contributions.

References

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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 herpetiforme. 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.

Disertation

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:

Editorial Office

Department of Dermatology and Venerology

Zagreb University Hospital Center

Šalata 4, 10000 Zagreb, Croatia

e-mail: *jasna.lipozencic@zg.tel.hr*

Manuscripts on Disks

Floppy disks should be 3.5-inch (1.44 MB) IBM formatted and labeled with the name of the author.

The file, the word-processing program, and version used should be indicated by pen. MS-Word for Windows is preferred, although manuscripts prepared using any other IBM-compatible word-processor are acceptable.

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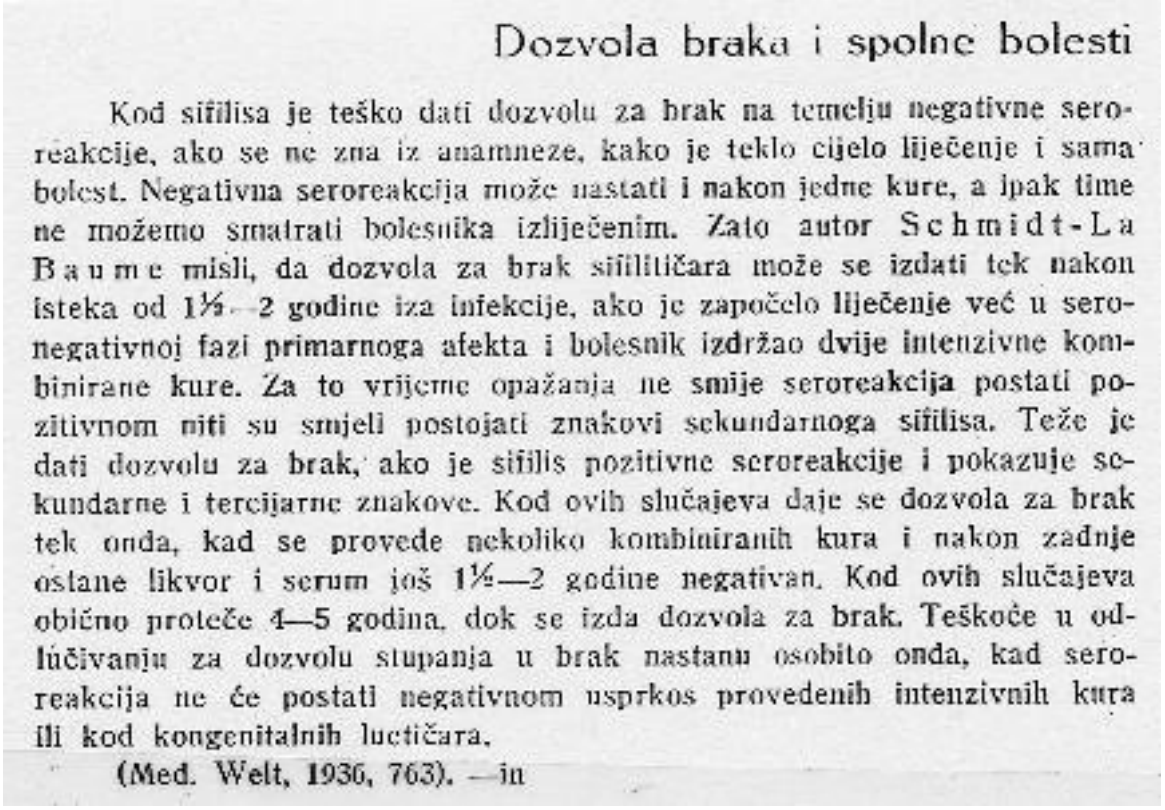

Dozvola braka i spolne bolesti

Kod sifilisa je teško dati dozvolu za brak na temelju negativne seroreakcije, ako se ne zna iz anamneze, kako je teklo cijelo liječenje i sama bolest. Negativna seroreakcija može nastati i nakon jedne kure, a ipak time ne možemo smatrati bolesnika izliječenim. Zato autor Schmidt-La Baume misli, da dozvola za brak sifilitičara može se izdati tek nakon isteka od 1½—2 godine iza infekcije, ako je započelo liječenje već u seronegativnoj fazi primarnoga afekta i bolesnik izdržao dvije intenzivne kombinirane kure. Za to vrijeme opažanja ne smije seroreakcija postati pozitivnom niti su smjeli postojati znakovi sekundarnoga sifilisa. Teže je dati dozvolu za brak, ako je sifilis pozitivne seroreakcije i pokazuje sekundarne i tercijarne znakove. Kod ovih slučajeva daje se dozvola za brak tek onda, kad se provede nekoliko kombiniranih kura i nakon zadnje ostane likvor i serum još 1½—2 godine negativan. Kod ovih slučajeva obično proteče 4—5 godina, dok se izda dozvola za brak. Teškoće u odlučivanju za dozvolu stupanja u brak nastanu osobito onda, kad seroreakcija ne će postati negativnom usprkos provedenih intenzivnih kura ili kod kongenitalnih luetičara.

(Med. Welt, 1936, 763). —in

Marriage Allowance and Sexually Transmitted Diseases

When it comes to syphilis, it is difficult to issue a marriage allowance on the basis of negative seroreaction, if it is not known from the medical history of the person how the treatment and the disease itself have passed off. Seroreaction may become negative after a single treatment, which does not mean that the patient is cured. This is why the author Schmidt-La Baume thinks that the marriage allowance can not be granted before 1.5–2 years elapse from the infection, if the therapy has started in the seronegative stage of the primary infect and the patient has endured two intensive combined treatments. During that period of time seroreaction should not become positive, and neither should the signs of the secondary syphilis appear. It is more difficult to issue the allowance if seroreaction is positive and signs of the secondary or tertiary syphilis are present. In such cases, the marriage allowance is issued only after several combined treatments, with liquor and serum remaining seronegative for a 1.5–2 years after the last treatment. It usually takes 4-5 years before the allowance can be granted. Difficulties in making the decision to issue the marriage allowance are encountered when the reaction does not become negative even after several treatments as well as in cases of congenital syphilis. (Med. Welt. 1936, 763.)

(Croatian translation of the text was issued in the journal Medicinsko farmaceutska pošta, 1937.)

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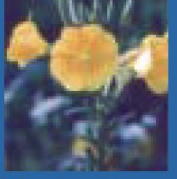

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