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E-mail: serbjdermatol@nadlanu.com, Tel: +381 21 484 3562; +381 21 451 781.

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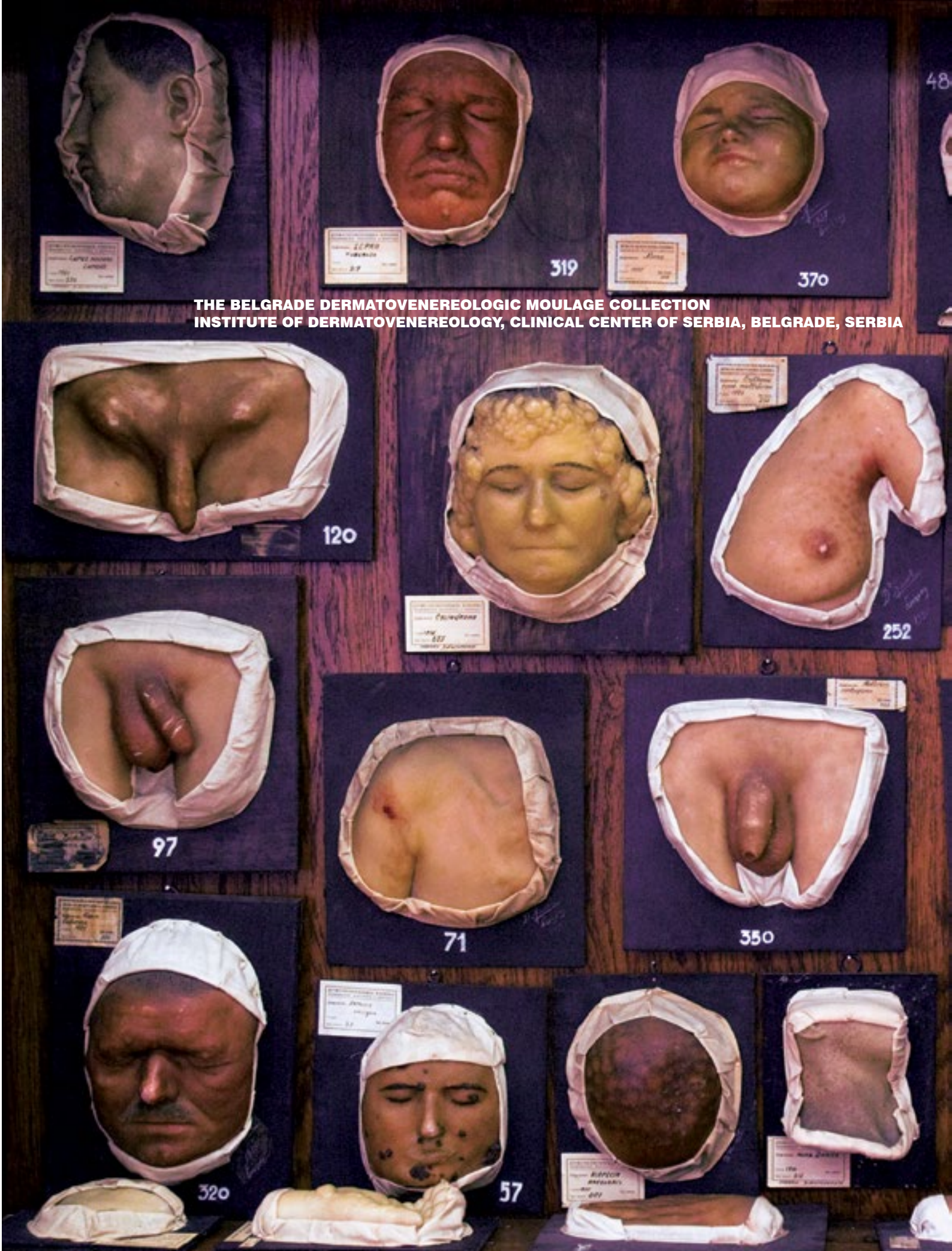

THE BELGRADE DERMATOVENEREOLOGIC MOULAGE COLLECTION
INSTITUTE OF DERMATOVENEREOLOGY, CLINICAL CENTER OF SERBIA, BELGRADE, SERBIA

Antiproliferative effect of docosahexaenoic acid on adult human keratinocytes *in vitro*

Svetlana POPADIĆ[1, 2], Zorica RAMIĆ[1], Ljiljana MEDENICA[2]
Marija MOSTARICA - STOJKOVIĆ[1] and Dušan POPADIĆ[1]

[1]Institute of Microbiology and Immunology,
[2]Institute of Dermatovenereology, School of Medicine, University of Belgrade, Serbia
*Correspondence: Svetlana POPADIĆ, E-mail: spopadic@med.bg.ac.rs

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Abstract

Numerous clinical studies demonstrate benefits of dietary supplementation with fish oils in autoimmune diseases and other inflammatory diseases such as psoriasis, multiple sclerosis, systemic lupus erythematodes and so on. Docosahexaenoic acid (DHA) is an omega-3 fatty acid which is abundantly found in fish oil. In the present study we investigated effects of DHA on proliferation of human keratinocytes established from skin of seven adult donors, cultivated in growth medium that allows optimal cell proliferation. We found a dose-dependent inhibition of cell proliferation when keratinocytes were incubated with 6.25, 12.5 and 25 –μM of DHA. Inhibition of proliferative capacity considerably varied in keratinocyte cultures derived from different donors, particularly when incubated with the lowest concentration of the assessed substance. Lactate dehydrogenase-release assay excluded necrosis of cultivated keratinocytes as a cause of decreased proliferation. Our results suggest that DHA may potentially be used as a routine adjuvant therapy, with classical therapy of inflammatory hyperproliferative skin diseases.

Omega-3 fatty acids are a family of unsaturated fatty acids**,** which have a final carbon–carbon double bond in the n–3 position in common, and cannot be synthesized by the human body. The most nutritionally important omega-3 polyunsaturated fatty acids (PUFAs) are: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).

PUFAs exhibit several potent immuno-modulatory features (1) and among the omega-3 PUFAs, those derived from fish oil - EPA and docosahexaenoic acid - are particularly biologically potent. Many of the placebo-controlled trials revealed significant benefit of fish oil and PUFAs in chronic inflammatory diseases, including decreased disease activity and decreased needs for use of anti-inflammatory drugs (2). Several of biologic effects of DHA have been demonstrated from feeding studies with fish or fish oil supplements in humans and animals. These include effects on triglycerides, high-density lipoprotein cholesterol, platelet function, endothelial and vascular function, blood pressure, and cardiac excitability, measures of oxidative stress, pro- and anti-inflammatory cytokines, and immune function (3).

Although it is well known that omega-3 fatty acids may affect the inflammatory components of skin diseases, the cellular and molecular basis of their beneficial effects is still not well delineated. Profound changes in the metabolism of eicosanoids, with increased concentrations of free arachidonic acid and its proinflammatory metabolites, have been observed in psoriatic lesions. Free eicosapentaenoic acid may compete with liberated arachidonic acid and result in an anti-inflammatory effect (4).

Effects of PUFAs have been investigated on immortalized HaCaT cell-line and it has been suggested that induction of cyclooxigenase-2 (COX-2) in keratinocytes may be important in the anti-inflammatory and protective mechanism of PUFAs action (5). It has been reported that DHA has antiproliferative effects on some epithelial cells: human

colon epithelial cell-lines and adenocarcinoma (HT-29, HCT-116) origin (7), PC-3 prostate carcinoma cells (8) and human endothelial cells (9).

Until now, the effects of DHA on keratinocytes have been explored in a single study, which demonstrated that DHA has antiproliferative effects on human papillomavirus type 16 (HPV-16) immortalized cervical keratinocytes in the presence of estradiol, a growth stimulator for these cells. The same study indicated that DHA inhibited proliferation of HPV immortalized foreskin cells, but it had no effect on the normal foreskin cell pool (6).

The present study shows for the first time, that DHA inhibits proliferation of adult human keratinocytes *in vitro.* However, substantial individual differences in keratinocyte response to DHA were found particularly when incubated with low concentrations of DHA.

Material and methods

Cell culture and reagents

Skin samples were obtained from seven healthy volunteers undergoing cosmetic surgery at the plastic surgery unit. The epidermis was separated from the dermis after overnight treatment (4°C) with dispase (5 U/ml), while a single-cell suspension was subsequently obtained upon treatment with trypsin (0.05%) and ethylenediaminetetraacetic acid (EDTA) (0.53 mM). Cells were seeded at a density of 5000 cells/cm^2 in 25 cm^2 flasks and further cultivated in keratinocyte growth medium (Invitrogen, Paisley, UK) at 37°C in an incubator with humidified atmosphere containing 5% CO_2. DHA was dissolved in dimethyl sulfoxide (DMSO) and stored in 10 mM aliquots at –20°C and protected from light. All reagents used in the study were from Sigma (St. Louis, MO, USA), unless stated otherwise. The cells were used for experiments after the third or fourth passage. They were seeded in 96-well plates in 200 µl of keratinocyte growth medium, for cell proliferation, and treated as described in the figure legends. The control cell cultures contained the amount of DMSO corresponding to its content in the solution, with the highest concentration of DHA.

Cell proliferation

Cell proliferation was measured by [^{3}H]thymidine incorporation into newly synthesized DNA of cultivated cells. For the assessment of proliferation, keratinocytes were cultivated in 96-well plates (3 × 10^3 cells/well) for 48 h, then washed and cultivated for additional 72 h in fresh medium containing 6.25, 12.5 and 25 µM DHA or 0.25% DMSO (corresponding to DMSO content in cultures treated with 25 µM DHA) as a control. During the last

Table 1. Proliferation of keratinocytes cultivated with various concentrations of DHA

^{3}H Thymidine incorporation (Mean ± Standard deviation of the triplicate)				
DHA (µM)	0**	6,25	12,5	25
I*	6714 ± 1140	1040 ± 256	224 ± 57	243 ± 153
II *	25359 ± 4038	16616 ± 2093	210 ± 16	279 ± 125
III*	3415 ± 653	1378 ± 445	157 ± 44	191 ± 37
IV*	6613 ± 500	2785 ± 320	2667 ± 538	223 ± 31
V*	16809 ± 1898	10784 ± 7522	4559 ± 5917	156 ± 29
VI*	11855 ± 3088	5227 ± 140	3119 ± 1298	209 ± 99
VII*	1534 ± 213	1210 ± 91	196 ± 47	184 ± 36

* different human keratinocyte cultures

**control

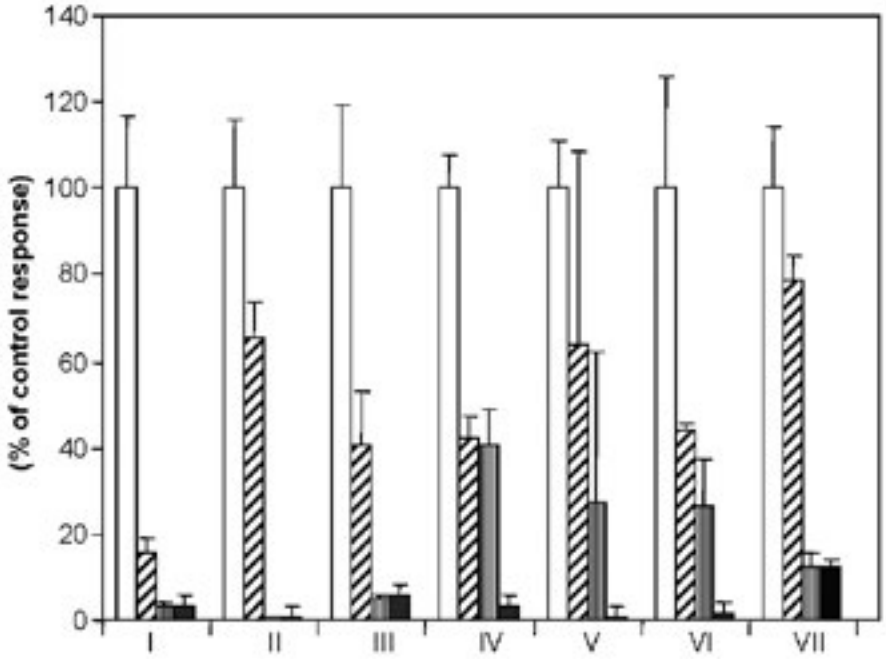

Figure 1. DHA inhibits keratinocyte proliferation *in vitro*

Keratinocytes were incubated without (control, open bars) or with 6.25 μM (cross hatched bars), 12.5 μM (vertical hatched bars), or 25 μM (black bars) of DHA for 72 h. The incorporation of [^{3}H]thymidine (1 μCi/well) was determined during the last 24 h of cultivation. Data are expressed as the percentage of the control response. Error bars represent standard deviations of the triplicate for each culture and treatment.

24h of incubation, keratinocytes were pulsed with 1 μCi of [^{3}H]thymidine per well, harvested and counted in a liquid scintillation counter as described previously (10). Results are expressed as a percentage of proliferation measured in control cultures.

Lactate dehydrogenase (LDH) release assay

LDH release assay was employed to assess the cell leakage of cytoplasm through damaged membrane that occurs during necrosis. To assess the LDH release, keratinocytes were cultivated under the same conditions as for the proliferation assay.

Measurement of lactate dehydrogenase activity was performed exactly as previously described (11, 12).

Statistical analysis

All experiments with keratinocyte cultures were performed in triplicates. The results are presented as mean ±SD of triplicate cultures, or as the percentage of inhibition of control response, as indicated in figure legends. Differences in proliferation of control vs. treated keratinocytes in the group of 7 donors, were analyzed by paired t-test.

Results

DHA inhibits keratinocyte proliferation

Effects of DHA on keratinocyte proliferation were first assessed. Although there was a considerable difference in inhibition of proliferation upon incubation with DHA among individual cultures (Table 1) (Figure 1), it was established that even in lowest tested concentrations, DHA significantly decreased the proliferative capacity of cultivated keratinocytes from 100 ± 15.8 in mock treated cultures, to 50.1 ± 11.7 (mean % of control culture proliferation ± standard deviation) in cultures treated with 6.25 μM DHA ($p=0.04$). DHA in concentration of 12.5 and 25 μM, decreased the proliferation of cultivated keratinocytes up to 16.5% ± 8.5% and 4.1% ± 1.1% of ^{3}H incorporation in control cultures, respectively ($p<0.01$). There was a significant difference between cultures treated with 6.25 μM DHA, and those treated with 12.5 μM DHA ($p=0.01$), whereas there was no significant difference between cultures treated with 12.5 and 25 μM DHA ($p=0.09$).

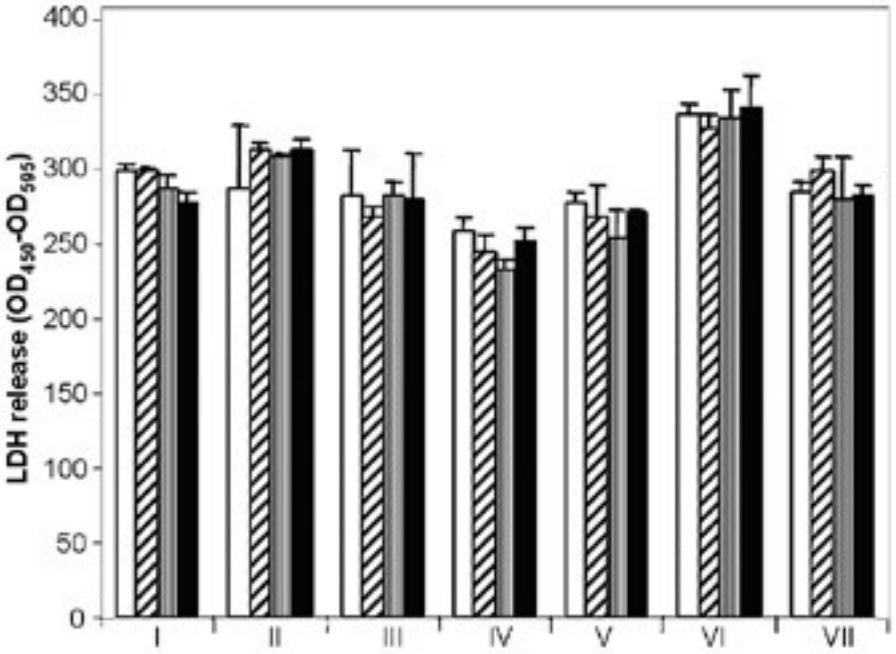

Figure 2. DHA does not induce necrosis in keratinocyte cultures

Keratinocytes were incubated without (control, open bars) or with 6.25 μM (cross hatched bars), 12.5 μM (vertical hatched bars), or 25 μM (black bars) of DHA for 72 h. The LDH release in the supernatant of cultures is expressed as OD_{450}-OD_{595}. Results are presented as mean ± SD for the triplicate of each culture and treatment.

DHA does not induce necrosis in cultivated keratinocytes

In order to test whether decreased proliferation of keratinocytes upon incubation with DHA is a result of necrotic death of cultivated keratinocytes, LDH release assay was performed. It was established that LDH activity in supernatants of cultures incubated with DHA was not significantly higher ($p>0.05$) than in control cultures (Figure 2), hence excluding that DHA induced necrosis in tested cultures.

Discussion

Omega-3 PUFAs are reported to reduce inflammation in various disorders including cardiovascular disease, ulcerative colitis, rheumatoid arthritis, and psoriasis (4, 13, 14). Potential beneficial mechanisms include modulation of pro-inflammatory cytokines production (15, 16) and n-6 eicosanoids synthesis (17).

Until now, the effects of DHA on keratinocyte proliferation have been tested in a single study which included normal foreskin keratinocytes, HPV 16 immortalized cervical keratinocytes, HPV 16 immortalized foreskin keratinocytes, normal laryngeal keratinocytes and keratinocytes derived from laryngeal papillomas (6). Study results revealed antiproliferative effects on HPV 16 immortalized cervical keratinocytes in the presence of estradiol, a growth stimulator for these cells. The same study indicated that DHA inhibited HPV immortalized foreskin cells, but did not affect normal cells and authors concluded that DHA has a profound growth inhibitory effect on HPV containing cells, but has no such effect on normal cells. Although pooled foreskin keratinocytes and transformed keratinocyte cultures are valuable systems for studying the biology of keratinocytes, they also have shortcomings: the former neglect individual variability by using pooled samples, while the latter disregard multiple molecular alterations in immortalized cell lines that can lead to different responses compared to primary cell cultures. Our previous study demonstrated that keratinocyte responsiveness to antiproliferative action of Vitamin A and Vitamin D derivates may be individual, if keratinocyte cultures are derived from different donors (18).

Furthermore, lack of DHA effect on neonatal keratinocytes, demonstrated by Chen and Auburn (6), may be at least partially explained by the fact that neonatal keratinocytes in comparison with those obtained from adult donors, have higher proliferative capacity that is maintained until the age of 10, while later it gradually decreases (19).

In the present study, we demonstrated a dose-dependent inhibitory effect of DHA on proliferation of adult human skin keratinocytes *in vitro,* with a DHA concentration one order of magnitude lower than reported by Chen and Auburn (6). The final DHA concentration used in our study was in the range of 6.25 - 25μM, based on findings that these concentrations may be achieved in plasma after daily intake of dietary or therapeutic doses of DHA (200 mg to 1,6g/ day) (20, 21). These concentrations may seem high, since individuals consuming typical Western diets have very low blood PUFA levels, but it has been shown that temporary levels of DHA, as high as 100 μM, can be achieved in plasma with dietary supplements (22).

Our results also indicate a considerable variability in responsiveness of keratinocytes from different adult donors to DHA. While a clear antiproliferative effect was uniformly obtained with 25 μM of DHA, a substantial variability in keratinocyte response was observed upon treatment with lower drug concentrations (6.25 and 12.5 μM).

In order to evaluate whether antiproliferative effect is a result of keratinocyte necrosis, LDH release assay was performed. LDH activity in supernatants was employed to assess leakage of cell cytoplasm through damaged membrane that occurs during the necrosis process. Our results indicate that antiproliferative effect of DHA is not due to keratinocyte necrosis induction, and that another process was involved in lower proliferative response of keratinocytes. Chen and Auburn suggested that DHA-induced lipid peroxidation may lead to arrest of proliferation in several types of keratinocytes. This finding may also apply to skin keratinocyte cultures. Further investigations are necessary to determine the exact mechanism of inhibition of skin keratinocyte proliferation.

Therefore, studies on keratinocytes obtained from different adult donors may be more suitable to examine the antiproliferative potential of DHA, as well as to predict their potential therapeutic effects in individual patients.

Conclusion

In conclusion, this study has demonstrated for the first time that DHA exhibits antiproliferative effects on adult human skin keratinocytes *in vitro*. Furthermore, our results imply that keratinocyte responsiveness to antiproliferative action of DHA is individual to certain extent, thus warranting further studies combining clinical research with dietary supplementation of DHA, and *in vitro* research to investigate whether *in vitro* keratinocyte response can possibly be a predictor of the therapeutic efficacy of DHA in hyperproliferative inflammatory skin diseases.

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Abbreviations

ALA - Alpha-Linolenic Acid
COX-2 - Cyclooxygenase-2
DHA - Docosahexaenoic Acid
DMSO - Dimethyl Sulfoxide
EDTA - Ethylenediaminetetraacetic Acid
EPA - Eicosapentaenoic Acid
HPV - Human Papillomavirus
LDH - Lactate Dehydrogenase
PUFA - Polyunsaturated Fatty Acids

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Antiproliferativni efekat dokosaheksanoične kiseline na adultne humane keratinocite *in vitro*

Sažetak

Uvod: Brojne kliničke studije ukazale su na povoljan efekat ishrane obogaćene ribljim uljem na tok autoimunih i zapaljenskih bolesti kao što su multipla skleroza, sistemski eritemski lupus, psorijaza itd. Dokosaheksanoična kiselina (DHA) je omega-3 masna kiselina koja je u visokoj koncentraciji prisutna u ribljem ulju.
Cilj: Zadatak ovog istraživanja bio je ispitivanje uticaja dokosaheksanoične kiseline na proliferaciju humanih keratinocita *in vitro.*
Materijal i metode: Proliferacija je određivana na osnovu ugradnje ^{3}H timidina u novosintetisanu DNK proliferisanih ćelija u kulturama keratinocita poreklom od 7 zdravih volontera. Za ispitivanje nekroze korišćen je test oslobađanja laktat-dehidrogenaze (LDH).
Rezultati: Dobijeni rezultati ukazuju da DHA značajno smanjuje prolifertivni kapacitet kultivisanih keratinocita i to od 100±15,8 u netretiranim kulturama, do 50,1±11,7 (% kontrolnog odgovora ± standardna devijacija) u kulturama tretiranim sa 6,25 μM DHA (p=0,04); dok u koncentraciji 12,5 i 25 μM smanjuje proliferaciju kultivisanih keratinocita na 16,5±8,5% i 4,1±1,1%, (p<0,01). Ustanovljena je statistički značajna razlika između kultura tretiranih sa 6,25 μM DHA i onih tretiranih sa 12,5 i 25 μM DHA (p=0,01), dok nije ustanovljeno postojanje statistički značajne razlike između kultura tretiranih sa 12,5 i 25 μM DHA (p=0,09).
Aktivnost LDH u supernatantima kultura nije bila

statistički značajno veća (p>0,05) od aktivnosti u kontrolnim, netretiranim kulturama.
Zaključak: Dobijeni rezultati ukazuju da DHA ispoljava antiproliferativni efekat na humane adultne keratinocite *in vitro* i da sniženje proliferacije nije posledica indukcije procesa nekroze u ovim ćelijama.

Neuropathic itch caused by nerve root compression: brachioradial pruritus and notalgia paresthetica

Joanna BERNY-MORENO[1], Jacek C. SZEPIETOWSKI [1,2]

[1] Department of Dermatology, Venereology and Allergology, Wroclaw, University of Medicine, Poland
[2] Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland
*Correspondence: Jacek C. SZEPIETOWSKI, E-mail: jszepiet@derm.am.wroc.pl

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Abstract

Neuropathic itch (itching or pruritus) arises from a pathology located at any point along the afferent pathway of the nervous system. It may be related to damage to the peripheral nervous system, such as in postherpetic neuropathy, brachioradial pruritus or notalgia paresthetica. It has many clinical features similar to neuropathic pain. Patients complain of itching, which is associated with burning sensation, aching, and stinging. Brachioradial pruritis (BP) is an intense itching sensation of the arm, usually between the shoulder and elbow of one or both arms. It is an enigmatic condition with a controversial etiology; some authors consider BP to be a photodermatosis, whereas other authors attribute BP to compression of cervical nerve roots. Notalgia paresthetica is an isolated mononeuropathy involving the skin over or near the scapula. Patients have a pruritus on the mid-upper back. The treatment is usually difficult, but capsaicin and local analgesic agents are the options of choice. Brachioradial pruritus and notalgia paresthetica are often unrecognized neurocutaneous conditions and therefore, a thorough history and physical examination are of utmost importance to distinguish symptoms and apply accurate therapeutic options.

Itch (itching or pruritus) is defined as a cutaneous sensation that provokes the desire to scratch. It has a protective function: to remove pruritogenic stimuli. Pruritus is a common manifestation of dermatologic conditions including xerotic skin, atopic dermatitis, and contact dermatitis, but may also result from systemic diseases. Up to 50% of patients with pruritus and without any obvious dermatological condition have an underlying systemic disease, such as chronic renal failure, cholestasis, hematological or neurological disorders (1).

Classification of pruritus

A neuropathophysiologically-based classification of itch was proposed in 2003 (2). Twycross et al. (2) classified itch according to its origin: cutaneous (pruritoreceptive-cutaneous nerves are activated by pruritogens at their sensory endings), neuropathic (damaged or lesioned pruritic neurons generate itch), neurogenic (itch is induced by mediators acting centrally in the absence of neural damage), psychogenic and mixed (e.g. uremia) (2,3). In 2007, Ständer et al. (3) proposed a clinical classification created by the members of the International Forum for the Study of Itch, which focuses on clinical signs and distinguishes between diseases with and without primary or secondary skin lesions. Three groups of conditions were proposed: pruritus on affected (inflamed) skin (group I), pruritus on non-affected (non-inflamed) skin (group II), and pruritus presenting with severe chronic secondary scratch lesions, such as prurigo nodularis (group III). The next part classifies the underlying diseases according to different categories:

I Dermatological diseases such as: inflammatory, infectious, autoimmune dermatoses, genodermatoses, dermatoses of pregnancy and neoplasms;

II Systemic diseases, including diseases of pregnancy and drug-induced pruritus, endocrine and metabolic diseases, infectious diseases, hematological and lymphoproliferative diseases;

III Neurological diseases: neurogenic origin - without neuronal damage and neuropathic diseases such as brachioradial pruritus and notalgia paresthetica, post-herpetic neuralgia etc.;

IV Somatoform pruritus: psychiatric/psychosomatic diseases;

V Mixed category - overlapping and coexistence of several categories;

VI Pruritus of unknown origin (3).

While many pruritic skin diseases can be diagnosed readily, this is more difficult with pruritus that occurs in apparently normal skin or accompanying secondary scratch-evoked lesion as a consequence of systemic disease (4).

Neuropathic itch: definition and clinical features

Neuropathic itch is defined as an itch initiated or caused by a primary lesion or dysfunction at any point along the afferent pathway of the nervous system. It can be acute, but in most cases it is chronic and persistent. In many cases neuropathic itch is accompanied by sensory impairment experienced as paresthesia, hyperesthesia, or hypoesthesia. It may also occur during recovery from isolated nerve injury such as after burns. Patients may feel both pain and itching at the same site. In many cases it involves peripheral and central sensitization of nerve fibers. This sensitization induces alloknesis, which is an itchy phenomenon that results from an innocuous stimulus that normally does not provoke itching. The characteristic features of neuropathic itch that differentiate it from other forms of pruritus are as follows: it is associated with other sensory symptoms in a dermatomal distribution and frequently with other neurological sensory signs or neural damage including motoric, or autonomic damage (4).

Mechanisms of neuropathic itch are incompletely understood. Some of the proposed mechanisms include itching associated with local nerve damage, central neuronal deprivation of afferent input and central hypersensitivity of nerve fibers. The first mechanism suggests that itching fibers, which have large innervation territories extending beyond dermatomes, arise from local damage to C nerve fibers that transmit both pain and itch. The second hypothetical mechanism suggests that central itch neurons fire excessively when they are deprived of their afferent input. Another possible mechanism is lack of inhibitory neurons for itch in the spinal tract (5). Neuropathic itch can originate at any point along the afferent pathway as a result of damage to the nervous system. Localized pruritus has been reported with peripheral nerve lesion in postherpetic neuralgia, notalgia paresthetica and HIV infection. Paroxysmal pruritus has been reported in multiple sclerosis. Unilateral pruritus is occasionally found with cerebral tumors, abscesses or thrombosis (2).

Neuropathic itch may coincide with pain, for example in postherpetic neuralgia. Patients with neuropathic itch may present with varying symptoms. Therefore, a thorough history and physical examination are essential in the evaluation of pruritus (1, 4). History-taking should include a detailed drug history, constitutional symptoms (fever, night sweats, weight loss). An accurate timing (e.g., predominantly nocturnal or diurnal) of itching helps fine-tune the antipruritic treatment (6). Close attention to features such as paresthesia, hypoesthesia, and hyperalgesia can help the clinician to diagnose neuropathic itch. A thorough neurologic examination, performed by a neurologist, may help finding associated sensory abnormalities, e.g., light touch, pinprick, thermal stimulation, perception, and vibratory sense. Electromyography and nerve conduction studies in cases suspected of nerve roots impingement may be considered. Magnetic resonance imaging of the spine is recommended to locate the suspected nerve impingement such as in brachioradial pruritus and notalgia paresthetica (4). Chest X-ray imaging may also be useful in localized neuropathic itch, e.g., due to spinal cord tumors, and nerve entrapment, due to degenerative spinal diseases (6). Neuropathic itch may occur with secondary skin findings, such as prurigo, lichenification, as well as excoriations; however, itching may also be without any skin signs (4).

Brachioradial pruritus

Brachioradial pruritus (BP) is a localized neuropathic pruritus affecting the dorsolateral aspect of the upper arm. It may also involve shoulders and the neck (7-9). There is a continuous controversy regarding the cause of brachioradial pruritus: is it caused by nerve compression in the cervical spine, or a prolonged exposure to sunlight. Brachioradial pruritus was first reported by Waisman (10) in 1968, who termed it "solar pruritus" of the elbows, describing its occurrence in patients in Florida who suffered from

a localized itch of the skin on the dorsolateral aspect of the arm. A group of 110 Hawaiian patients with chronic intermittent pruritus have been described in two reports (11, 12). In one of these, Walcyk and Elpern (11) suggested that brachioradial pruritus is a photoneurological disorder caused by sun-induced damage to nerve endings that results in pruritus and altered sensation in susceptible individuals. On the other hand, Heyl (13), in South Africa, suggested that brachioradial pruritus may be caused by nerve injury to the cervical spine, or by nerve compression at other locations, because five of his 14 patients had a history of neck trauma or arthritis.

In recent years, Wallengren at al. (14) showed that BP is associated with a reduction in epidermal and dermal nerve fibers. These findings strikingly resemble the ones they observed in the skin after serial phototherapy (14). The cutaneous innervation of pruritic skin normalizes during the symptom-free period. The results indicate that BP can be elicited by exposure to sunlight or by heat. The occurrence of brachioradial pruritus in black patients suggests that melanin offers no protection. The localization of BP to dermatome C5-7, frequent neck pain and spinal pathology, as shown radiologically, indicate the cervical spine disease to be a predisposing factor. Hypothetically, photodamaged nociceptors can start firing spontaneously, and nerve impulses generated in this way can be amplified by neurogenic mechanisms elicited by nerve compression, which is secondary to the cervical spine disease (8). Rarely, BP can also be associated with spinal tumors, especially in those patients who present with multiple sensory and motor deficits (4).

Brachioradial pruritus is often refractory to treatment. However, successful treatments were achieved with topical capsaicin, oral gabapentin and pregablin, carbamazepine, lamotrigine, and surgical procedures for tumors, or when there are significant sensory and motor deficits. Capsaicin, isolated from pepper plants of the genus *Capsicum*, depletes substance P release from C- fibers when applied repeatedly and reduces both pain and itch (2). Topical capsaicin exerts its effects by rendering the skin insensitive to pain. At higher concentrations than 0.075% and 0.1% topical capsaicin seems to be significantly more effective than the lower one of 0.025%. Addition of topical anesthetic EMLA® cream, prior to initiation of topical capsaicin has been instituted to further counteract the sensation and irritation, and can also increase the antipruritic effect, as both medications target different receptors (7, 15). Sometimes, the only treatment that can provide relief is application of an ice pack, chilling the skin to numbness, therefore a common clinical symptom in patients with BP is the "ice pack sign" (4).

Notalgia paresthetica

Notalgia paresthetica (NP) was first described and named in 1934 (16). It is a sensory nerve entrapment syndrome involving the posterior rami of T2-T6 nerve roots associated mainly with degenerative vertebral changes (17). The etiology of this condition has not been completely elucidated. Some hereditary cases have been noted, mainly in young patients, associated with multiple endocrine neoplasia type 2A. However, NP mainly occurs in older patients, and most of observed disturbances are sporadic pathologies associated with musculoskeletal spinal nerves compression (18). In their studies, Springall at al. (19) have shown that there is an increase in the sensory epidermal innervation in the affected skin areas in notalgia paresthetica, which may contribute to the symptoms, and that neural immunohistochemistry of skin biopsies can be helpful in diagnosing the disease. Patients typically present with unilateral, well-demarcated itching of the mid and upper back in the distribution of T2-T6 dermatomes, sometimes accompanied by sensory neuropathies and/or electrical conductivity disorders, or burning pain. A well-circumscribed hyperpigmented patch in the symptomatic area, similar clinically to macular amyloidosis, is frequently observed due to long-term scratching (4, 19, 20). It is very characteristic that patients may easily draw the itchy area under the skin.

Notalgia paresthetica can be successfully treated with capsaicin, gabapentin, EMLA® cream, and paravertebral local anesthetic blocks, cervical epidural steroid injections, and phenytoin. Other therapies include physiotherapy, neck traction, and cervical manipulation (4).

Recently, a pilot study described the successful use of botulinum toxin A in the treatment of NP in two patients. The toxin was injected to several points along

the involved dermatome at doses ranging between 16 and 25 units. The rationale for using botulinum toxin is that it blocks acetylcholine, which is a mediator involved in itch transmission (21, 22).

Conclusions

Pruritus is a major symptom of various skin diseases and many systemic diseases. Despite this, a clinically based classification of pruritic diseases did not exist, to assist diagnosing, and managing these patients. In 2007, Ständer et al. (3) created the first version of clinical classification of itch, formulated by the members of IFSI (International Forum for the Study of Itch). It considered the origin and clinical manifestations of pruritus occurring in the affected and normal skin. This classification provides practical and useful clinical approach to patients with chronic pruritus. Increased knowledge and understanding of itch mechanisms, including neuropathic diseases such as notalgia paresthetica and brachioradial pruritus, should encourage us to develop new therapeutic regimens to treat severe and distressing symptoms of pruritus (23).

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Neuropatski pruritus (svrab) prouzrokovan kompresijom nervnih korenova - brahioradijalni pruritus i nostalgija parestetika

Sažetak

Savremeni koncept: Neuropatski pruritus (svrab) povezan je s patološkim procesom koji može da se pojavi na bilo kojoj tački duž aferentnog toka nervnog sistema, a mogu da ga prouzrokuju povrede perifernog nervnog sistema.

Etiopatogeneza: Mogu da ga prouzrokuju povrede perifernog nervnog sistema, kao što je slučaj kod postherpetične neuropatije, brahioradijalni pruritus i notalgija parestetika.

Kliničke osobenosti: Mnoge kliničke osobine neuropatskog svraba slične su osobinama neuropatskog bola. Bolesnici se žale na svrab udružen sa žarenjem, probadanjem i jakim bolom.

Brahioradijalni pruritus: Predstavlja intenzivan svrab koji se najčešće javlja između ramena i lakta jedne ili obe ruke. To je zagonetno stanje sa kontroverznim uzrocima; neki autori smatraju da je brahioradijalni pruritus fotodermatoza, dok ga drugi smatraju posledicom kompresije cervikalnih nervnih korenova.

Notalgija parestetika: Ovo je posebna mononeuropatija koja zahvata kožu iznad ili u blizini skapule. Oboleli se žale na svrab gornjeg i središnjeg dela leđa.

Lečenje: Obično je teško, dok *Capsaicin* i lokalni analgetici predstavljaju terapiju izbora. Zaključak: Brahioradijalni pruritus i notalgija parestetika su patološka stanja koja često nisu prepoznata i zbog toga je veoma važno uzeti detaljnu istoriju bolesti i izvršiti detaljan klinički pregled radi prepoznavanja simptoma i primene odgovarajućih terapijskih opcija.

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Digital dermoscopy analysis in the diagnosis of acral and nail melanocytic tumors

Danijela D. DOBROSAVLJEVIĆ[1], Dimitrije BRAŠANAC[2]
Silvana LUKIĆ[3] and Ljiljana MEDENICA[1]*

[1]Institute of Dermatovenereology, Clinical Center of Serbia, Belgrade, Serbia
[2]Institute of Pathology, School of Medicine, Belgrade
[3]Institute of Oncology of Serbia, Department of Pathology

*Correspondence: Danijela D. DOBROSAVLJEVIĆ, E-mail: danijela_dobrosavljevic@yahoo.co.uk

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Abstract

Digital dermoscopy (epiluminiscence microscopy) is a technology for in vivo imaging of the skin used for the differentiation of pigmented skin lesions. Melanocytic tumors and pigmentations of the nails and acral skin regions represent differential diagnostic problems that can hardly be evaluated with the naked eye, especially at an early stage. Two patients with a total of three very suspicious lesions underwent dermoscopy. Clinical diagnoses were as follows: subungual hemorrhage, plantar wart (previously treated as a plantar wart several times) and acral melanoma. Dermoscopy increased the suspicion to: subungual melanoma, acral amelanotic melanoma and acral nevus, respectively. Histologic examination has verified the following diagnoses: subungual melanoma, acral lentiginous melanoma and acral junctional nevus. Dermoscopic examination of pigmented structures on the above-mentioned sites is a very useful adjunct in establishing accurate diagnosis that can help in differentiating benign from malignant lesions.

Plantar and subungual melanomas, compared with other lower extremity melanomas, are very difficult to diagnose, especially at an early stage (1, 2). Numerous studies have shown that in case of atypical presentation of acral melanoma, benign types are more frequently diagnosed (2-5).

Melanomas, nevi and pigmented lesions in the acral regions, represent an important clinical diagnostic problem related to their specific location, hindered dermoscopy examination and different interpretation criteria in regard to those applied for skin lesions on other sites (6).

Dermoscopy (epiluminiscence microscopy (ELM), *in vivo* surface skin microscopy, dermatoscopy, and videodermatoscopy) is a non-invasive diagnostic technique which provides visualization of structures under the skin surface, thus opening a whole new world of colors and structures, invisible with the naked eye (7-13). Dermoscopy is used for early diagnosis of melanocytic lesions, especially for the diagnosis of cutaneous melanoma (6-15). Also, it enables differentiation of benign and malignant pigmented skin lesions: pigmented basal cell carcinoma, seborrheic keratosis, dermatofibroma, as well as vascular and some other non-melanocytic lesions. Today, dermoscopy is a routine technique in Europe, and with growing number of practitioners using it in other countries (14).

Patients and methods

This paper presents two patients with a total of three lesions at the above-mentioned localities. Dermoscopy examination of these three lesions enabled further correct diagnosis and treatment.

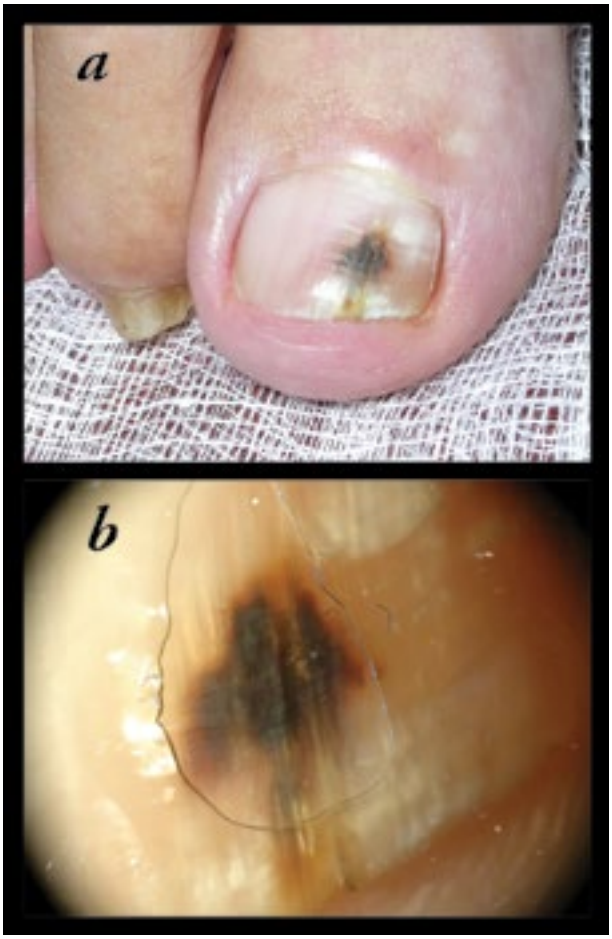

Figure 1. Subungual lesion: a) clinical appearance; b) dermoscopy

Dermoscopic images presented in this paper were obtained using the Heine Delta 10 Dermatoscope and immersion oil, 4 megapixel digital camera, Pentium IV computer and a Samsung Syncmaster 959NF monitor. The initial 10-fold magnification was raised to 60 x.

Patient No. 1

Clinical features

A female, aged 61 years, was referred for a toenail pigmentation on the right foot observed 5 months earlier. No trauma was recalled by the patient. Family and personal history for melanoma and skin cancer were negative. A dark diffuse pigmentation appeared on the great toenail 6x5 mm in size (Figure 1a).

Digital dermoscopy

Dermoscopy revealed an irregular pigmented lines, uneven in color and spacing, and some disrupted parallelisms on a brown background. The colors of the pigmented lines were: pale and dark brown, blue-grey and black (Figure 1b). There were no elements for subungual hematoma. The lesion was suspicious for subungual melanoma.

Histopathology

Histopathology confirmed an acral lentiginous melanoma.

Patient No. 2

Clinical features

A female, aged 83 years, was examined for two lesions on the left foot (Figure 2a). One lesion was located on the heel. A plantar wart was diagnosed by a dermatologist and cryotherapy with keratolytic therapy was applied. Within five weeks, two curettages were performed, and after the second curettage**,** light bleeding occurred. The patient was re-examined on the third appointment and referred to surgery because another lesion on the arch of the foot was considered to be an acral melanoma. The examination

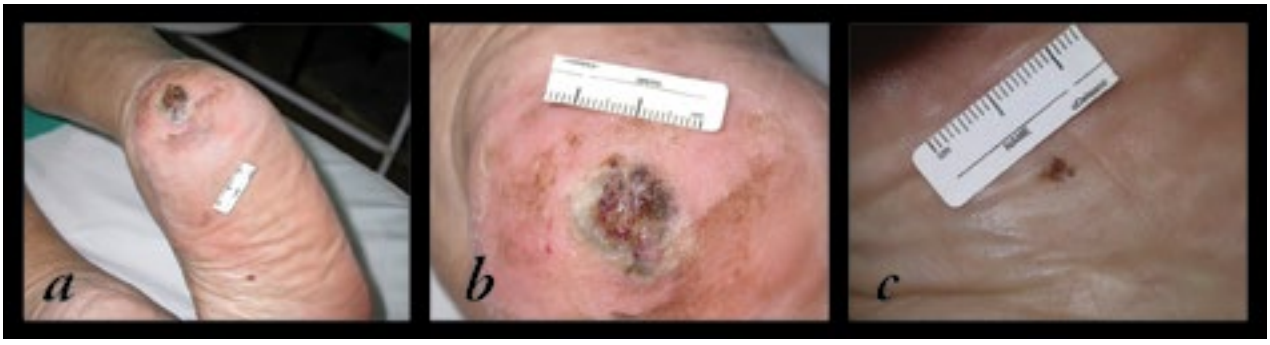

Figure 2. Plantar lesions on the same foot: a) heel and the arch; b) heel; c) arch.

in our institution revealed a heel lesion, was 19 mm in diameter. The lesion had a few smaller ulcerations with hematoma around them and black and bluish-black pigmentation on the edge (Figure 2b). The pigmented tumor on the arch of the foot was 6 mm in diameter with marked asymmetry (Figure 2c). Family and personal history for melanoma and skin cancer were negative.

Digital dermoscopy

a) Dermoscopy revealed a fresh hemorrhage and a few crusts in the center of the lesion on the heel. Abundant dark pigment might have been related to hemosiderin, but also to melanin pigmentation. On the very edge of the lesion, pigment that followed the ridges of the skin surface was observed (Figure 3a). This was the clue to suspect acral melanoma.

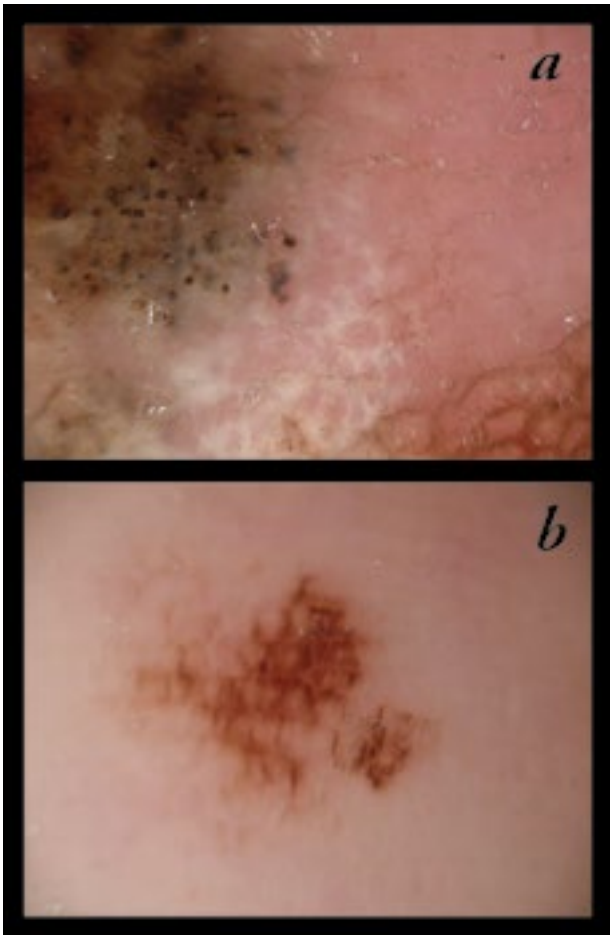

Figure 3. Dermoscopic examination of the plantar lesions on the same foot: a) heel; b) arch

b) A ladder type melanin pigment was observed on dermoscopy of the lesion on the arch of the foot. Eccrine glands ostia were visible without obliteration (Figure 3b). After dermoscopic examination, acral melanocytic nevus was suspected.

Histopathology

a) Lesion on the heel presented an acral lentiginous melanoma, Breslow thickness of 1.43 mm, Clark level III/IV with 7 mitoses per square millimetre, with lymphocytic infiltration of „brisk"-type with regression**:** large, atypical melanocytes were distributed mostly along the basal layer of the epidermis (lentiginous pattern); irregular nests at the dermal-epidermal junction and infiltrations by rare single cells were present in the upper epidermis (Pagetoid distribution) (hematoxylin-eosin stain, original magnification 100x) (Figure 4).

b) Lesion on the arch of the foot pathohistologically presented a lentiginous junctional melanocytic nevus.

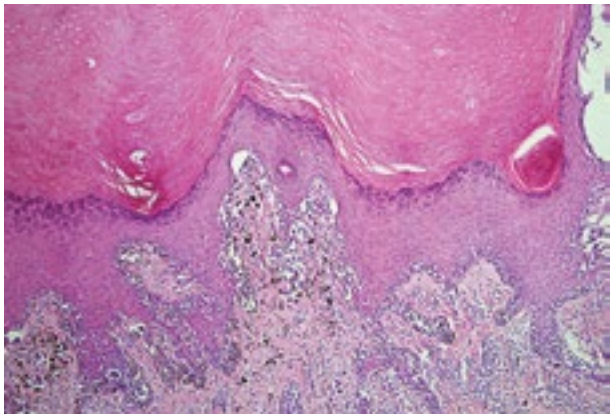

Figure 4. Histolopathology of the acral melanoma on the heel presenting lentiginous and nest-type of radial growth phase (hematoxylin and eosin x100)

Discussion

Acral melanoma is an anatomical term for melanoma located on the palms, soles and subungual regions. On the other hand, the frequently used term „acral lentiginous melanoma" as a synonym, includes histological specific subtypes of melanoma which is characterized by marked acanthosis, elongation of rete ridges, as well as lentiginous proliferation of atypical melanocytes in epidermis (16). So, acral melanomas comprise both acral lentiginous melanomas, as well

as superficial spreading melanomas and nodular melanomas that may develop in acral sites. Acral lentiginous melanoma is the most frequent histological subtype in acral locations (1, 3). Comparing to growing incidence of other subtypes of melanomas (17) the incidence of acral and acral lentiginous melanomas has not changed for many years (18). The total number of acquired melanocytic nevi is a significant risk factor for nonacral melanoma, but not for the acral type (18). The appearance of acral lentiginous melanoma is associated with worse prognosis, because it is often more advanced at the time of diagnosis (1, 19, 20). Acral melanomas are rare: they represent 1-3% of all melanoma cases in Caucasians (21). It presents a diagnostic challenge, disregarding whether worse prognosis of acral melanoma is connected to late diagnosis in advanced stage, or it is a tumor with more aggressive biological features. Increased mortality associated with acral melanoma requirers earlier and better diagnostics (22).

In the first patient, suspicion of subungual melanoma was established based on dermoscopic features which are characteristic for subungual melanoma - brown background and longitudinal lines of irregular thickness, spacing and coloration (23). Although several clinical criteria for early diagnosis of subungual melanoma have been proposed (24), none of the suggested clinical criteria or a combination with symptoms are significant to avoid unnecessary painful biopsies of the nail matrix that may leave dystrophic scars (25). It is especially important in the case of benign lesions and pigmentations. For now, the only improvement considering preoperative diagnosis has been achieved with dermoscopic examination. It sholud be used not only for subungual melanoma, but also for subungual hematoma, nevus, drug induced pigmentation, subungual lentigo and ethnic type of pigmentation (23).

After establishing a benign lesion (e.g. plantar wart) on the heel, aggressive treatment was performed in the second patient (22). Thick melanomas frequently occur on acral locations with an average thickness of 3.03 mm (2) and 3.31 mm (22). Breslow thickness of melanoma in our patient was 1.43 mm, which is lower than the average in the literature. It is also a fact that the existence of another lesion - acral nevus that was suspected to be a melanoma, proposed the idea of dermoscopic examination. Based on dermoscopy, suspicions of acral melanoma on the heel and nevus on the sole were confirmed. Dermoscopic criteria for acral pigmented lesions were precisely defined. Acral melanoma is dermoscopically characterized by a pigmentation that follows the ridges of the skin, or it has a non-specific pigment pattern (6, 26), whereas benign acral nevus is characterized by pigment within the sulci or it has characteristic fibrillar, globular or some other regular pigment pattern (6, 26).

The ABCD (A - asymmetry, B - border, C - colour and D - diameter) rule was introduced into the clinical diagnostics of melanoma in the eighties (7-9). Still, sensitivity of clinical diagnosis according to the ABCD rule was 65-80% and even lower in small diameter melanomas (less than 5 mm) (7-9). Small melanomas often have homogenous color and regular shape, and therefore a minimum of 25-30% of melanomas still escape clinical diagnosis (27). Addition of the E criterion (E - enlargement) has raised the sensitivity of ABCDE rule by 3-8% (10). Further steps in improving the diagnosis of melanoma have been taken to visualize the structures under the skin surface e.g. structures that were not visible by the naked eye. Introduction of dermoscopy has increased the sensitivity in melanoma diagnosis by 10-27% comparing to the sensitivity of clinical ABCD criteria (7-9).

Dermoscopy has limitations, especially in the case of very early stage melanomas without developed dermoscopic characteristics (28, 29) and false positive and false negative results (30). Because of that, dermoscopy cannot replace the gold standard – histology, but results of meta analyses point to more accurate diagnosis with the use of dermoscopy (31). Dermoscopy should be performed by experienced persons, since better sensitivity and specificity is gained, while less experienced examiners show poor results (11-13).

Dermoscopy was introduced by the Ministry of Health, as a new, highly specialized service in

the Serbian health system in September 2005. New technologies and instruments for *in vivo* melanoma diagnosis are being developed in the world. There are great expectations, not only from new dermatoscopes, but also from devices for multispectral skin analysis, confocal scanning laser microscopy, ultrasound, even experimental use of nuclear magnetic resonance (15). It is a realistic expectation that in the future, preoperative diagnosis of melanoma, melanocytic and non-melanocytic lesions, will be improved.

Conclusion

There is a need for more precise methods for the evaluation of pigmented lesions in acral locations. According to the results of numerous studies published in the last two decades, digital dermoscopy has found its place in the diagnosis of pigmented skin lesions, especially melanocytic lesions and melanomas. Our positive experience might be an example for wider employment of dermoscopy, especially digital dermoscopy, in our country.

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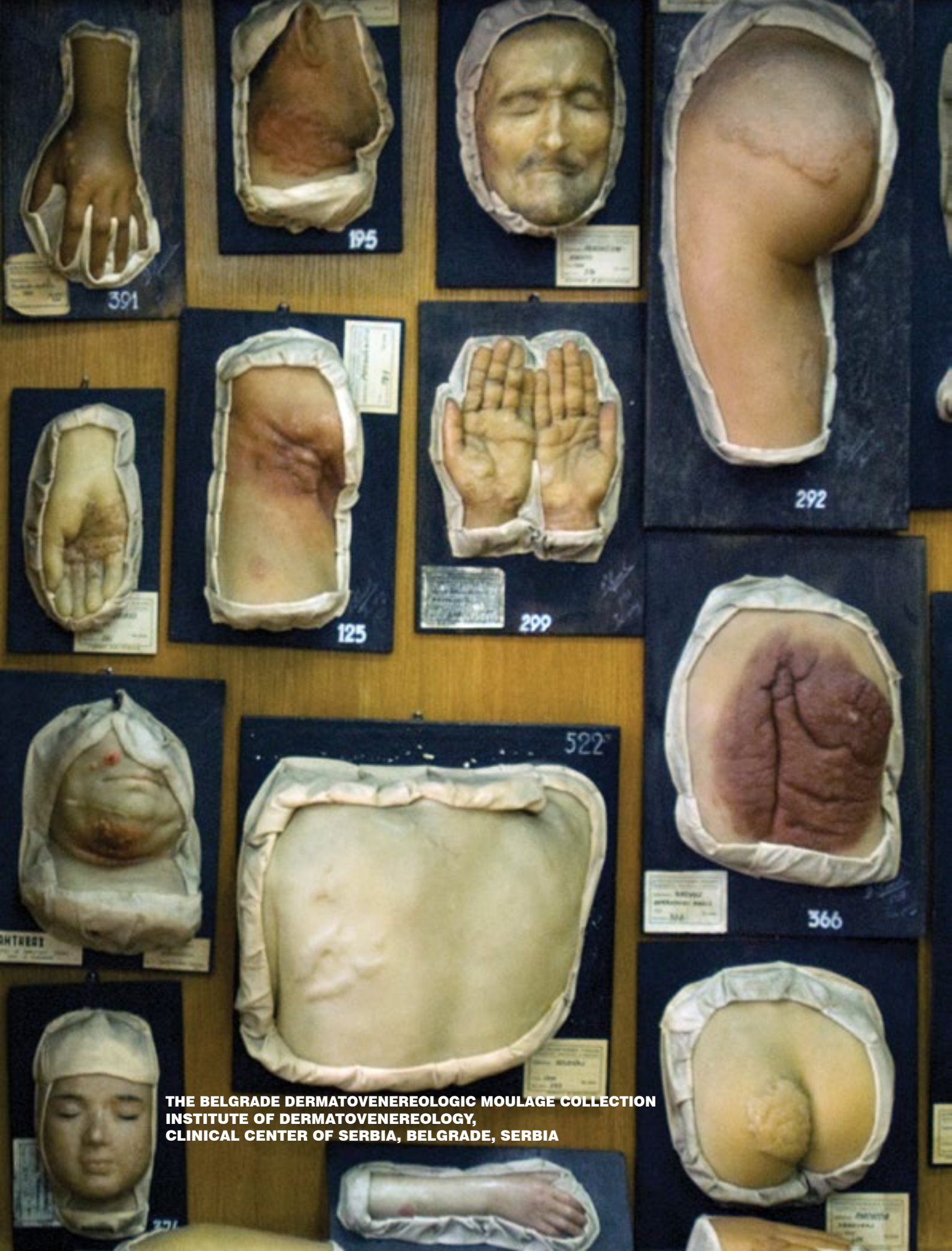
Digitalna dermoskopija u dijagnozi melanocitnih tumora noktiju i akralnih delova tela

Sažetak

Uvod: Digitalna dermoskopija (epiluminiscentna mikroskopija) je in vivo mikroskopija kože koja omogućava diferencijaciju pigmentnih lezija kože. Melanocitni tumori i pigmentacije noktiju i akralnih delova tela predstavljaju diferencijalno-dijagnostički problem koji se teško prepoznaje golim okom, posebno u ranom stadijumu.

Prikaz 2 slučaja. Ovo je prikaz dve bolesnice koje su podvrgnute dermoskopiji zbog ukupno 3 veoma sumnjive lezije. Njihove kliničke dijagnoze bile su sledeće: subungualni hematom, plantarna bradavica (prethodno lečena kao takva u nekoliko navrata) i akralni melanom. Dermoskopijom se došlo do sledećih rezultata: subungualni melanom, akralni amelanocitni melanom i akralni nevus. Histološkom analizom postavljene su sledeće dijagnoze: subungualni melanom, akralni lentiginozni melanom i akralni lentiginozni junkcioni nevus.

Zaključak: Dermoskopski pregled pigmentnih struktura na gore navedenim lokalizacijama veoma je korisna dodatna metoda u postavljanju tačne dijagnoze koja može da se koristi u diferencijaciji benignih i malignih lezija.



THE BELGRADE DERMATOVENEREOLOGIC MOULAGE COLLECTION
INSTITUTE OF DERMATOVENEREOLOGY,
CLINICAL CENTER OF SERBIA, BELGRADE, SERBIA

History of dermatology and venereology in Serbia - part II: Dermatovenereology in Serbia from 1804 - 1880

Bosiljka M. LALEVIĆ-VASIĆ*

Institute of Dermatology and Venereology, Clinical Center of Serbia, Belgrade, Serbia
*Correspondence: Bosiljka LALEVIĆ-VASIĆ, E-mail: labuba@eunet.rs

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Abstract

This paper deals with historical aspects of the development of dermatovenereology in Serbia in the period of liberation wars against Turkey until gaining complete independence (1804 – 1878). Communicable diseases were a major health problem of that time. One of the most important infectious diseases was syphilis, and the development of dermatovenereology in Serbia began with fighting this disease. Special emphasis was put on the origin of the first hearth of the disease and prevalence of syphilis in the country. In this period, two dates were associated with eradication of syphilis: in 1846, the true nature of "frenga" (the term people used for syphilis) was established, and in 1851, the first hospital for venereal diseases was founded in Knjazevac. Another disease important for the development of dermatovenereology was scabies, which was also rather spread and required organized eradication. "Instructions on Scabies" were published in 1845, its treatment was mandatory, whereas people had a legal duty to report the disease. In both cases, the western medical doctrine was applied. The study also deals with a number of other skin and venereal diseases, which points to good professional knowledge of health professionals of that time.

At the beginning of the 19th century, Serbian resistance to the Turkish rule started with the First and Second Serbian Uprising, which lasted over a decade: from 1804 to 1815. In 1830, Turkey granted autonomy to Serbia, but formal independence was gained in 1878 and it was recognized at the Congress of Berlin (1). Restoration and organization of Serbia started during this period, through establishment of its political identity and of all institutions of supreme and local authorities, as well as health care services.

Political, socio-economic and health conditions in Serbia in the 19th century

After the uprisings, social and cultural circumstances in Serbia were still at a low level; there were no physicians, hospitals, schools and roads, while the vast majority of people, even the leaders of the uprisings, were illiterate (2, 3, 4). The situation was worst in the North-East Serbia, where people lived in shabby houses; shared beds and cookware, often even with the live-stock (5, 6, 7). The long-lasting conflicts, associated with migrations, but also with the development of political and trade relations, influenced spread of communicable diseases that dominated the 19th century (2, 3, 4).

In such a situation, in the first decades of the 19th century, folk healers used to play a significant role in the treatment of skin and venereal diseases, whereas some of them became "specialists for syphilis". However, some of them were given permissions to practice medicine by the authorities, probably because they thought it was better to have anyone than no one (3, 4). Gojko Marković was one of the best known empircs[1], and the most significant representative among them. He was from North-East Serbia, but in 1813 he was captured and delivered to one Greek **"**Ećim**"**, who lived in Alexandria and Smyrna, and where Gojko learned about "practical healing" of syphilis (SY) (4). However, Serbian Constitutions

[1] Empircs were self-taught persons who gained their knowledge from physicians and who were recognized by the authorities (2).

from 1835 and 1838, paid special attention to "public health" (2), and a Sanitary Quarantine Department was established within the Ministry of Internal Affairs (8, 9). The first physicians at position of the Head of the Department were: Dr. K. Pacek (1839 – 1842), Dr. J. Stejic (1842 – 1845) and Dr. E. Lindenmajer (1845 – 1859) (9). This was the true beginning of the professional and organized health care in Serbia**.** The physician staff best illustrated it, since the first educated physician in Serbia, Dr. Alexandridi started working in 1819 (10), there were 4 physicians in 1829 (11), in 1830 there were 9 (9), in 1852 there were 21 physicians and 5 surgeons, while in 1870 there were 73 physicians (2).

Dermatovenereology diseases

During the 19th century, people of Serbia were subject to the same diseases as under the Turkish occupation, but venereal diseases spread widely in the population (2). Syphilis (SY) soon became one of the major health problems, and somewhat later scabies (SC) as well. That is why there is so much data about these diseases and using them it is possible to follow the development of dermatovenereology in Serbia. The frequency of dermatovenereology diseases, due to the lack of other sources, can approximately be assessed based on the fifteen-year "Review of Diseases in the Serbian Army" (1840 – 1875), which was taken as the basis for analysis. Out of all diagnosed diseases of that period (82.435), dermatovenereology diseases accounted for 19.7% (65.6% skin diseases and 34.4% venereal diseases) (12).

North-East Serbia is considered to be the cradle of Serbian dermatovenereology, because the first epidemics and endemics of syphilis occurred there. Just like in Europe, this disease had significantly affected morals and measures of public health (13), but also stimulated the development of venereology, as well as health care**,** generally speaking. Although they were rather frequent, skin diseases were neglected for a long time in Serbia, as well as in other countries, where "dermatology was considered to be the poor sister of venereology" (14).

Venereal diseases

In the 19th century, in Serbia people frequently suffered from syphilis, gonorrhoea (GO) and Ulcus molle (UM). According to insufficient data, the ratio between the number of people suffering from venereal and the total number of diseased people varied from 6.78% (12) to 13.7% (1871 – 1875); similar values (10.5%) were gathered in 1868 in a group of 4000 healthy soldiers (2). The average frequency of certain diseases within venereal diseases obtained from three medical reports in the period 1871 – 1874 is as follows: GO – 30.7%, SY – 29.5%, UM – 26.3**%** and undefined venereal diseases – 13.5% (2). At that time the causative agents of these diseases were still unknown.

Syphilis

In the 19th century, syphilis (SY) was called "frenga" in Serbia. The term originated from the Turkish language – "frenga ilata", meaning "French disease" (5) or "European disease" (3). People used only this term, but some physicians used it as well. Some considered it a disease special for Serbia, and it was compared with *Morbus Scrilevo* (a place in Croatia) (2). The nature of the disease was uncertain, even to some physicians (2, 7), but it was considered to be venereal and contagious (7). However, people in the North-East Serbia used the term "frenga" for a non-venereal, endemic disease, whereas syphilis was a sexually transmitted disease (6).

The appearance and spreading of syphilis in Serbia

It seems that syphilis was not frequent before the beginning of the liberation wars, which is evident from the appearance of endemic syphilis since the second and fourth decades of the 19th century (2, 5). The first hearth of syphilis appeared in the North-East Serbia, whereas during the following 20 years**,** the disease spread over the whole region of the East and Central Serbia, while the West regions were partly spared (2).

Syphilis invaded Serbia by the conquering Ottoman troops mostly over the Eastern border, from Asia, which was the major source of contagious diseases (15). Syphilis also spread from Romania, because the endemic seat of the disease in the North-East Serbia coincided with the immigration of the Romanian population (5), but it was also present in Bulgaria. Russian troops, who came to help Serbian uprising in 1810, were also important, because some soldiers were from the regions with endemic syphilis. These troops remained in Serbia for several months and even got to Belgrade (2, 5). To a lesser extent, syphilis was also transmitted from the west border, from Bosnia,

Herzegovina and Dalmatian Coast (5, 16). The northern border was the safest, due to strict sanitary measures in Austria (3). However, the Austrian army fought the Turks on the Serbian territory, soldiers mingled with the local population, while prostitutes and adventurers were always close behind (2).

Syphilis and organization of health care services

The first archive document on the appearance of syphilis in Serbia originates from 1818 and refers to the treatment of four "servants" of the Prince (4). As early as 1829, Vuk Karadžić recommended Prince Miloš Obrenović to build a hospital for free treatment of those with the widespread "venereal disease" (10). In 1835, 30 prostitutes underwent medical check-up in Belgrade and 19 were infected (2). In 1838, one third of the Gurgusovac[2] County population were infected by "frenga", and young persons "without lips and noses" (4) could be seen, whereas in the Kruševac County there were 500 inhabitants with "frenga" (3). Empirics and quacks played an important role in that period and V. Mihajlović believed that without writing about them the history of venereal diseases would be neither complete nor informative (2). The most famous among them was the abovementioned Gojko Marković. Since 1836, he treated syphilis in the Gurgusovac County (2), but also owned a private hospital (4). As syphilis was spreading, an "informal" hospital for patients with syphilis was opened in a Gurgusovac inn in 1838 with the approval of authorities and Gojko Marković was appointed a "physician". Although there were many comments, it was the first attempt for organized hospital-based treatment of syphilis in Serbia (2, 4). There were other empirics, of whom the authorities were aware of, but also travelling quacks, adventurers and imposters as well (3). Folk healers were confused by venereal diseases. Under the term "frenga", Gojko Marković used to treat various diseases, whereas venereal diseases were included in the group of "moist frenga" (2, 3). The most frequently used medication was mercury (pills, inunction, fumigation), then gunpowder, "green stone", antimony, Spanish fly powder ("pulvis cantharidum") and turpentine, and potassium iodide (2, 3, 18), as well as great quantities of *Sarsaparilla* (a climbing plant whose roots were used for "blood purification") (2, 19). Unfortunately, it was all done unprofessionally, without any insight into dosing and signs of intoxication.

At the beginning, folk healers were allowed to work, but after the establishment of the Sanitary Quarantine Service (1839), the Chief of Staff, Dr. K. Pace started fighting against quackery, primarily in the treatment of syphilis. Moreover, in 1840, he tried to investigate the work of the hospital for treatment of syphilis, as well as the nature of "frenga". The turbulent political situation, frequent changes of governments, and certainly lack of physicians, resulted in postponing this project (4). In 1846, a Medical Board was founded and it treated four selected patients suffering from still unclear disease frenga, in the separate room in the Military Hospital in Belgrade. In the end, the Board established that it was in fact syphilis, and suggested treatment modalities, which were to be performed in hospital settings (2, 20). The first hospital intended for the treatment of syphilis in Serbia and the first official venereology hospital at the same time, was opened in 1851 in Gurgusovac (Knjazevac). It was managed by surgeons or graduate physicians, while patients with syphilis were treated free of charge (17). Some other hospitals were also opened for the treatment of patients with syphilis: Dr. Šauengel's Private Hospital in 1847 (2); small hospitals, mostly in private residencies, were opened in 9 counties in 1853, and they were called "syphilitic hospitals"; Hospital in Sklapnica (1859 – 1864) (2). That is why syphilis is considered to be the reason for the implementation of the hospital policy in Serbia (2, 21). In 1852, when the organization of syphilis treatment in Serbia passed into professional hands completely, Chief of Staff, Dr. Lindenmajer reported that the number of patients with syphilis had significantly decreased. The decline continued until the Serbian-Turkish war (1876 – 1878), when the sanitary work stopped due to war conditions, causing spreading of syphilis again (2, 3). During the war, Gurgusovac was burnt down by the Circassians and Turks, and so was the first hospital (2, 17). The destiny was fulfilled: everything had to be started from scratch.

Gonorrhoea and Ulcus molle

Gonorrhoea (GO) and Ulcus molle (UM) were frequent diseases in Europe of the 19th century. In Serbia, these diseases together, were almost

[2] In 1859, Gurgusovac was renamed into Knjaževac (17)

twice more frequent than syphilis (see Venereal Diseases). In areas where it was endemic, syphilis was predominant, whereas in urban and suburban areas UM and particularly GO were more frequent (2). The difference was even greater, considering the fact that registration of patients with syphilis was mandatory. However, the term gonorrhoea also included the following conditions: chronic GO (2, 12), blenorrhagic ophthalmia, whereas orchitis was established in 35.7% of GO cases (2). Nevertheless, no data about treatment modalities are available.

Prostitution

Prostitution was also spreading after the uprisings and it was first mentioned in 1822. It was present in urban areas, in taverns and inns, later in brothels usually kept by older women (3). Instead of lacking laws, Prince Miloš made decisions about everything, including prostitution (22), but the Belgrade Court and Archbishop also took part (3). Prostitutes with venereal diseases had to seek treatment themselves; they were not allowed to have intercourses with men (22), and unpaid labor was also used as a punishment (12). People were given advice to take good care (22); guild members were asked to teach their journeymen decency, but there was also a threat that those "who get venereal diseases from prostitutes" will not get any help. Banishing from the country was one of the solutions, but Prince Miloš was against it in order to "stop spreading sexual promiscuity" (3). The first legal act with fines for prostitutes spreading venereal diseases was brought in 1850 (17); in 1860 prostitutes were demanded to leave the surroundings of military camps, and in 1861 the authorities took measures and prostitutes were occasionally treated from venereal diseases (12). In 1879, health-check-ups were regular for prostitutes of the Knjazevac County (17). Since 1827, infanticide was sometimes punished by death penalty; duties were established for the pregnancy outcome for the future father, the state and the whole village (3).

Skin Diseases

During the transition from the 18th to the 19th century, dermatological pathology has not changed significantly, but more data became available after the foundation of military hospitals (1835 – 1836), and the Sanitary-Quarantine Service (1839). According to the "Review on the Diseases in the Army" (1840 – 1875), skin diseases were diagnosed in 12.9% of patients (12).

Scabies

Scabies (SC) was established in 55.3% of all dermatoses in the above mentioned series (12). The first archive document about this disease dates back to 1819 (23), while an epidemic was recorded in the army in 1837 (4). Scabies was also spread in Europe, but there were other dermatoses described under that term. After the discovery of *Sarcoptes scabiei* in 1834, and experiments of F. Hebra in 1844, it was possible to define clearly the *Sarcoptes* related disease (24). The discovery of this parasite has completely changed the understanding of the etiology of skin diseases (25). In 1845, due to great incidence of scabies, the Chief of Staff of the Sanitary Department, E. Lindenmajer published "Instructions on Scabies", which were distributed in all counties in Serbia in 1845, 1857, and 1960. According to these instructions, treatment of scabies was either "external" or "internal", but in both cases, it was treated by sulphur (22). Since the 6th decade of the 19th century, patients received only local therapy, because "the true nature of scabies was already known" (3, 12). This shows that even though Serbia remained isolated from the civilization for several centuries, it succeeded to reach the standards of scientific dermatology of the 19th century rather early. In 1852, the Sanitary-Quarantine Service initiated free mandatory treatment of scabies, as well as registration of patients and keeping records (3). It means that these measures were successful, because among Serbian soldiers recruited in 1879 – 1880, scabies was diagnosed only in 2% (17).

Scrophuloderma

Scrophuloderma was also rather frequent (11.6%).

Other dermatoses

Other dermatoses (11.4%) included: skin rashes, eruptions, parasitic diseases except scabies, frostbite, bullous rashes, herpes zoster, eczema (12), leprosy, elephantiasis (4), open wounds (skin cancers), urticaria, miliaria (17). This clearly shows that the diagnosis range of skin diseases was high and that knowledge of skin diseases was good. Data on treatment modalities are poor, including only herbs (4), probably from written documents of the medieval medical practice. Wounds, including syphilis, were treated with oil of vitriol, *lapis causticus* and phagedenic water (2). Spa treatment was an innovation, and it was recommended since 1834,

when chemical analysis of our "medicinal waters" was performed in Vienna. It was advised for infant eczema ("firciger"), scabies, chronic eczema, eruptions and old wounds (3). After the foundation of the Serbian Medical Society in 1872, dermatovenereology problems already dominated the first sessions, and due to dermatovenereology terms, important question of medical terminology was opened (26).

Conclusion

Despite the fact that dermatovenereology did not exist in Serbia of that time, it is obvious that dermatovenereology was being formed as an independent profession.

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Abbreviations:

SY – Syphilis;
SC – Scabies;
GO –Gonorrhoea;
UM – Ulcus Molle

Istorija dermatovenerologije u Srbiji - II deo: Dermatovenerologija u Srbiji od 1804. - 1880. godine

Sažetak

Dermato-venerološka oboljenja: U XIX veku u Srbiji su vladala ista oboljenja kao i za vreme vladavine Turaka, ali su se značajno proširile venerične bolesti. Prema statističkim podacima o stanju zdravlja u srpskoj vojsci, od svih oboljenja, kožnih i venеričnih bolesti bilo je 19,7% (65,6% kožnih a 34,4% venеričnih bolesti).

Venerične bolesti: Zbog pojave epidemija i endemija, centralno mesto je zauzimao sifilis, koji se prvo raširio u severoistočnoj Srbiji odakle je borba protiv ove bolesti pokrenula razvoj dermatovenerologije. Lečenje su u početku sprovodili nadrilekari, a kasnije lekari, pa je 1851. godine podignuta prva zvanična venerološka bolnica gde je lečenje sprovođeno besplatno. Situacija se popravljala do Srpsko-turskog rata (1876-1878) , kada je sifilis ponovo počeo da se širi.

Bolesti kože: Druga bolest, takođe značajna za razvoj naše struke bio je *Scabies*, koji je predstavljao više od polovine svih dermatoza. Zbog toga su 1845. godine izdate „Pouke o šugi“, s obaveznim lečenjem i prijavljivanjem obolelih.

Zaključak: U oba slučaja je primenjena medicinska doktrina koja je važila u Evropi. Istovremeno je bio poznat i veći broj drugih kožnih i venеričnih bolesti, o kojima su podaci oskudniji.

A report on the 17th Congress of the European Academy of Dermatology and Venereology

The Annual Congress of the European Academy of Dermatology and Venereology was held in Paris from September 17-20, 2008. The main idea of the Congress was ''Understanding new developments for better care". The Congress was based on scientificity, great clinical commitment and openness to many voices of international dermatology. Paris impressed and excited a great variety of nationalities, because representatives from more than 80 countries took part in its program.

There were more than 150 free communications in special sessions, and over 1700 posters. Many new experiences were presented, such as: diagnosis and classification criteria for pemphigus vulgaris, dermatoscopy in surgical management of basal cell carcinoma, split-skin grafting in vitiligo surgery and drug hypersensitivity syndrome. The following topics were especially attractive: the future of acne treatment, acne scarring, new antifungals in dermatology, news about scabies, pediculosis, leishmaniasis and borreliosis, vaccination for infectious deseases, immunomodolatory strategies in skin cancer treatment, nail surgery, vitiligo treatment, news in hair research, development of a guideline for the biology of psoriasis, nutrition and skin aging... More than 150 companies were present and 27 satellite symposia were held during 4 days dealing with hair problems, chronic hand eczema, skin aging and so on.

Participants from Serbia presented 65 posters, whereas Professor Ljiljana Medenica was the chair of the free communication session on "Skin Cancers".

Zoran GOLUŠIN

Clinic of Dermatovenereology Diseases,
Clinical Center of Vojvodina, Novi Sad, Serbia
*Correspondence: Zoran GOLUŠIN,
E-mail: zgolusin@eunet.rs

Hair and Nails – What's New? Scientific Meeting at the Academy of Medical Sciences of the Serbian Medical Society

In January 2009, the Academy of Medical Sciences of the Serbian Medical Society in Belgrade, organized a meeting entitled "Hair and Nails – What's New?" The meeting was organized by regular members of the Academy, dermatologists: Prof. Dr. Đorđije Karadaglić and Prof. Dr. Sava Konstantinović. Prof. Dr. Pavle Milenković, the President of the Academy, welcomed the gathering. The introductory word was given by Prof. Dr. Konstantinović, who emphasized that in the last 8 years there were 6 scientific meetings in the field of dermatology and venereology. The meeting was attended by around 150 dermatovenereologists from whole Serbia, and a total of ten papers were presented.

Prof. Dr. Marina Jovanović, from the Clinic of Dermatovenereology Diseases of the Clinical Center of Vojvodina, Novi Sad, a newly elected associate member of the Academy, gave a lecture on standard and new therapeutic approaches to *alopecia areata* (AA). She provided a detailed review of how the immune privilege collapse (the resistance to induction of acquired immune response, due to the lack of MHC antigen expression and unique ability for deposition of apoptotic materials within the dermis), leads to the initiation of AA, and how regarding genetic variability, each patient may present with a different type or subtype of AA. In conclusion, the author stated that the aim of the therapy should primarily be to restore the collapsed immune privilege, and that every initial treatment, if it is successful, is the primary promoter of a spontaneous hair re-growth in the short term, while in the long term, treatment should always be required in order to maintain a spontaneous hair growth cycle.

Prof. Dr. Ivana Binić, from the Clinic of Skin and Venereal Diseases of the Clinical Center in Niš, gave an update on androgenetic alopecia. She provided a clear review on many advances regarding androgenetic alopecia, which included hair culture systems, pathogenesis, hair cycle dynamics, latent

phase in the hair re-growth cycle, description of chronic *telogen effluvium,* histological diagnostic criteria for androgenetic alopecia in women, identification of stem cells in the hair follicle, as well as the possibility of targeting these cells for gene therapy.

Dr. Petar Bojanić, a dermatovenereologst from the Health-Care Center in Kruševac, provided some new perspectives on *tinea capitis,* such as the necessity for systemic therapy. He emphasized the following therapeutic imperatives: good knowledge of the pharmacological features and adverse effects of current antimycotic agents, optimal choice of dosage, and length of treatment. Local preparations, including shampoos, are insufficiently efficient, due to the fact that they do not penetrate the hair shaft. In conclusion, the author pointed to the importance of treating asymptomatic infections in order to prevent further spread of infections.

Dr. Zoran Golušin, MD, MS, from the Clinic of Dermatovenereology Diseases of the Clinical Center of Vojvodina, Novi Sad, reported on hair and nail disorders in sexually transmitted infections. In conclusion, he pointed out that these disorders may exist alone, but they often occur as a manifestation of sexually transmitted infections. However, in most cases they are nonspecific for certain sexually transmitted infections.

Prof. Dr. Milenko Stanojević, from the Clinic of Skin and Venereal Diseases of the Clinical Center in Niš, presented the state of the art knowledge on *seborrheic dermatitis* of the scalp. This rather common inflammatory disease affects 2–5% of the adult population. The author pointed out that in the multifactorial etiology of the disease, *Malassezia ovalis*, a microorganism of the yeast family, plays an important role and that presence of parakeratotic squamous crusts arising from the dilated hair follicles in the histopathological finding, with anamnesis and clinical picture, are of utmost importance in establishing the diagnosis. The treatment should be based on local preparations with combined keratolytic anti-inflammatory and antimycotic effects.

Dr. Alma Krdžović-Marjanović, a dermatologist from the Institute for Student Health Care in Belgrade, tried to answer the question if there was any progress regarding the therapy of scarring alopecia. She provided a detailed review on the efficacy of various treatment modalities. The emphasis was on the advanced technique of the follicular unit transplantation surgery of mini and micro grafts using high-intensity lasers (pulse energy of 80–100 J/cm^3). The author also pointed to the need for new knowledge in the field of immunology and molecular biology of the hair follicle, especially for future researches. The answer to the question from the beginning of this lecture was positive, but with one condition: early diagnosis and prompt treatment.

Dr. Jasmina Kozarev, a dermatovenereologist from a Specialist office "Dr. Kozarev" in Belgrade, lectured on *hypertrichosis* and hair removal treatment modalities. She has an impressive practical experience in this field and pointed to the fact that successful hair removal depends on differentiating primary from secondary forms of *hypertrichosis*. She demonstrated some methods and techniques for temporary hair removal, temporary hair reduction, and permanent hair removal. The available laser techniques for hair removal were also mentioned, together with their success rate. Blend electrolysis and radio frequency are the most successful techniques for hair removal. The author also presented *eflornithine* – an effective hair growth inhibiting agent, but also called for caution related to possible complications of all hair removal techniques and pointed to the importance of training

Figure 1. Presentation of Certificates of Appreciation to the Lecturers: Prof. Dr. Sava Konstantinović, Prof. Dr. Đorđije Karadaglić and Dr. Zoran Golušin

and experience in order to increase the treatment success rate.

Dr. Danijela Dobrosavljević, MD, MS, from the Institute of Dermatovenereology of the Clinical Center of Serbia, Belgrade, provided her view of the current perspectives on *onychomycosis*. It is well known that dermatophytes, yeasts, moulds and *Candida spp*. are potential causative agents of *onychomycosis,* whereas *Trichophyton rubrum* is the most common dermatophyte worldwide. Systemic use of antimycotic agents in clinical practice is recommended if ≥ 50% of the distal part of the nail is affected, and if the nail matrix and/or more than 4 nails are affected. In conclusion, the author mentioned that although there are good antimycotics, such as *azoles* and *allyamines* for long-term or pulse therapy, with addition of local agents, *onychomycosis* is still a therapeutic challenge for clinicians, due to the fact that in ideal conditions the treatment success rate is usually lower than 80%.

Figure 2. Presentation of Certificates of Appreciation to the Lecturers: Prof. Dr. Đorđije Karadaglić and Dr. Petar Bojanić

Prof. Dr. Đorđije Karadaglić, from the Faculty of Medicine of the University of Podgorica, Montenegro, discussed the importance of differential diagnosis in the treatment of nail diseases. He pointed to the diagnostic significance in differentiating morphologic changes affecting the nails associated with certain dermatoses and systemic diseases, both acquired and congenital. Special emphasis was placed on the correlation between *psoriasis* and *onychomycosis*. Professor Karadaglić also presented a lecture on the treatment of nail *psoriasis*, dealing with its clinical manifestations, which may affect 80 – 90% of patients, as well as current therapeutic and systemic treatment agents. In conclusion, the author emphasized that, contrary to high prevalence of these manifestations of *psoriasis,* their treatment is unfortunately being neglected, while topical therapy is easy to use and presents a relatively efficient treatment modality.

The lectures were followed by a discussion, exchange of experiences and a cocktail party.

Ljuba VUJANOVIĆ*

Clinic of Dermatovenereology Diseases,
Clinical Center of Vojvodina, Novi Sad, Serbia
*Correspondence: Ljuba VUJANOVIĆ
E-mail: vujanovici@yahoo.com

FORTHCOMING EVENTS

Dermatology and Venereology Events 2009

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
23-26 April, 2009	6th EADV Spring Symposium, Bucharest, Romania	28 November, 2008	www.eadv.org/bucharest2009
3-6 May, 2009	12th World Congress on Cancers of the Skin, Tel Aviv, Israel	5 January, 2009	www.kenes.com/wccs2009
12-16 May, 2009	7th World Congress on Melanoma and 5th Congress of the EADO, Vienna, Austria	31 January, 2009	www.worldmelanoma2009.com
20-24 May, 2009	10th International Congress of Dermatology, Prague, Czech Republic	30 October, 2008	www.icd2009.com
4-6 June, 2009	18th Congress of Dermatologists of Serbia, Sava Center, Belgrade, Serbia	06 April, 2009	www.udvs.org
6-10 June, 2009	27th EAACI Congress, Warsaw, Poland	14 January, 2009	www.eaaci2009.com
14-17 June, 2009	Occupational and Environmental Exposure of Skin to Chemicals, Edinburgh, Scotland	1 November, 2008	www.oeesc2009.pwp.blueyonder.co.uk
18-23 June, 2009	15th International Congress on Photobiology, Duesseldorf, Germany	31 March, 2009	www.iuf.uni-duesseldorf.de/ICP2009
24-28 June, 2009	2nd World Psoriasis and Psoriatic Arthritis Conference, Stockholm, Sweden	1 March, 2009	www.ifpa-pso.org
17-19 September, 2009	8th Congress of the Baltic Association of Dermatovenereologists, Vilnius, Lithuania	31 July, 2009	www.badv2009.com
18-19 September, 2009	Photodermatology Meeting & Photopatch Test Course, Krakow, Poland	No abstract submission	www.photopatch.eu
23-26 September, 2009	4th Congress of the Dermatovenereologists of Macedonia GDE-MESTO	In construction	www.unet.com.mk/dermatology
7-11 October, 2009	18th EADV Congress, Berlin, Germany	4 March, 2009	www.eadvberlin2009.com
9-12 November, 2009	11th IUSTI World Congress, Spier Wine Estate, Cape Town, South Africa	1 June, 2009	www.iusti.co.za
12-14 November, 2009	2nd IDS Congress, Barcelona, Spain	15 July, 2009	www.idsdermoscopycongress2009.com

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia

AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists*. The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

Categories of Manuscripts

1. Editorials *(limited to 5 pages) generally provide commentary and analyses concerning topics of current interest in the field of dermatology and venereology. Editorials are commonly written by one author, by invitation.*

2. Original studies *(limited to 12 pages) should contain innovative research, supported by randomized trials, diagnostic tests, outcome studies, cost-effectiveness analysis and surveys with high response rate.*

3. Review articles *(limited to 10 pages) should provide systemic critical assessment of literature and other data sources.*

4. Professional articles *(limited to 8 pages) should provide a link between the theory and practice, as well as detailed discussion or medical research and practice.*

5. Case reports *(limited to 6 pages) should be new, interesting and rare cases with clinical significance.*

6. History of medicine *(limited to 10 pages) articles should be concerned with all aspects of health, illness and medical treatment in the past.*

The journal also publishes book reviews, congress reports, as well as reports on local and international activities, editorial board announcements, letters to the editor, novelties in medicine, questions and answers, and "In Memoriam". All submitted manuscripts will undergo review by the editor-in-chief, blind review by members of the manuscript review panel or members of the Editorial Board. Manuscripts submitted to this journal must not be under simultaneous consideration by any other publisher. Any materials submitted will NOT BE RETURNED to the author/s.

All manuscripts should be submitted to the **Editor in Chief: Prof. Dr. Marina Jovanović***, Clinic of Dermatovenereologic Diseases, Clinical Center of Vojvodina, Hajduk Veljkova 1-3, Novi Sad, Serbia, by mail to: serbjdermatol@nadlanu.com.*

Manuscripts for submission must be prepared according to the guidelines adopted by the International Committee of Medical Journal Editors (www.icmje.org). Please consult the latest version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

1. Manuscript Preparation Guidelines

The manuscript should be written in English, typed in double spacing throughout on A4 paper, on one side only; Use Times New Roman, font size 12, with 30 lines and 60 characters per line. Articles must be written clearly, concisely and in correct English. Accepted manuscripts in need of editing will be returned after editing to the corresponding author for approval. When preparing their manuscripts, authors should follow the instructions given in the *Categories of Manuscript:* the number of pages is limited (including tables, figures, graphs, pictures and so on to 4 (four)), and all the pages must be numbered at the bottom center of the page.

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

- The title of the article, which should be informative, without abbreviations and as short as possible;

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- Authors' names and institutional affiliations;

- The name, mailing address, telephone and fax numbers, and email of the corresponding author responsible for correspondence about the manuscript. Furthermore, authors may use a footnote for acknowledgements, information and so on.

1.2. Abstracts

A structured abstract in English *(limited to 150 words) should follow the title page. The abstract should*

provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors should avoid using abbreviations.

- An **abstract in Serbian language**, *(limited to 150 words) should follow the second page. It should contain a briefing on the purpose of the study, methods, results and conclusions, and should not contain abbreviations.*

1.3. A list of abbreviations

Use only standard abbreviations, because use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units – SI, available at http://www.bipm.fr/en/si/.

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Manuscripts must be accompanied by a cover letter, which should include a date of submission, statement that the manuscript has been read and approved by all the authors and that the authorship requirements have been met. It should also include the name, address, and telephone number of the corresponding author, who is responsible for communicating with other authors about revisions and final approval of the proofs. The original copy of the cover letter, signed by all authors, should be enclosed with the manuscript.

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Tables *should capture information concisely and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.*

- Submit tables in separate files, not included in the manuscript. Tables are to be double spaced and numbered sequentially, with Arabic numbers (Table 1, Table 2, etc.), in order of text citation. Each column, including the first, must have a heading. Provide a brief title for each table. Put all explanatory matter in footnotes, including any nonstandard abbreviations used in the table.

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References in the text, tables and legends should be identified by Arabic numerals in parentheses. Number references consecutively in the order in which they are first mentioned in the text. The *Vancouver System* of referencing should be used. List each author's last name and initials; full first names are not included. List all authors, but if the number exceeds six, give the first six followed by „et al." National journals, which are not indexed in *Index Medicus*, should be abbreviated according to the style in the *List of Abbreviated Titles of Yugoslav Serial Publications* available on http://vbsw.vbs.rs. For further information please visit www.ICMJE.org.

4. Additional information

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