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A kind of Mozart of medicine: JOSEPH PLENCK (1735-1807)*

Viennese, surgeon, professor of surgery, obstetrics, chemistry and botanics, etc., secretary of the Imperial Military Medical Academy, prolific writer, and protodermatologist.

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SUMMARY This is a tribute to one of the fathers of modern European dermatology and venereology, Dr Joseph Plenck, the Viennese protodermatologist of two hundred years ago, 1735-1807, who was professor and secretary of the Imperial Medical Josephine Academy, where today is the Institute for the history of medicine. Plenck introduced the systematization of dermatovenereological diseases based on their paradigmatic differences, which is deemed as "the only (system) with pretensions to accuracy". A man of diversified interests and a fruitful author, he wrote many treatises covering various fields from dermatology, venereology, and dentistry to surgery, obstetrics, anatomy, pediatrics, pharmacology, and botany. This remarkable physician definitely left a deep trace in the history of dermatology and venereology, and marked the transition from text-based to visually dependent culture in the field of dermatovenereology.

עין נבי בעירו

(There is no prophet in his own land)[**]

This is a program of dermatologic luminaries within the framework of the annual meetings of the European Society for the History of Dermatology and Venereology (ESHDV) on occasion of the Annual Congresses of the EADV. The men we deal with include the few we speak of as *protodermatologists:* Charles-Anne Lorry, Joseph Plenck (Fig. 1), if we include venereology, and Jean Astruc – who all lived in the 18th century. This notwithstanding the merits of the early writers: Mercuriale, Riolan, Haffenreffer, and Turner.

From 1770 to 1805, Plenck was active at three universities: Tyrnau (Nagyszombat/Trnava), Buda & Pest, and Vienna. In Vienna he lectured at Military Medical Academy, which is today the home of the history of medicine.

Twenty years ago I busied myself for more than two full years, trying to elucidate some of the personal data on Plenck (1). Ironically, Plenck is mentioned by all dermato-historians of repute in their writings but in his native city, he was an unknown personality. The Biblical quotation above, expresses this phenomenon.

I underwent my training at the Hebra department but I never heard his name mentioned. With all admiration and respect I hold for my late teacher and chairman, Professor Josef Tappeiner (1909-1996), I feel sorry that I have never heard him allude to Plenck although he was interested in the history of the discipline. All the more I concentrated on Plenck

*Presented at the Annual Meeting of the European Society for the History of Dermatology and Venereology (ESHDV) in the "Luminaries of Dermatology" program, on occasion of the 12th Congress of the EADV, Barcelona, 14-18 October, 2003

**Usually translated as "…in his own land"; literally, however, it reads "…in his own city".

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Figure 1. Joseph Plenck (1735-1807). Painting by an unknown artist. (Property and copyright by the Museum of the City of Vienna, Vienna, Austria).

biography so many years ago and I am still happy that I could unravel some of the details of his life.

Plenck was born in Vienna on November 28, 1738, as a son of a bookbinder. In baptismal records his name was "Josephus Andreas", in his books "Josephi Jacobi", and on his death certificate "Jacob". Such differences in details were not uncommon for the century he lived in. He had been apprenticed to a reputable surgeon for three years (1753-1756) before he entered the Imperial Army during the Seven Years War in 1758. He served in military until the end of the war and obtained the rank of a regimental surgeon. He attended lectures at Vienna University before and after the war and became a master of surgery and obstetrics, but he never graduated as an MD. Eventually, he sold his parental estate to be able to buy a surgeon's license and office. The reference to a call to Basel University, so often repeated in the literature, I was unable to confirm.

In 1769, Empress Maria Theresa decided to found a university in Hungary. The earlier universities, founded in Pécs (Fünfkirchen, Quinqueecclesiae) in 1367 and in Budapest by King Matthias Corvinus in the *quattrocento*, ceased to exist when the better part of Hungary was conquered by the Turks after the battle of Mohács (August 29, 1526). The city Maria Theresa chose was Tyrnau/ Nagyszombat/ Trnava, sometimes referred to as the "Slovakian Rome". Plenck was one of the five professors called to hold chairs at the medical faculty, and was appointed a professor of surgery and obstetrics. During these years, he wrote the treatise on skin disease. In 1777, the University was moved to Buda and shortly after to Pest (the name "Budapest" dates from 1872). In 1783, he appealed to the Emperor Joseph II to be allowed to return to Vienna and take the position of supreme inspector of military pharmacies. Permission was granted under the condition that he finds a suitable successor for him in the chair in Pest. (The request was dated November 1783, whereas Joseph's permission arrived in January 1784). Plenck moved and upon opening of the new Military Medical Academy (today the home of history of medicine; Fig. 2) on November 7, 1785, he was named professor of chemistry and botanic, and shortly after the Secretary of the Academy. He was ennobled under Hungarian Law, became imperial counselor, and served until 1805 when he became very sick and asked for permission to retire, which was customarily done upon reaching the age of seventy.

Figure 2. View of the former Imperial Military Medical Academy (1785) located at eastside of the historical hospital complex in downtown Vienna. (©Institute for the History of Medicine, Vienna, Austria).

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His private life was a series of tragedies. He buried two wives and four sons and when he died, he left two daughters, one still unmarried. Unfortunately, I was unable to find any trace of one of these two ladies.

His last years brought him health problems, and finally he was unable to walk and had to be carried from bed to table to be able to write.

In their epochal history of our field, John Crissey and Larry Parish (2) compared him to Mozart, who was Plenck's neighbor in downtown Vienna, close to *Weihburg Gasse*, Plenck's residence next to St. Stephen's, with *Rauhenstein Gasse*, where Mozart died, or *Dom Gasse*, just around the corner, and *Trattnerhof,* only a few blocks away where the composer lived. The authors made comparison on the basis of steady flow of publications pouring from Plenck's pen. Vinczenzio Chiarugi (1759-1820), another of our early heroes, called him "l'infatigabile Giuseppe Plenck", emphasizing the same fact.

His treatises, all succinct and handy, covered various fields of medicine, dentistry as much as dermatology, surgery, venereology, obstetrics, ophthalmology, anatomy, pediatrics, pharmacology, and botanic terminology (3-21) as well as a posthumously published paper in which he recommended the use of "gloves" for obstetricians and midwives (22).

Venereologists will find it interesting that his booklet on a new variety of administration of mercury (for syphilis) with gum arabic was the first from the above series, printed in 1765, just one century before the real first professor of "venereology" (literally, of "syphilis") in Vienna and in the world, Carl Ludwig Sigmund von Ilanor (1810-1883) wrote his paper on the use of "grey" mercury ointment in *topical* treatment of syphilis.

The treatise *Doctrina de morbis cutaneis* (Fig. 3) was first published in Latin, in Vienna in 1776 (6), and then in German in Warsaw and Dresden the

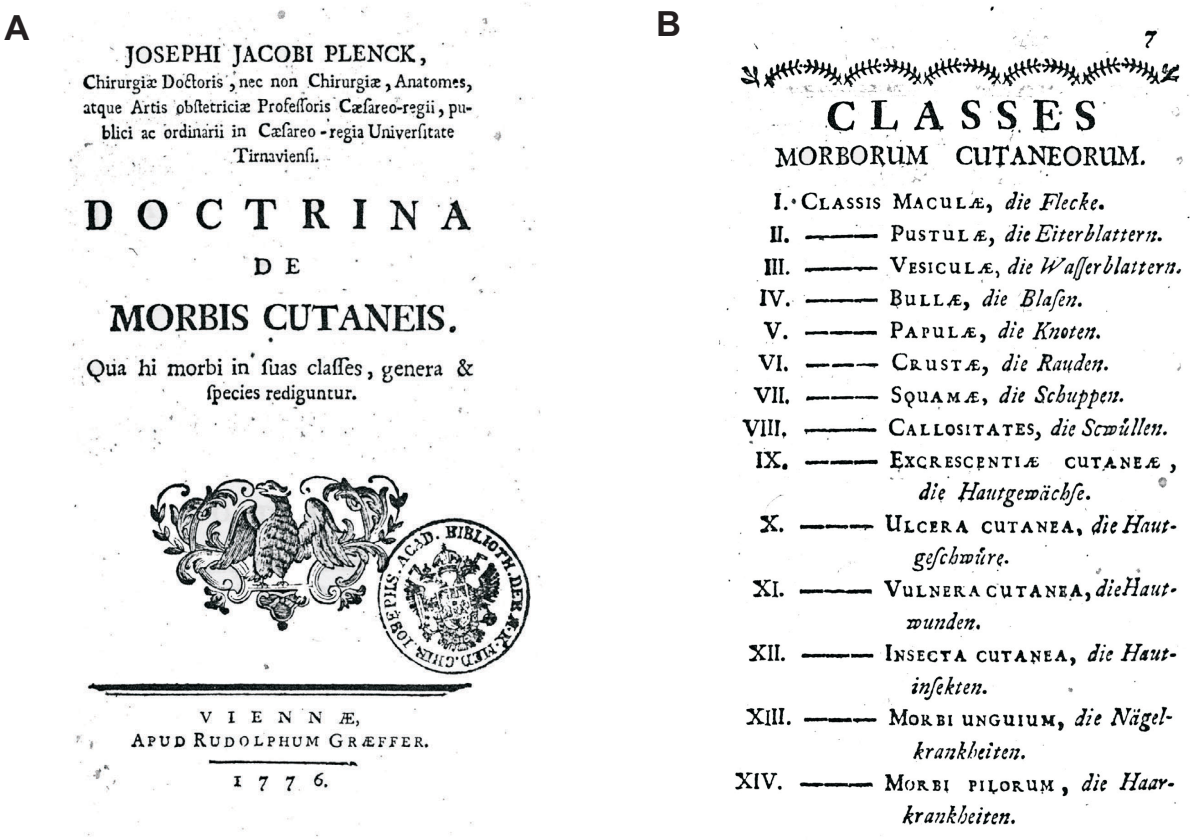

Figure 3. Frontpiece of treatise on skin of 1776 (**A**) and the list of lesions (**B**) for dermatological diagnosis proposed by Plenck in 1776 (from his treatise of 1776; *Doctrina de morbis cutaneis*; ref. 6; ©Institute for the History of Medicine, Vienna, Austria).

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subsequent year; in 1779, a treatise of venereal affections followed (10). Plenck's approach was new and made history. Robert Willan, named by the Royal Society of Medicine the *dermatologist of the millennium* in February 1999, did what Anglo-Saxons can do so well: he streamlined and simplified Plenck's scheme in which form it survived until today. Willan did quote Plenck from 1798 (23) in his first fascicle (and later). Bateman, in the preface to the final edition of Willan's text, called Plenck's system "the only one with pretensions to accuracy"(24). Vinczenzio Chiarugi, Laurent-Théodore (Duosch) Biett, Pierre-François-Olive Rayer, William James Erasmus Wilson, they were all familiar with his idea.

Visible aspects of our surface were addressed in the *Book of Leviticus* as much as in classical literature, e.g. Menandros, or Ovidius putting words in Sappho's mouth, or in the reflexive lines of the greatest Chinese poetess (25). Plenck was a man who, in the spirit of enlightenment, in an aura of opening up the mind, and perhaps of revolutionary prodromes, took individual lesions and their aspects as paradigms of differentiation. *Systematization* was the topic of the time anyway. In medicine, with regard to the outer appearance, dermatology has always had a prime position, and Plenck was quick-witted enough to grasp it. He may be seen as a harbinger of what was to come, namely, the era of picturing sickness. Claudia Benthien in her book *Haut* (skin) (26) and Barbara Maria Stafford in her more extensive oeuvre put their finger on this special point in history of culture, the move "from a text-based culture to a visually dependent culture (27)."

While serving as a president and vice president of our dermatological society and thereafter, I was fortunate enough to convince my colleagues at the board to have a Plenck Lecture for Investigative Dermatology established and delivered annually at our main session, with a Plenck Medal to be given to the lecturer. Our *medailleur,* to whom our gratitude for his mastership may be expressed at this point, Mr. Joseph Kampfl from Budapest, created a wonderful piece, which is handed to the awardee every fall. Normally, our society convenes last weekend in November because it coincides with Plenck's birthday (another detail I saw to be introduced by the board of our society).

In this context, we should remember a corona of men linked by spirit, work, and history of medicine. Joseph Plenck did for dermatology what Carl Linnaeus did for the flora or François Boissier de Sauvages for diseases in general. Plenck tried to establish a system of visible lesions of skin disease. Neither should we forget John Fothergill (1712-1780), Willan's mentor, whose name was immortalized by John Coakely Lettsom, founder of the Medical Society of London (1773), who established the John Fothergillian Medal. Willan was the first to receive that Medal *lege artis* on March 8, 1790 (second over all) for his paper *Cuticulam curare paratus*, which provided the basis for his grand opus. This was the first award ever to be given to an author of a treatise on skin diseases. Suffice it to mention that Linnaeus named not only a plant *Sauvagesia*, a South American weed, after Sauvages, but he also named a hardy American shrub after John Fothergill – the genus *Fothergilla,* displaying white fragrant blossoms in spring to be followed by leaves in gorgeous colors every fall. I have one in my garden, reminding me everyday of all these prominent gentlemen; the only plant I regularly water myself.

A postscript. Did I commit some transgression? Overstep the lines drawn for any author, even given literary license for special emphasis? I think not.

John Crissey is as much my idol as Joseph Plenck is. The former came to my city well over half a century ago as an American Armed Forces Medical Officer and plunged into dermatology. I came to *his* Buffalo more than three decades ago and dived into immunopathology. John is the undisputed grandmaster of dermato-history. No one nowhere can match his knowledge and few if any, has his power of the word. He has been my mentor, teacher, and fatherly friend, and if I – being from a family of musicians myself – have used his allusion to a grandmaster of music in the title of this text, I have done it because I admire his knowledge and literary prowess as much as I admire the genius from Salzburg. For more than seventeen years I have sat and worked in the part of the Old Vienna Hospital complex where Plenck worked, and for more than a dozen years I occupied his "chair"; by now – history of medicine. The gentle reader should, therefore, not take offense at my wording.

Once upon a time when I visited John in Pasadena, he offered me a volume of Plenck's 1776 book on the skin as a personal present. I was hesitant and tried to be modest and refused, saying that once it had come over the ocean it should remain here. It did, however, find its way back across the waters and now it rests at an elevated place – delight and decorum for its owner.

References

1 Holubar K, Frankl J. Joseph Plenck (1735-1807) – a forerunner of modern European dermatology. J Am Acad Dermatol 1984;10:326-32.

2 Crissey JT, Parish LC. The dermatology and syphilology of the nineteenth century. New York (NY): Praeger; 1981.

3 Plenck JJ. Methodus nova et facilis argentum vivum aegris venerea labe infectis exhibendi. Accedit hypothesis nova de actione metalli huius in vias salivales. Vindobona: Berhardi; 1766.

4 Plenck JJ. Primae lineae anatomes in usus praelectionum. Vienna: Graeffer; 1775.

5 Plenck JJ. Pharmacia chirurgica seu doctrina de medicamentis praeparatis ac compositis, quae ad curandos morbos externos adhiberi solent. Vienna: Graeffer; 1775.

6 Plenck JJ. Doctrina de morbis cutaneis. Vienna: Graeffer; 1776.

7 Plenck JJ. Doctrina de morbis oculorum. Vienna: Graeffer; 1777.

8 Plenck JJ. Materia chirurgica. Vienna: Graeffer; 1777.

9 Plenck JJ. Doctrina de morbis dentium ac gingivarum. Vienna: Graeffer; 1778.

10 Plenck JJ. Doctrina de morbis venereis. Vienna: Graeffer; 1779.

11 Plenck JJ. Bromatologia seu doctrina de esculentis et potulentis. Vienna: Graeffer; 1784.

12 Plenck JJ. Toxicologia seu doctrina de venenis et antidotis. Vienna: Graeffer; 1785.

13 Plenck JJ. Elementa medicinae et chirurgiae forensis. Vienna: Graeffer; 1786.

14 Plenck JJ. Icones plantarum medicinalium secundum systema Linnaei digestarum cum enumeratione virium et usus medici, chirurgici atque diaetetici. Centuria 1-7. Cent. 1-4; Vienna: Graeffer; 1788-1792; Cent.5-6; Vienna: Blumauer; 1794; Cent. 7; Vienna: Camesina; 1803.

15 Plenck JJ. Hydrologia corporis humani sive doctrina chemico-physiologica de humoribus, in corpore humano contentis. Vienna: Blumauer; 1794.

16 Plenck JJ. Physiologia et pathologia plantarum. Vienna: Blumauer; 1794.

17 Plenck JJ. Elementa terminologiae botanicae ac systematis sexualis plantarum. Vienna: Blumauer; 1796.

18 Plenck JJ. Compendium institutionum chirurgicarum in usus tironum. Vienna: Blumauer; 1797.

19 Plenck JJ. Elementa pharmacocatagraphologiae seu doctrinae de praescriptione formularum medicinalium. Vienna: Wappler; 1799.

20 Plenck JJ. Elementa chymiae. Vienna: Wappler & Beck; 1800.

21 Plenck JJ. Doctrina de cognoscendis et curandis morbis infantum. Vienna: Geistinger; 1807.

22 Plenck JJ. Doctrina de morbis sexus feminei. Vienna: JG Binz; 1808.

23 Willan R. Description and treatment of cutaneous diseases. Order I. London: Johnson; 1798.

24 Bateman T. Delineations of cutaneous diseases exhibiting the characteristic appearances of the principal genera and species comprised in the classification of the late Dr. Willan and completing a series of engravings by that author. London: Longman Hurst Reese Orme and Brown; 1817.

25 Holubar K. Zur Darstellung der Königin von Saba auf dem Verduner Altar. In: Holubar K, editor. Jahrbuch des Stiftes Klosterneuburg. Wien-Klosterneuburg: Verlag Mayer & Comp.; 1994. p. 67-9.

26 Benthien C. Haut. Literaturgeschichte – Körperbilder-Grenzdiskurse. Reinbek: Rowohlt; 1999.

27 Stafford BM. Body criticism. Imaging the unseen in Enlightenment art and medicine. Cambridge: MIT; 1993.

Acta Dermatovenerol Croat 2003;11(4):212-216 CLINICAL ARTICLE

Familial Cutaneous and Uterine Leiomyomas: Case Report

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SUMMARY Cutaneous leiomyomas are rare, benign tumors arising from the arrectores pilorum muscles of the skin, the tunica dartos of the scrotum, muscles of the areola of the nipple, and vulvar or vascular smooth muscles. Multiple cutaneous leiomyomas originate from the arrectores pilorum muscles of the skin (piloleiomyomata cutis). Occasionally, they seem hereditary and may be associated with uterine myomas. We present a family in which the mother and 4 of her 6 daughters had uterine myomas. All sisters had to undergo hysterectomy before the age of 40, and three of them had multiple cutaneous leiomyomas simultaneously. Our observations support the suggestion that this kind of leiomyomas is a disorder with autosomal dominant inheritance with incomplete gene penetration. Moreover, the data indicate the necessity of periodical examinations to rule out the presence of uterine myomas not only in cutaneous leiomyoma patients, but also in other women in a given family.

KEY WORDS leiomyoma; leiomyomatosis; myoma; uterus; skin

INTRODUCTION

Cutaneous leiomyomas are rare benign tumors arising from the superficial smooth muscle cells: arrectores pilorum muscles of the skin, lamina media of subcutaneous blood vessels, or dartoic muscles of genital regions and nipples. The lesions could be single or multiple (1-3). Multiple cutaneous leiomyomas are caused by the proliferation of pilorum muscle cells and are most common among leiomyomas. Clinically, piloleiomyomas appear mostly on the face, back, and dorsal areas of the limbs as painful redish or bluish papules or nodules, frequently aggregated in the nevoid fashion (1,3,4). Touching, straining, cold, and stress can aggravate pain, which is sometimes associated with the skin lesions (1,3,5,6). Multiple leiomyomas predominantly occur in young adults and are twice as common in women as in men. The number of lesions and their size increase with time and have no tendency toward spontaneous remission (1,4,7,8). Many studies described cutaneous leiomyomas as a familial disorder that may coexist with uterine leiomyomas (1,3,6,7,9-15).

Here we report about a family in which the mother and 4 of her 6 daughters had uterine leiomyomas. Three of these daughters showed the coexistence of uterine and cutaneous leiomyomas (Fig. 1).

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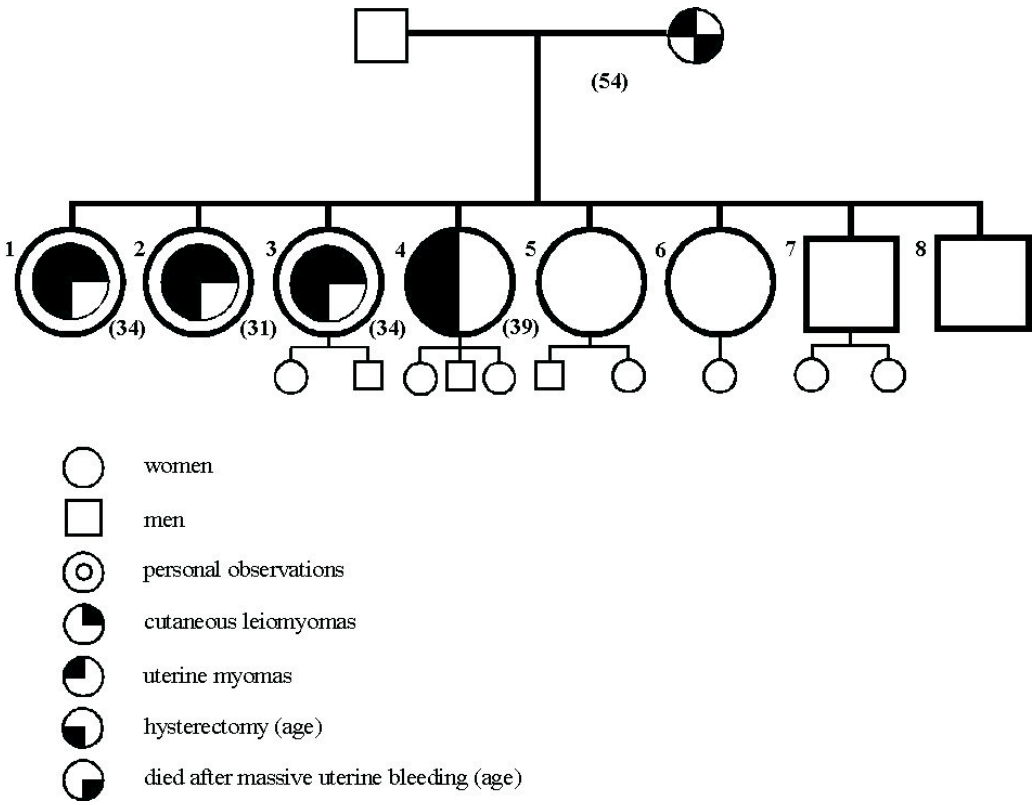

Figure 1. Familial tree.

CASE REPORT

Case 1

A 56-year-old apparently healthy woman first noticed the onset of multiple cutaneous nodes on the face, neck, extensor surface of forearms, and trunk when she was at the age of 20 (Fig. 2). In time, the lesions increased in number and size. They were red-bluish, or had a color of normal skin. The nodes were mostly asymptomatic, but a few largest ones were accompanied by pain precipitated by mechanical pressure and changes of temperature. A few painful lesions located on the face and forearms were surgically removed. At the age of 23, the diagnosis of uterine leiomyomas was made. At the age of 34, a hysterectomy was performed. Histopathologic examination revealed the existence of uterine myomas, ovarial cyst, and extensive chronic salpingitis.

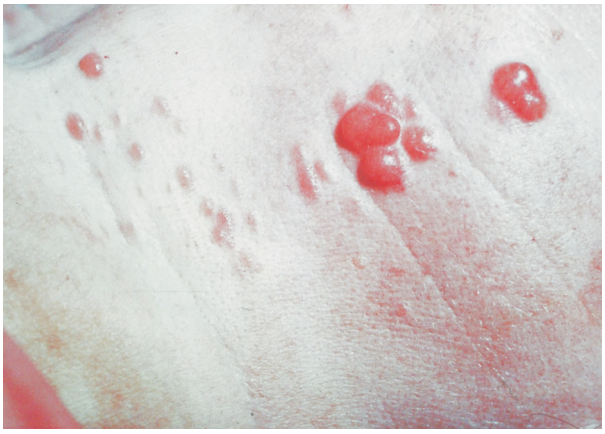

Figure 2. Multiple nodular lesions on the trunk of one of the sisters (case 1).

Case 2

A 58-year-old married woman presented with multiple nodules of 0.2-1.0 cm in diameter on the face, extensor surface of extremities, and hips. The patient first noticed the appearance of nodules when she was a teenager. The lesions were partly aggregated in linear, nevoid fashion. The nodules were mainly asymptomatic. The patient suffered occasionally from pain and/or itching of the lesions, which was probably caused by stress. At the age of 31 she underwent a hysterectomy due to uterine leiomyomas and persistent bleeding. Histopathologic examination confirmed uterine myomas. One cutaneous nodule located on the hip was also removed surgically.

Case 3

A 49-year-old married woman had a few asymptomatic cutaneous nodules on the arms and extensor surfaces of upper extremities since her childhood. One of the lesions has recently started to enlarge and has been removed. At the age of 19 and 23 the patient delivered two healthy children. After the pregnancies uterine tumors were diagnosed. At the age of 34 the patient underwent hysterectomy due to persistent bleeding and anemia.

Histopathology of Cutaneous Nodules

The samples of cutaneous nodes of the three patients were stained with hematoxylin-eosin, Masson's trichrome, and van Gieson method. The results of histological examination were similar in all three cases and confirmed the diagnosis of leiomyomas (Figs. 3-5). The epidermis overlying the lesions was thin. Poorly delimitated tumors located in the dermis contained fascicles of smooth muscles fibers separated by the surrounding collagen.

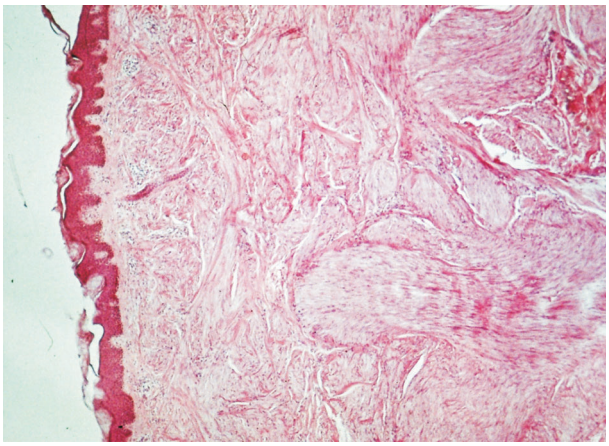

Figure 3. Poorly demarcated, interlacing bungles of smooth muscle fibers intermingled with collagen bundles. Hematoxylin-eosin staining (x 40).

Family History

Parents. The mother of the three patients was pregnant eight times and delivered eight children. She died at the age of 54 after massive genital bleeding caused by uterine tumors. She did not consent to surgery.

Siblings. Our three patients were born in a large family (eight siblings – six sisters and two brothers). One of the other three sisters had hysterectomy for uterine leiomyomas at the age of 39. None of the other siblings beside our three patients had similar skin lesions caused by leiomyomas.

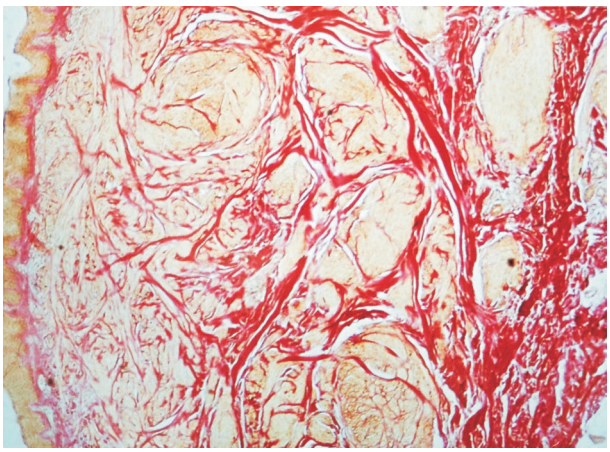

Figure 4. Van Gieson staining: muscle stained yellow, and collagen stained red (x 40).

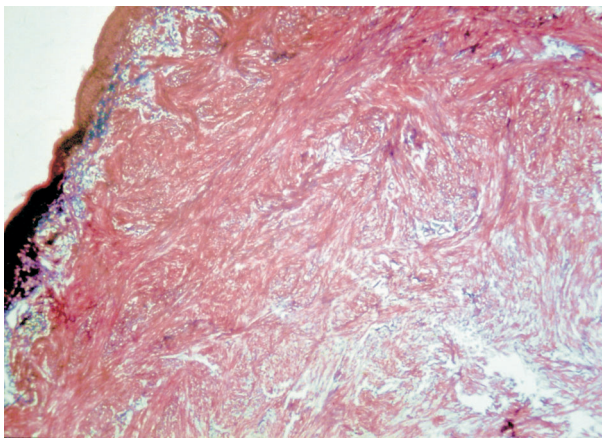

Figure 5. Masson staining: muscle stained dark red, and collagen stained blue (x 40).

Children. Children of the described patients have not complained of leiomyomas either of the skin or the uterus.

DISCUSSION

Cutaneous leiomyoma is a rare disorder and the diagnosis may be problematic. Among 45 cases of leiomyomas described by Raj *et al* (6), only six were suspected and three diagnosed as leiomyomas on the basis of clinical features. Clinical symptoms in other cases raised suspicion of other diseases, i.e. histiocytoma, sebaceous cyst, neurofibroma, intradermal nevus, fibroma, urticaria pigmentosa, seborrheic keratosis, wart, basal cell carcinoma, eccrine

spiradenoma, lymphangioma, and granuloma annulare (6). Histology revealed poorly circumscribed tumors with fascicles of well-differentiated smooth muscle cells and little contamination of collagen. Special stains can help to distinguish muscle cells from collagen (Masson's trichrome staining: muscle – yellow, collagen – red; van Gieson staining: muscle – purple, collagen – blue) (2,5,8). In contrast to leiomyosarcoma, there are no mitoses, necrosis, or cellular atypia in leiomyoma (6). In immunohistochemical staining, tumor cells give positive reactions with desmin and smooth muscle acting antibodies S-100, neuron specific enolase (NSE), protein gene product 9.5 (PGP), and neurofilament antibodies (6,16). The presence of nerve fibers in the stroma and nearest surrounding could be one of the reasons of the pain connected with leiomyomas (6,15). An increase in cholinergic activity due to the absence of cholinesterase and destruction of neuron myelin by tumor muscle cells are also regarded as a cause of pain in particular nodules (2,3,9,17). Multiple leiomyomas are twice as common in women as in men (3,4,6). An autosomal dominant inheritance with irregular gene penetration has been suggested (18) Multiple leiomyomas have been observed in monozygotic twins (1,14), siblings (1,6,12), and few generations of a particular family (1,3,6,7,9,11,15). In certain cases, the simultaneous presence of both cutaneous and uterine leiomyomas has been reported. Moreover, the presence of cutaneous and/or uterine leiomyomas in particular family members is characteristic (7,10-15). On the other hand, coincidental leiomyomas and fibromas, epidermal cysts, osteoma, multiple endocrine cysts, intestinal papillomatosis, angioleiomyomas have seldom been described (4,7,16,19). There is a hypothesis that the aberration of high-mobility-group protein gene (HMG) could play an important role in the pathogenesis of leiomyomas (20). The gene is localized in chromosome 12, band q 15, a region often rearranged in benign mesenchymal tumors (20). This kind of gene abnormalities has been observed in 17% of women with especially expansive uterine leiomyomas (21). Dynamic course of uterine leiomyomas is often observed in patients with concomitant cutaneous lesions. The surgical removal of leiomyomas localized only in uterus is rarely required, but if they are accompanied by cutaneous tumors, the hysterectomy is often obligatory before the age of 35 (7,11). Uterine leiomyomas are the most common benign tumors in women of childbearing age and occur in 10% of women population (12,22). The frequency of this lesions increases in the families with cutaneous leiomyomas up to 45-54% (7,11).

In the reported family, five out of seven women in two generations (71%) had uterine leiomyomas. Two of them had only uterine leiomyomas, whereas three had both uterine and cutaneous leiomyomas. Four of them, including the described three women, underwent hysterectomy at the age between 31 and 39. Two patients (cases 1 and 2) were fertile, whereas the third one (case 3) had leiomyomas of both uterus and skin, accompanied by ovary cysts. No male family members seemed to be affected with cutaneous leiomyomas. This family resembled the one described by Garcia-Muret *et al* (11), who suggested an X-linked dominant inheritance of this disease. Nevertheless, several authors reported multiple cutaneous leiomyomas in female and male members of particular families and suggested an autosomal dominant pattern of inheritance of this disorder (7,18). In our three patients, cutaneous leiomyomas preceded the diagnosis of uterine tumors. None of our patients needed medical help for a number of years. One of the patients had a discomfort related to a quickly enlarging, painful tumor on the face and asked for medical treatment. None of our patients suffered from nausea, vomiting, micturition, dilation of the pupil, hypotension, or pallor that were previously described as possibly accompanying the skin lesions (7).

The treatment of leiomyomas is the resection of the largest, painful lesions, with uncomfortable localization (23). Surgical excision should reach into the margins of healthy tissue around the tumor to avoid frequent recurrences (1,15). Pain can be alleviated with oral nitroglycerin (10), nifedipine (23,24), phenoxybenzamine (25), or the combination of these medications (15). Only one of our patients (case 1) had discomfort due to cutaneous leiomyomas, which were therefore surgically removed. Two other patients (cases 2 and 3) had only one tumor removed for the need of histological examination. The diagnosis of cutaneous leiomyomatosis requires a careful dermatological and gynecological examination of all women in a particular family. Uterine myomas, often coexisting with

multiple cutaneous leiomyomas, could be the cause of infertility and hysterectomy at an early age. Women with multiple cutaneous leiomyomas should be informed about the prognosis and systematically gynecologically examined.

References

1 Fisher WC, Helwig EB. Leiomyomas of skin. Arch Dermatol 1963;88:510-20.

2 Lever WF, Schamburg-Lever G. Histopathology of the skin. 4th ed. Philadelphia (PA): J.B. Lippincot Co.; 1983.

3 Montgomery H, Winkelmann RK. Smooth-muscle tumors of the skin. AMA Arch Derm 1959;79:32-40.

4 Burg G. Atlas of cancer of the skin. New York (NY): Churchill Livingstone Inc.; 2000.

5 Albrechts S, Froml L. Neoplasias and hyperplasias of neural and muscular origin. In: Fitzpatrick TB, Eisen AZ, Wolf K, Freedberg IN, Austen KF, editors. Dermatology in general medicine. 5th ed. New York (NY): McGraw-Hill; 1999. p. 1269-79.

6 Raj S, Calonje E, Kraus M, Kavanagh G, Newman PL, Fletcher CD. Cutaneous pilar leiomyomas: clinicopathologic analysis of 53 lesions in 45 patients. Am J Dermatopathol 1997;19:2-9.

7 Fernandez-Pugnaire MA, Delgado-Florencio V. Familial multiple cutaneous leiomyomas. Dermatology 1995;191:295-8.

8 Sherwood KA, Chalet MD. Tumors with smooth muscle differentiation. In: Former ER, Hood AE, editors. Pathology of the skin. Norwalk (CT): Appleton and Lange; 1990. p. 847-53.

9 Sun CC, Zelman J, Toker C. Familial cutaneous leiomyomata: a case report with electron microscopic study. Mt Sinai J Med 1980;47:40-4.

10 Engelke H, Christophers E. Leiomyomatosis cutis et uteri. Acta Derm Venereol (Stockh) 1979;59: 51-4.

11 Garcia Muret MP, Pujol RM, Alomar A, Calaf J, de Moragas JM. Familial leiomyomatosis cutis et uteri (Reed's syndrome). Arch Dermatol Res 1988;280 Suppl:S29-32.

12 Jolliffe DS. Multiple cutaneous leiomyomata. Clin Exp Dermatol 1978;3:89-92.

13 Reed WB, Walker R, Horowitz R. Cutaneous leiomyomata with uterine leiomyomata. Acta Derm Venereol 1973;53:409-16.

14 Rudner EJ, Schwartz OD, Grekin JN. Multiple cutaneous leiomyomas in identical twins. Arch Dermatol 1964;90:81-2.

15 Thyresson HN, Su WP. Familial cutaneous leiomyomatosis. J Am Acad Dermatol 1981;4:430-4.

16 Rikihisa W, Kiryu H, Furue M. Multiple piloleiomyomas associated with solitary angioleyomioma. Eur J Dermatol 1999;9:309-10.

17 Mann PR. Leiomyoma cutis: an electron microscope study. Br J Dermatol 1970;82:463-9.

18 Kloepfer HW, Krafchuk J, Derbes V, Burks J. Hereditary multiple leiomyoma of the skin. Am J Hum Genet 1958;10:48-52.

19 Burton JL, Hartog M. Multiple endocrine adenomatosis (Type I) with cutaneous leiomyomata and cysts of Moll. Br J Dermatol 1977;97 Suppl 15:74-5.

20 Gattas GJ, Quade BJ, Nowak RA, Morton CC. HMGIC expression in human adult and fetal tissues and in uterine leiomyomata. Genes Chromosomes Cancer 1999;25:316-22.

21 Rein MS, Powell WL, Walters FC, Weremowicz S, Cantor RM, Barbieri RL, *et al*. Cytogenetic abnormalities in uterine myomas are associated with myoma size. Mol Hum Reprod 1998;4:83-6.

22 Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990;94:435-8.

23 Callies R. Surgical ablation of multiple leiomyomas. J Dermatol Surg Oncolog 1980;6:944-5.

24 Abraham Z, Cohen A, Haim S. Muscle relaxing agent in cutaneous leiomyoma. Dermatologica 1983;166: 255-6.

25 Venencie PY, Bigel P, de la Charriere O, Lemonnier V, Thebaut-Gerbaud D, Saurat JH. Multiple cutaneous leiomyomatosis. Treatment with phenoxybenzamine [in French]. Ann Dermatol Venereol 1982;109:819-20.

Acta Dermatovenerol Croat 2003;11(4):217-220 CASE REPORT

Syphilitic Aneurysm: Case Report

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SUMMARY Tertiary syphilis is a rare, slowly progressive inflammatory disease that becomes clinically visible years after initial infection. Although it can affect any organ in the body, it shows a predilection for the cardiovascular and nervous systems. Today, however, cardiovascular syphilis is a medical curiosity because the disease can successfully be treated with antibiotics in its early phase. We present a case of a 43-year-old male patient with a syphilitic aneurysm of the descendent aorta and our choice of treatment.

KEY WORDS aortic aneurysm, thoracic; aneurysm, infected; syphilis, cardiovascular; syphilis serodiagnosis

INTRODUCTION

Syphilis is a chronic, systemic, sexually transmitted disease caused by a microaerophilic spirochete *Treponema pallidum.* Due to its multiple clinical presentations, the disease is also called "the great imitator". The natural course of syphilis can be divided clinically into three phases: primary, secondary, and tertiary. The primary stage, which develops after an incubation period of about 3 weeks, is characterized by a non-painful skin lesion, the so-called chancre, usually associated with regional lymphadenopathy and early bacteremia. Florid secondary bacteremia, generalized mucocutaneous lesions, lymphadenopathy, and protean clinical findings are characteristic of the secondary, or disseminated, stage. The period of subclinical infection (latent syphilis) that can be detected only by reactive serologic tests is the next phase of the disease. In a small number of patients, latent syphilis is followed by a late or tertiary stage of the disease characterized by progressive development and involvement of the aorta, and/or the central nervous system, and/or the development of a characteristic granulomatous lesion – gumma.

There are two histopathologically distinguishing features of syphilis regardless of the stage of disease and location of lesions: obliterating endarteritis and plasma cell-rich mononuclear infiltrates. Endarteritis is caused by the binding of spirochetes to endothelial cells, mediated by host fibronectin molecules bound to the surface of the spirochetes, and heals with scar tissue formation (1). The obliterative

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endarteritis characteristic of tertiary syphilis may involve small vessels in any part of the body, but it is clinically most devastating when it affects the vasa vasorum of the aorta. The narrowing of the lumina of the vasa causes ischemic injury of the aortic media, with uneven patchy loss of the medial elastic fibers and muscle cells followed by inflammation and scarring. With destruction of the media, the aorta loses its elastic support and becomes dilated, producing a syphilitic aneurysm (2).

A patient with a syphilitic aneurysm can have respiratory difficulties due to the encroachment upon the lungs and airways, swallowing difficulties due to compression of the esophagus, persistent cough due to irritation of or pressure on the recurrent laryngeal nerves, and pain caused by the erosion of bone (i.e., ribs and vertebrae). The aortic aneurysm leads to aortic valve dilation with valvular insufficiency or narrowing of the coronary ostia causing myocardial ischemia and rupture of the aneurysm. Today, however, cardiovascular syphilis is a medical curiosity because the disease can successfully be treated with antibiotics in its early phase.

CASE REPORT

A 43-year-old man was admitted to our hospital because of severe chest and back pain. He was not married and had no children. His general health was good and his personal and family medical history unremarkable. He denied having any recollection of ulcerations on his genitals or elsewhere and negated having any sexually transmitted disease, skin eruptions, or neurological symptoms. There were no abnormal findings on physical examination and examination of the skin and genitals. Chest X-rays showed a sharply delineated round shadow on the left side of the aorta. Bronchoscopy and cytological examination of the bronchoscopic aspirate were normal. Computed tomography (CT) chest scans revealed a saccular aneurysm on the proximal part of the descendent aorta, measuring 6.6 cm in diameter. After contrast application, a crescent parietal thrombus was found, with the circulating lumen of the aneurysm of 4.14 cm (Fig. 1). Angiography confirmed these findings, showing a 57 x 46 mm aneurysmal dilation of the descendent aorta (Fig. 2). Serologic testing on syphilis yielded the following results: VDRL test was

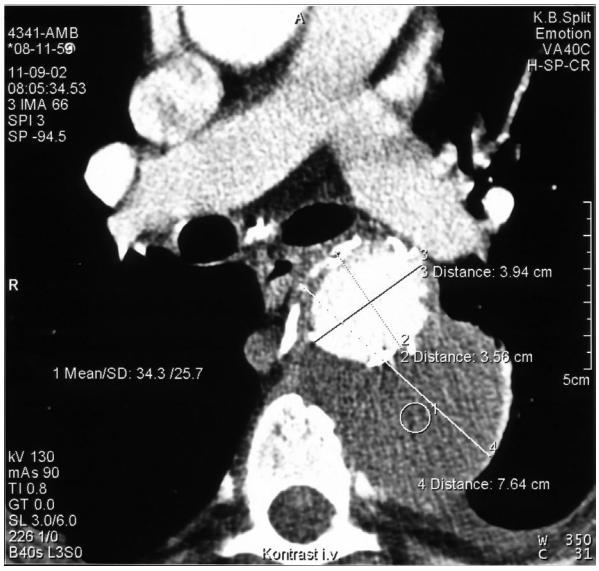

Figure 1. A crescent parietal thrombus with the descendent aorta revealed by computed tomography of the chest after contrast medium application. Circulating lumen of the aneurysm measured 4.14 cm.

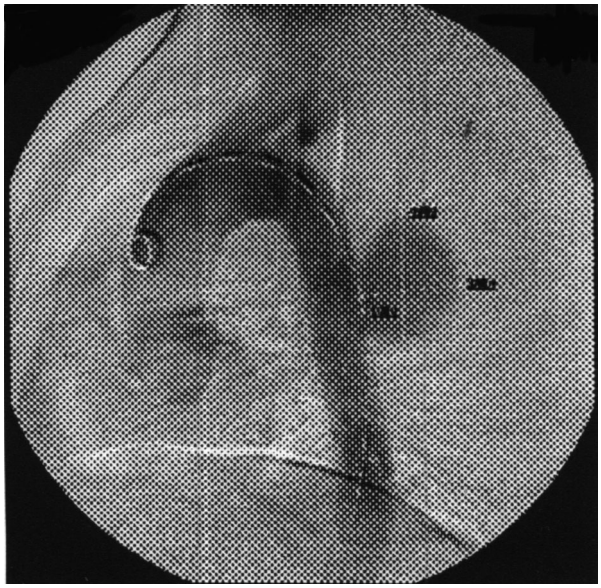

Figure 2. Aneurysmal dilation (57 x 46 mm) of the descendent aorta revealed by angiography.

reactive 1:2, TPHA was 1:5120, IgM-FTA-ABS was negative, and IgG-FTA-ABS was positive 1:10. Anti-HIV1/HIV2 was negative, ANA titer was 1:20, and anticardiolipin (aCL) antibody test was negative. Ultrasonography of the abdomen showed no abnormalities.

The neurologist found no clinically apparent neurological abnormalities. Analysis of the cerebrospinal fluid (CSF) showed white blood cell count, protein concentration, and total CSF-IgG to be

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within normal limits. VDRL was also negative, but TPHA titer was 1:160.

The patient was transferred to the Department of Surgery, where he underwent endovascular treatment of the aneurysm. A talent stent-graft was implanted and antibiotic treatment introduced, with benzathine penicillin 2.4 million IU i.m. administered once a week for 7 weeks according to the scheme of the Department of Dermatology and Venerology, Zagreb University Hospital Center. The antibiotic treatment was preceded by administration of 4 mg of dexamethasone. Serological testing was repeated after two months, with the following results: VDRL became non-reactive, TPHA titer decreased to 1:640, and FTA-ABS was negative.

DISCUSSION

Only 40% of untreated patients develop late or tertiary stage syphilis characterized by progressive disease involving primarily the aorta, the central nervous system, and the development of gummata.

Syphilitic aneurysm is most frequently localized in the ascending part (60%) or the arch (30-40%) of the aorta, whereas the descendent thoracic aorta is affected in only 10-15% of the cases. Only in 5% of patients, the aneurysm affects the abdominal aorta (3-6). Saccular aortic aneurysms above the level of the renal arteries are mostly caused by fungi or syphilis (7), which is the reason why serologic testing on syphilis was performed in our patient after a saccular aneurysm was detected, despite the fact that the patient denied having any sexually transmitted disease.

Our patient did not experience or notice having any ulcerations or skin eruptions. This absence of typical clinical symptomatology of the first and second stage of syphilis is not rare (8-10). Since his health was generally good, the patient had never visited a physician and had never been treated with an antibiotic. This fact and the remarkable ability of *Treponema pallidum* to evade the humoral immune response due to its unique ultrastructure (11) can explain the consequent development of the tertiary syphilis in our patient.

Because asymptomatic neurosyphilis is the most common presentation of neurosyphilis (12), our patient had to undergo screening for gummata and neurosyphilis. Lumbar puncture was necessary to evaluate the diagnosis of asymptomatic neurosyphilis. The results of biochemical and cytological analysis of CSF were within normal limits. TPHA titer in CSF was 1:160, i.e. within normal limits according to the National Guidelines for the Management of Late Syphilis from 2002 (positive TPHA titer $\geq$320) (13).

On account of the absence of neurological symptoms and signs, HIV negativity, and the patient's relative refusal to cooperate, we opted for benzathine penicillin, not procaine penicillin (13), as the treatment of choice.

The Jarisch-Herxheimer reaction occurs in 75% of patients with secondary syphilis. In tertiary syphilis, it is very rare, but can be catastrophic, especially in case of cardiovascular disease and neurosyphilis. There is a concern that in late syphilis, this reaction might be associated with local edema around syphilis lesion (13). In severe aortitis, an aortic rupture can be precipitated (14). Therefore, in case of our patient we decided first to stabilize the aneurysm by implanting the stent. Only afterwards we administered the antibiotic and thus diminished the risk of possible baneful consequences of Jarisch-Herxheimer reaction. Millan *et al* (15) applied the same sequence of treatment in their patient.

Recently, an increase in syphilis infections has been reported not only in Eastern Europe, but also in England (16). The case of our patient can serve as a reminder for clinicians to be alert to the possibility of encountering patients presenting with syphilis in different stages.

References

1 Thomas DD, Baseman JB, Alderete JF. Enhanced levels of attachment of fibronectin-primed *Treponema pallidum* to extracellular matrix. Infect Immun 1986;52: 736-41.

2 Schoen FJ, Cotran RS. Blood vessels. In: Cotran RS, Kumar V, Collins T, editors. Robbin's pathologic basis of disease. 6th ed. Philadelphia (PA): W. B. Saunders Co.; 1999. p. 493-541.

3 Boyd LJ. A study of four thousand reported cases of aneurysm of the thoracic aorta. Am J Med Sci 1924; 168:654-68.

4 Heggtveit HA. Syphilitic aortitis: a clinicopathologic autopsy study of 100 cases, 1950 to 1960. Circulation 1964;29:346-55.

5 Jackman JD Jr, Radolf JD. Cardiovascular syphilis. Am J Med 1989;87:425-33.

6 Kampmeier RH. Saccular aneurysms of the thoracic aorta: a clinical study of 633 cases. Ann Intern Med 1938;12:624-51.

7 Lukehart SA, Holmes KK. Syphilis. In: Wilson JD, Braunwald E, Isselbacher KJ, Peersdorf, Martin JB, Fanci AS, *et al*, editors. Harrison's principles of internal medicine. 12th ed. New York (NY): McGraw Hill Inc; 1991. p. 651-61.

8 Hemadevarajan, Williams J, Gopikreishnan. Syphilitic abdominal aortic aneurysm in a middle-aged married villager. Int J STD AIDS 2000;11:485-6.

9 Rühlmann Ch, Wittig K, Koksch M, Muller J. Aneurysm of the ascending aorta in tertiary syphilis [in German]. Dtsch Med Wochenschr 1996;121:550-5.

10 Mickley V, Mohr W, Orend KH, Sunder-Plassmann L. Aneurysm of the descending thoracic aorta in tertiary syphilis [in German]. VASA 1995;24:72-6.

11 Cox DL, Chang P, McDowall AW, Radolf JD. The outer membrane, not a coat of host proteins, limits antigenicity of virulent *Treponema pallidum*. Infect Immun 1992;60:1076-83.

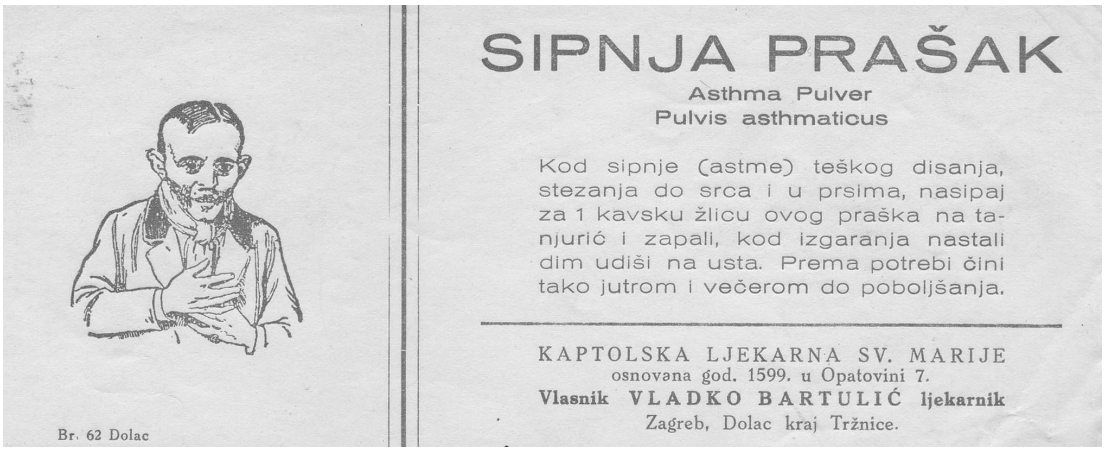
12 Tramont EC. *Treponema pallidum*, (syphilis). In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infections diseases. 5th ed. Philadelphia (PA): Churchill-Livingstone; 2000. p. 2474-90.

13 2002 national guidelines for the management of late syphilis. Available from: *http://www.guideline.gov/summary/summary.aspx?doc_id=3037*. Accessed: September 14, 2003.

14 Braun-Falco O, Plewig G, Wolf HH, Burgdorf WH. Sexually transmitted bacterial diseases. In: Braun-Falco O, Plewig G, Wolf HH, Burgdorf WH. 2nd ed. Dermatology. Berlin: Springer-Verlag; 2000. p. 245-98.

15 Salas Millan J, Martinez Calzon JL, Gonzalez de Vega N, Castillo Castro JL. Cardiovascular syphilis: a case report [in Spanish]. Rev Esp Cardiol 2000;53:1656-8.

16 Doherty L, Fenton KA, Jones J, Paine TC, Higgins SP, Williams D, *et al*. Syphilis: old problem, new strategy. BMJ 2002;325:153-6.



Asthma Pulver (*pulvis asthmaticus*) to help alleviate morning and evening breathing difficulties.
From the collection of Assist. Prof. Stella Fatović-Ferenčić, MD, PhD.

Acta Dermatovenerol Croat 2003;11(4):221-224 CASE REPORT

Nevus Comedonicus – Case Report and Review of Therapeutical Approach

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SUMMARY Nevus comedonicus is uncommon abnormality of pilosebaceous unit, clinically characterized as confluent clusters of dilated follicular orifices plugged with pigmented keratinous material that resembles open comedones. It is suggested that nevus comedonicus is an uncommon variant of adnexal hamartoma, which clinically appears as linear group of open comedones. Since Kofmann's description of nevus comedonicus in 1895, there have been reports of this rare cutaneous disorder associated with developmental anomalies. We present a case of a 19-year-old woman with numerous 1-3 mm size darkly pigmented, keratic plugs clustered in linear unilateral patches on left abdominal part. Our treatment consisted of the avoidance of the formulations containing nickel sulfate and carba mixture, daily local application of tretinoin 0.1% gel and corticosteroid ointment (momethasone furoate). After 4 weeks of local therapy cosmetic result was evident. The slight resolution of keratin plugs could also be seen. Two months after the treatment, there were no visible skin exacerbations.

KEY WORDS keratosis; nevus; nevus, pigmented; skin diseases; tretinoin

INTRODUCTION

Nevus comedonicus is uncommon abnormality of pilosebaceous unit, clinically characterized as confluent clusters of dilated follicular orifices plugged with pigmented keratinous material that resembles open comedones (1). The undifferentiated epithelium of the hair follicles produces keratin, which is packed in laminated layers and forms keratin plug (2). The condition is usually asymptomatic, but may be complicated by infection and scarring. It is suggested that nevus comedonicus is an uncommon variant of adnexal hamartoma, which appears clinically as linear group of open comedones (3). Since Kofmann's description of nevus comedonicus in 1895, there have been reports of this rare cutaneous disorder in association with irregularities affecting the skeletal system, central nervous system, the skin, and the eye (Table 1).

We present a case of a 19-year-old women with coexisting nevus comedonicus and contact allergic dermatitis (CAD) to nickel sulfate and carba

Table 1. Findings associated with nevus comedonicus (adapted from ref. 4)

Abnormality	No. of reference	Author, publication year
Skeletal:		
congenital scoliosis	7	Carney, 1952
developmental anomaly of T4-T5	8	Cripps & Bertram, 1976
dextroscoliosis of thoracic spine with levoscoliosis of cervical spine	9	Bleiberg & Brodkin, 1969
hemivertebrae, fused vertebrae, scoliosis, spina bifida occulta, foot deformity		this report
Central nervous system:		
epileptiform attacks	10	Rook, 1952
EEG changes	11	Popov and Boianov, 1962
transverse myelitis		this report
Skin:		
trichilemmal cysts	12	Leppard, 1977
linear basal cell nevus	7	Carney, 1952
	9	Bleiberg and Brodkin, 1969
leukoderma	8	Cripps and Berttram, 1976
	13	Wood and Thew, 1968
	14	Paige and Mendelson, 1957
Sturge-Weber syndrome	10	Rook, 1952
lichen planus	15	Bernucci, 1930
ichthyosis	16	Piers, 1945
herpes zoster	17	Blaschko, 1916
Ocular:		
congenital cataract (ipsilateral)	18	Whyte, 1968
(bilateral)	11	Popov and Boianov, 1962

mixture, who was treated with combined retinoid and corticosteroid local therapy.

CASE REPORT

A 19-year-old woman visited Outpatient Allergy Clinic of the Department of Dermatology and Venerology, Zagreb University Hospital Center, because of numerous skin lesions on her abdomen. The lesions were present since birth but showed a tendency of worsening after the beginning of puberty, and were accompanied with rare infections, especially in the previous few months. They were characterized by numerous 1-3 mm, darkly pigmented, keratic plugs clustered in linear, unilateral patches on the left half of the abdomen. Several inflammatory papules and crusts could be seen around umbilicus, especially around the area in contact with a metal button (Fig. 1). Diagnostic procedure included patch test to standard series of allergens, and the reaction to nickel sulfate and carba mixture was positive. In general, she was healthy, without any pathologic laboratory findings.

She had been treated previously with keratolytics, local antibiotics, manual extraction, and cryotherapy, but all these treatment approaches were either ineffective or had minimal effects. Our treatment consisted of daily application of local tretinoin (Retin A micro® 0.1% gel) together with local corticosteroid ointment (momethason furoat), with strict avoidance of nickel sulfate and carba mixture. Corticosteroid ointment was used only a few days to suppress severe inflammation caused by contact allergy.

After 4 weeks of local therapy, cosmetic result became evident. Slight resolution of keratin plugs was also visible. After two more months of treatment, no skin exacerbation could be seen.

DISCUSSION

The etiology of nevus comedonicus is still unknown. It has been suggested that it is a hamartoma arising from defective development of the mesodermal component of the pilosebaceous complex, with subsequent abnormal differentiation

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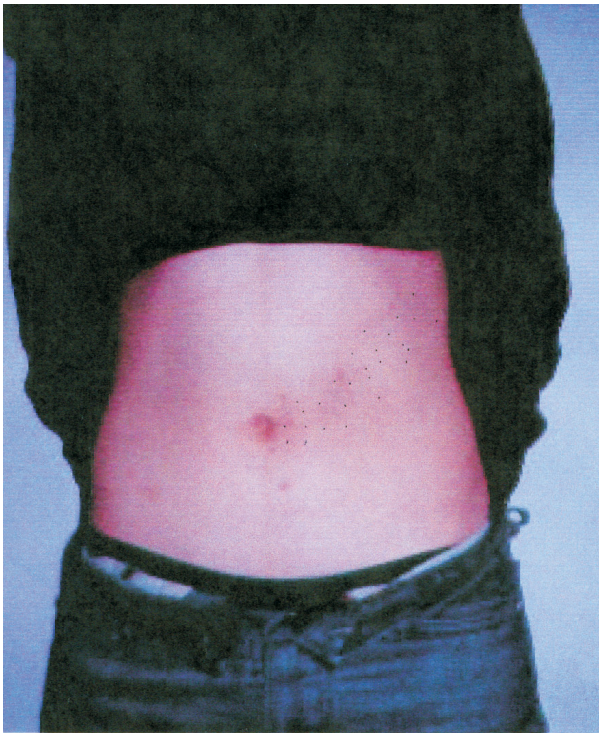

Figure 1. A 19-year-old woman with numerous 1-3 mm darkly pigmented, keratic plugs clustered in linear, unilateral patches on the left side of the abdomen.

of the epithelial portion (3). Since sebaceous glands are rudimentary or absent and cannot play a role in the formation of follicular plugs, these lesions are not true comedones (3). Nevus comedonicus has been considered a developmental abnormality of the follicular apparatus, distinctive by its ability to form keratin plugs within epidermal invaginations and to produce the characteristic clinical appearance as in our patient (4). Nevus comedonicus can become clinically apparent after, or together with, some other conditions, such as herpes zoster, lichen planus, ichthyosis, or trauma.

There is an absence of racial or sexual predisposition. Characteristically, nevus comedonicus is present from birth but may only become apparent at puberty, probably because of hormone-induced activity of the pilosebaceous structures or at any other time after birth after an obscure triggering mechanism (4).

Clinical findings are characterized by a localized grouping of comedones, which are better described as dilated plugged follicles. Hairs are usually completely absent. In most cases, the lesions are asymptomatic, but may sometimes become inflamed and thus confused with papule-pustules, as it was the case in our patient (5). Patches may occur unilaterally, bilaterally, segmentally, or linearly, and have zoster form, often following in parallel Voight's or Blaschko's lines (3). Face, trunk, neck, upper arms, and chest are the sites of predilection. In rare cases, nevus comedonicus was described on palms, scalp, and glans penis (6). Our patient, however, had unilateral nevus comedonicus distribution.

Histopathologic examination of the lesion shows epidermis with dilated, papulous plugged hair follicles and small cysts. Acne comedones typically have a small orifice, whereas the lesions in nevus comedonicus are barrel shaped and contain almost no coryneform bacteria (5). Apocrine glands are absent (4).

Differential diagnosis includes various types of epidermal nevi (especially the linear epidermal nevus), familial dyskeratotic comedones, and linear comedonic formations usually linked with acne vulgaris or chronically sun-damaged skin (Favre-Racouchot disease; ref. 3). Atrophoderma vermiculata and keratosis pilaris atrophicans may be confused with nevus comedonicus, but are distinguished principally by their symmetry.

The treatment depends on the severity of clinical lesions. Indications for treatment are recurrent infections and cosmetic reasons. Excision is the only successful therapy, but can be done only for the localized, small lesions (5). Nevus comedonicus in our patient was too extensive for excision. For more extensive lesions, the most effective treatment is the topical application of ammonium lactate lotion (12%), which prevents not only comedo production, but also inflammatory cyst formation (1). Other therapeutic approaches include topical keratolytic agents (salicylic, lactic, *d*-tartaric and α-hydroxy acid, or benzoyl peroxide), ammonium lactate, topical retinoic acid, manual extraction of comedones, pore strip pack, dermabrasion, tissue expansion in extensive nevus comedonicus lesions, hormonal (estrogen and progesterone) therapy, and oral isotretinoin. Oral isotretinoin has been reported to decrease cyst formation without improving the appearance of comedones, whereas in some cases nevus comedonicus was improved by hormonal (estrogen and progesterone) therapy. Topical and systemic antibiotics are

indicated to control infection in inflammatory, cystic, and scarring type of nevus comedonicus (3).

According to the typical clinical features and patch test results, we concluded that the best therapeutic approach in our patient with nevus comedonicus is local application of tretinoin. The patent was successfully treated with retinoic acid.

To the best of our knowledge, application of retinoid acid accelerates the exfoliation of the epithelium and the expulsion of the keratin layers but does not eliminate the crypts and pits in the skin. To date, there is no single treatment of choice for nevus comedonicus. In our patient, the choice of treatment was local retinoid.

References

1 Milton GP, DiGiovanna JJ, Peck GL. Treatment of nevus comedonicus with ammonium lactate lotion. J Am Acad Dermatol 1989;20 (2 Pt 2):324-8.

2 Decherd JW, Mills O, Leyden JJ. Naevus comedonicus – treatment with retinoic acid. Br J Dermatol 1972;86:528-9.

3 Lefkowitz A, Schwartz RA, Lambert WC. Nevus comedonicus. Dermatology 1999;199:204-7.

4 Engber PB. The nevus comedonicus syndrome: a case report with emphasis on associated internal manifestations. Int J Dermatol 1978;17:745-9.

5 Braun-Falco O, Plewig G, Wolf HH, Burgdorf WH. Nevus comedonicus. In: Braun-Falco O, Plewig G, Wolf HH, Burgdorf WH, editors. Dermatology. 2nd completely revised ed. Berlin: Springer Verlag; 2000. p. 1410-1.

6 Fitzpatrick TB, Pathak MA. Epidermal and appendageal tumors. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, editors. Fitzpatrick's dermatology in general medicine. 6th ed. New York (NY): McGraw-Hill; 2000. p. 862.

7 Carney RG. Linear unilateral basal cell nevus with comedones. Arch Dermatol Syphilol 1952;65:471-6.

8 Cripps DJ, Berttram JR. Nevus comedonicus bilateralis et verruciformis. J Cutan Pathol 1976;3:273-81.

9 Bleiberg J, Brodkin RH. Linear unilateral basal cell nevus with comedones. Arch Dermatol 1969;100: 187-90.

10 Rook AJ. Clinical reports. Case 3. Nevus comedonicus unilateralis with partial Sturge-Weber syndrome and extensive vascular naevi with haemagiectatic hypertrophy of the leg. In: Proceedings of the 10th International Congress of Dermatology, London. London: British Medical Association; 1952. p. 421-2.

11 Popov L, Boianov L. Undescribed congenital cutaneo-ocular syndrome (congenital cataract-comedo syndrome) [in Bulgarian]. Suvr Med (Sofiia) 1962;13:49-50.

12 Leppard BJ. Trichilemmal cysts arising in an extensive comedo nevus. Br J Dermatol 1977;96:545-8.

13 Wood MG, Thew MA. Nevus comedonicus. A case with palmar involvement and review of the literature. Arch Dermatol 1968;98:111-6.

14 Paige TN, Mendelson CG. Bilateral nevus comedonicus. Arch Dermatol 1967;96:172-5.

15 Bernucci F. Considerazione su di un nevo-acrino lineare a comedoni. Arch Ital Dermatol Syphilol 1930; 6:26-7.

16 Piers F. Linear comedo naevus with ichthyosis. Br J Dermatol Syphilol 1945;57:138-40.

17 Blaschko A. Acne zosteriformis. Arch Dermatol Syphilol 1916;128:242-3.

18 Whyte HJ. Unilateral comedo nevus and cataract. Arch Dermatol 1968;97:533-5.

Acta Dermatovenerol Croat 2003;11(4):225-230 REVIEW

Protein p53 – Structure, Function, and Possible Therapeutic Implications

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SUMMARY Cell cycle is driven by a number of positive and negative regulatory phosphorylation and dephosphorylation events that ultimately influence the activity of transcription factors. Normal skin architecture depends on the regulation mechanisms of cell proliferation and differentiation and on apoptosis. Complex interaction of different factors in the regulation of these mechanisms, aimed at maintaining constant desquamation, is often changed in skin diseases. The main difference between normal cells and tumor cells results from discrete changes in specific genes important for cell proliferation control mechanisms and tissue homeostasis. These genes are mainly proto-oncogenes or tumor-suppressor genes, and their mutation could play a role in cell hyperproliferation and carcinogenesis. Tumor-suppressor genes normally function as a physiological barrier against clonal expansion or mutation accumulation in the genome. They also control and arrest growth of the cells that hyperproliferate due to oncogene activity. Alteration or DNA damage in tumor-suppressor genes and oncogenes are considered key events in human carcinogenesis. Tumor-suppressor protein p53 is an important transcription factor, which plays a central role in the cell cycle regulation mechanisms and cell proliferation control, and its inactivation is considered a key event in human carcinogenesis. The role of p53 protein in the cell cycle, high proportion of tumors with mutated p53 gene, and accumulation of significant amount of knowledge on molecular biology of this protein make this molecule especially attractive for development of new therapeutic approaches. Main strategies for development of new antineoplastic therapies are based on "wild-type" p53 protein acting as a tumor suppressor, selective apoptosis inductor, and a protein able to arrest cell cycle.

KEY WORDS antineoplastic agents; genes, p53; neoplasms; protein p53

INTRODUCTION

The mutated p53 tumor-suppressor gene and its protein product can be found in about half of almost all types of cancer in humans (1), and its inactivation is considered a key event in human carcinogenesis (2). Tumor-suppressor protein p53 is an important transcription factor and central to the cell cycle regulation mechanisms (3-7).

The importance of p53 protein is not limited to malignant diseases only. As a "guardian of the genome", p53 protein in normal tissues rapidly induces a response to DNA damaging agents (8-12). Mutation of the p53 gene results in the loss of p53 functions, i.e. in the exertion of oncogenic functions (6,13-16). Mutation of p53 gene is also

the main cause of p53 protein overexpression due to prolongation of its half-life (1,2,17,18). In the absence of functional wild-type p53, its protective function is lost. As a consequence, cells accumulate genetic damage and exhibit pronounced genetic instability, with possible progression to malignancy (2,4,5,17,19). This is the reason why the p53 protein overexpression is usually seen in malignant tumors (15,16,18,20).

Studies have shown that p53 protein overexpression is an important characteristic of skin tumors, such as squamous cell carcinoma (20-26), basal cell carcinoma (20-25), keratoacanthoma (20-22,26), and Mb. Bowen (20-22), as well as of precancerous lesions, such as actinic keratosis (21,22). It has been shown that aberrant p53 expression occurs widely in squamous epithelium of inflammatory skin diseases, such as lichen planus (3,22), psoriasis (21,23,27,28), chronic dermatitis (21), and lupus erythematosus (30,31). Protein p53 overexpression could also be found in epithelium of noninflammatory skin diseases, such as keloid (32,33) and seborrheic keratosis (21,22). These diseases are characterized by cell hyperproliferation. There could be an association between p53 positivity and the number of Ki-67 positive cells and mitoses (21), suggesting that aberrant p53 expression is enhanced by cell proliferation. Since p53 is essential for the regulation of cell proliferation (4-6,14), and the "wild-type" p53 protein has been shown to down-regulate the expression of proliferating cell nuclear antigen (PCNA) (34), its accumulation could be a physiological reaction involved in the inhibition of increased cell proliferation (21,28).

STRUCTURE OF P53 TUMOR-SUPPRESSOR GENE AND PROTEIN

Gene p53 is located on chromosome 17 at position 13.1. It spans 20 kb and consists of 11 exons, the first one uncoding. In cancer tissues, region 17p is often reduced to homozygosity (15). The overall structure of the gene and the sequence of several domains corresponding to key structural features of the protein are well conserved in all vertebrates. The highest homology (around 60%) can be seen in the DNA binding domain (14).

Protein p53 is an oligomeric transcription factor of 393 residues organized in five structural and functional regions (Fig. 1; ref. 11,14,16,17,19,35).

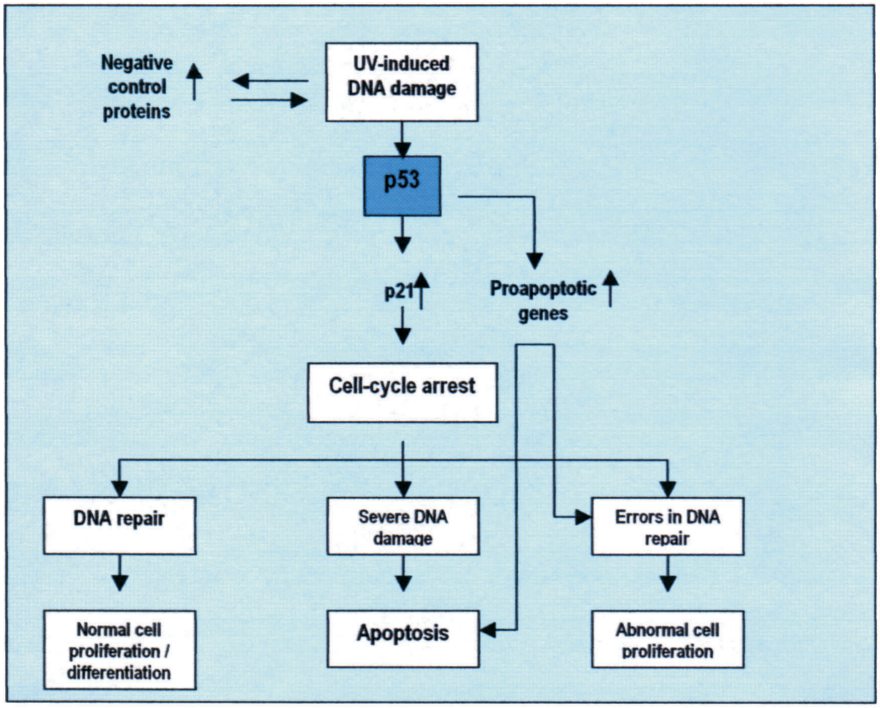

Figure 1. Structure of p53 protein (modified from ref. 1). Functional domains (sites for transactivation and DNA binding), evolutionally conserved domains (I to V), and binding sites for cellular (MDM2) and oncoviral proteins (SV40 T antigen, HPV E6, and adenoma virus E1b proteins) (14,16,17,19,36,37).

These regions include an N-terminal or transcriptional activation domain (TA), a proline-rich regulatory domain (PRD), a sequence-specific DNA-binding domain (DBD), an oligomerization domain or nuclear localization signal (NLS), and a multifunctional carboxy-terminal domain (CTD) involved in the regulation of DNA-binding (1,6,14,16,19,35). TA is also a region where MDM2 protein and TATA-binding protein (TBP)-associated factor (TAF) bind. The central, DNA-binding domain is responsible for protein conformation. The DBD is the site where a vast majority of tumor mutations occur (15). Binding of simian virus 40 (SV40) large T antigen to this region inactivates p53 protein (1,35,36). Oligomerization domain (NLS) is responsible for oligomerization of p53 protein into dimers and tetramers and is important for ability to bind DNA. CTD is considered the region of major allosteric regulation of p53 function and contains the sequences necessary for dimerization and tetramerization. It is, also, responsible for maintaining p53 protein in its latent form. Neutralization of this domain by specific antibodies results in structural changes of p53 protein and enables DNA binding (1,35-37).

PROTEIN p53 – GUARDIAN OF THE GENOME

The p53 protein was first described in 1979 as a cellular nuclear protein of 53 kDa complexing with SV40 large T antigen (37). Activity of p53 protein is linked with cell cycle control, DNA repair and synthesis, reaction to stress, cell differentiation, apoptosis, and maintenance of genome stability and tumor suppression (2,4,5,11,12,14,15,19,38, 39). The p53 protein is constitutively expressed in almost all cells types but has a very rapid turnover and seems to be latent under normal conditions. In normal cells, concentration of “wild-type” protein p53 is usually bellow detection level for standard immunohistochemical methods on paraffin imbedded sections (2,14,17,21). Activation or stabilization of p53 protein as well as a point mutation of p53 gene result in p53 protein accumulation, which allows immunohistochemical detection.

Protein p53 is essential for coordinating cell response to various forms of stress (6). Protein activity is tightly controlled by keeping it at low concentration within the cell (2,6,11,12,17). Lane *et a*l (39) suggested that p53 protein could be a “guardian of the genome”. Levels and activity of p53 protein in normal tissue are rapidly induced as a response to a number of physical or chemical DNA-damaging agents (11,12), such as X- or gamma-irradiation (11), UV rays (7-10), ribonucleotide depletion (40), oncogenic stimuli (41,42), oxidizing agents, and ischemic or hypoxic damage of tissues (43). Active form of p53 protein, which accumulates in the cell, causes cell cycle arrest in G1 phase, giving extra time for DNA repair (1,4,5,11,12,39). In case of errors in DNA repair it can induce apoptosis (4,5,15,39,41). In case of p53 protein mutation, there is no DNA repair or apoptosis and the result is an abnormal proliferation of the cells. Even though cells possess mechanisms to repair DNA damage, some damage remains and accumulates in the cell, leading sometimes to cell carcinogenesis (6,11,12, 39). The central role of p53 protein in cell cycle arrest, DNA repair, and apoptosis following UV irradiation in keratinocytes provides as example of its importance (Fig. 2).

The critical role of the p53 gene in maintaining the integrity of human genome is evident from the fact that p53 is the most commonly altered gene in human cancer (1). Gene p53 mutations are the most common in skin cancers (8,13-15,20-26). Mutated form of p53 protein can act as dominant oncogene (45), whereas its normal “wild-type” acts as a recessive tumor-suppressor protein (2,4,5,17, 39). Mutation of p53 gene also results in formation of dominant-negative conformation form able to inactivate protein product by heterotetramer formation (46). In the absence of functional wild-type p53, the protective function of the gene is lost – cells accumulate genetic damage and exhibit pronounced genetic instability with possible progression to malignancy (2,4,5,17,19,39). Since mutation is the most common cause of p53 protein overexpression (2,17), positive immunohistochemical staining is considered a marker of malignancy (18). Gene p53 mutations are found in Li-Fraumeni syndrome, inherited disorder characterized by high risk of formation of different sorts of malignancy in early life (47). It is considered that p53 gene changes are more important than it is shown by statistical analysis of gene mutations.

The “wild-type” p53 protein can be inactivated not only by mutation, but also by viral oncogenes (6). As mentioned earlier, many of DNA viruses

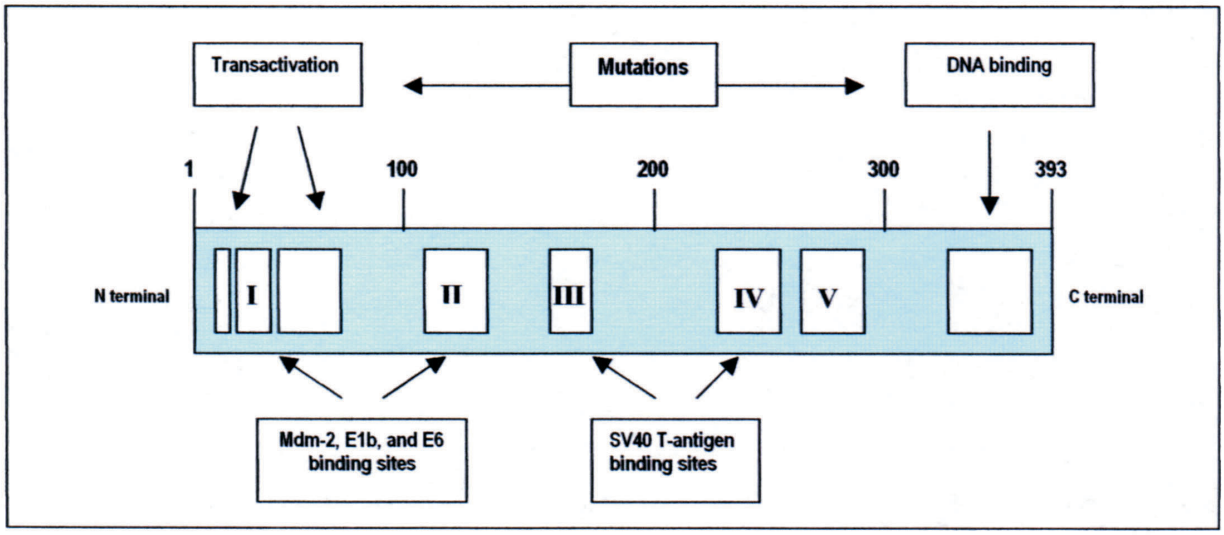

Figure 2. The central role of p53 in cell-cycle arrest, DNA repair, and apoptosis following UV irradiation (modified from ref. 6). Skin cells contain mechanisms to prevent such DNA damage from leading to skin carcinogenesis. The accumulation of p53 protein after exposure to UV irradiation plays a central role in these mechanisms. Protein p53 induces p21, which inhibits formation of complexes required for the cell cycle and thereby leads to cell-cycle arrest. Cell-cycle arrest can provide the cell with time to achieve successful DNA repair and the cell proliferates as normal. If the DNA damage caused by UV irradiation is too severe and cannot be repaired, apoptotic pathways are activated to eliminate damaged cells. If normal DNA repair is not achieved, for instance because of mutations in p53, the cell proliferates abnormally, which can lead to carcinogenesis. As a transactivator of transcription, p53 can induce apoptosis by up-regulating the expression of apoptosis-promoting (pro-apoptotic) genes such as Bax, Fas/Apo-1, death receptor 5 (DR5) (44), or by down-regulating the expression of apoptosis protein 2 (c-IAP2) and neuronal apoptosis inhibitory protein 1 (NAIP 1) (34). If apoptosis is not achieved, because of p53 mutation, it could lead to abnormal cell proliferation and result in skin cancer formation. Tumor-suppressor activity of p53 protein is inhibited by rapid degradation through MDM2 protein. Gene encoding the MDM2 protein is activated by p53 protein what insures negative control (6).

have developed mechanisms to ensure replication in the genome of the infected cell, mainly by p53 protein inactivation through binding or its rapid degradation by proteolysis (37,48).

PROTEIN p53 AND POSSIBLE THERAPEUTIC APPROACHES

Central role of p53 protein in cell cycle and cell proliferation control (14,39,43), high proportion of tumors with mutated p53 gene, and the knowledge accumulated about molecular biology of this protein, make this molecule especially attractive for development of new therapeutic approaches. The fact that the introduced "wild-type" p53 gene inhibits growth and/or tumorigenicity of cancer cell (49-51), whereas p53 protein overexpression in a healthy cell has only minimal activity, suggests high therapeutic index of p53 gene in human cancers. Major strategies for development of new antineoplastic therapies use the "wild-type" p53 protein acting as a tumor-suppressor, apoptosis inductor, and a protein able to arrest cell cycle (1,4,5,11, 12,14, 15,39). Since the reactivation of "wild-type" p53 protein can help in removing p53-deficient tumor cells by activating an apoptotic process (49,50,51), the main focus of research is the ability of "wild-type" p53 protein to selectively induce apoptosis (11,12,14,39,41,42).

In recent years, researchers developed peptides able to restore DNA-binding capacity in mutated p53 protein and regenerate p53 functions in tumor cells. This approach is especially attractive since it does not cause global DNA damage, as other antineoplastic drugs do (49). Restored p53 protein function could be achieved by introducing a "wild-type" p53 protein in tumor cell through a recombinant virus vector (50). Selective destruction of p53-deficient cells could be achieved by introducing recombinant adenovirus unable to reproduce in cells with normal p53 protein (50). Induction of overexpression of newly discovered homologues p73 and p51/p40/ket can result in apoptosis of tumor cells lacking p53 protein (49).

Also, promising results are achieved by soluble p53 antigen vaccination to activate immune response with tumor-suppressor function. It is believed that vaccine development could be used in prevention of tumor recidivation (51). In tumors retaining normal p53 function and in other pathological conditions characterized by cell hyperproliferation, it is possible to selectively block interaction between "wild-type" p53 protein and neutralizing MDM2 protein. This type of therapy could be useful in non-neoplastic conditions with no presence of p53 gene mutation or loss of p53 protein function, whereas enhanced activation of p53 protein could be of help in cell proliferation regulation (1). Because some of p53 gene mutations result in the gain of oncogenic functions (15,45), one of the possible approaches could be the inhibition of new characteristic development (1,2).

Although clinical studies on the possible therapeutic use of p53 gene and protein are under way, it will probably take some time before the experience and experimental results show the best way in which p53-based treatment could be used in clinical practice.

References

1 Harris CC, Hollstein M. Clinical implications of the p53 tumor-suppressor gene. N Engl J Med 1993;329: 1318-27.

2 Furihata M, Sonobe H, Ohtsuki Y. The aberrant p53 protein. Int J Oncol 1995;6:1209-26.

3 Lane DP, Benchimol S. p53: oncogene or anti-oncogene. Genes Dev 1990;4:1-8.

4 Haake AR, Polakowska RR. Cell death by apoptosis in epidermal biology. J Invest Dermatol 1993;101: 107-12.

5 Milner J. The role of p53 in the normal control of cell proliferation. Curr Opin Cell Biol 1991;3:282-6.

6 Deppert W, Buschhausen-Denker G, Patschinsky T, Steinmeyer K. Cell cycle control of p53 in normal (3T3) and chemically transformed (Meth A) mouse cells. II. Requirement for cell cycle progression. Oncogene 1990; 5:1701-6.

7 Matsumura Y, Ananthaswamy HN. Short-term and long-term cellular and molecular events following UV irradiation of skin: implications for molecular medicine. Expert Rev Mol Med 2002;4:1-22.

8 Liang SB, Ohtsuki Y, Furihata M, Takeuchi T, Iwata J, Chen BK, *et al*. Sun-exposure- and aging-dependent p53 protein accumulation results in growth advantage for tumor cells in carcinogenesis of nonmelanocytic skin cancer. Virchows Arch 1999;434:193-9.

9 Hall PA, McKee PH, Menage H, Dover R, Lane DP. High levels of p53 protein in UV-irradiated normal skin. Oncogene 1993;8:203-7.

10 Jonason AS, Kunala S, Price GJ, Restifo RJ, Spinelli HM, Persing JA, *et al*. Frequent clones of p53-mutated keratinocytes in normal human skin. Proc Natl Acad Sci USA 1996;93:14025-9.

11 Kastan MB, Onyekwere O, Sidransky D, Vogelstein B, Craig RW. Participation of p53 in the cellular response to DNA damage. Cancer Res 1991;51(23 Pt 1): 6304-11.

12 Nelson WG, Kastan M. DNA strand breaks: the DNA template alterations that trigger p53-dependent DNA damage response pathways. Mol Cell Biol 1994;14: 1815-23.

13 Hoffman B, Liebermann DA. Molecular controls of apoptosis: differentiation/growth arrest primary response genes, proto-oncogenes, and tumor suppressor genes as positive & negative modulators. Oncogene 1994;9:1807-12.

14 Hainaut P, Hollstein M. p53 and human cancer: the first ten thousand mutations. Adv Cancer Res 2000;77: 81-137.

15 D'Errico MR, Dogliotti E. The role of p53 mutations in skin cancer. Chronica Dermatologica 1996;6:27-35.

16 Mowat MR. P53 in tumor progression: life, death, and everything. Adv Cancer Res 1998;74:25-48.

17 Levine AJ, Momand J, Finlay CA. The p53 tumor suppressor. Nature 1991;351:453-6.

18 Hall PA, Ray A, Lemoine NR. p53 immunostaining as a marker of malignant disease in diagnostic cytopathology. Lancet 1991;338:513.

19 Ko LJ, Prives C. p53: puzzle and paradigm. Genes Dev 1996;10:1054-72.

20 Helander SD, Peters MS, Pittelkow MR. Expression of p53 protein in benign and malignant epidermal pathological conditions. J Am Acad Dermatol 1993;29(5 Pt 1):741-8.

21 Soini Y, Kamel D, Paakko P, Lehto VP, Oikarinen A, Vahakangas KV. Aberrant accumulation of p53 associates with Ki67 and mitotic count in benign skin lesions. Br J Dermatol 1994;131:514-20.

22 Ro YS, Cooper PN, Lee JA, Quinn AG, Harrison D, Lane D, *et al*. p53 protein expression in benign and malignant skin tumors. Br J Dermatol 1993;128: 237-41.

23 Helander SD, Peters MS, Pittelkow MR. p53 expression and localization in normal skin, psoriasis, cutaneous carcinoma and cultured keratinocytes. J Invest Dermatol 1992;98: 636-41.

24 McNutt NS, Saenz-Santamaria C, Volkenandt M, Shea CR, Albino AP. Abnormalities of p53 protein expression in cutaneous disorders. Arch Dermatol 1994;130: 225-32.

25 McGregor JM, Yu CC, Dublin EA, Levison DA, MacDonald DM. Aberrant expression of p53 tumor-suppressor protein in non-melanoma skin cancer. Br J Dermatol 1992;127:463-9.

26 Stephenson TJ, Royds J, Silcocks PB, Bleehen SS. Mutant p53 oncogene expression in keratoacanthoma and squamous cell carcinoma. Br J Dermatol 1992; 127:566-70.

27 Tadini G, Cerri A, Crosti L, Cattoretti G, Berti E. p53 and oncogene expression in psoriasis. Acta Derm Venereol Suppl (Stockh) 1989;146:33-5.

28 Hannuksela-Svahn A, Paakko P, Autio P, Reunala T, Karvonen J, *et al*. Expression of p53 protein before and after PUVA treatment in psoriasis. Acta Derm Venereol 1999;79:195-9.

29 Bianchi L, Farrace MG, Nini G, Piacentini M. Abnormal Bcl-2 and "tissue" transglutaminase expression in psoriatic skin. J Invest Dermatol 1994;103: 829-33.

30 Chung JH, Kwon OS, Eun HC, Youn JI, Song YW, Kim JG, *et al*. Apoptosis in the pathogenesis of cutaneous lupus erythematosus. Am J Dermatopathol 1998;20: 233-41.

31 de Jong EM, van Erp PE, Ruiter DJ, van de Kerkhof PC. Immunohistochemical detection of proliferation and differentiation in discoid lupus erythematosus. J Am Acad Dermatol 1991;25(6 Pt 1):1032-8.

32 Saed GM, Ladin D, Olson J, Han X, Hou Z, Fivenson D. Analysis of p53 gene mutations in keloids using polymerase chain reaction-based single-strained conformational polymorphism and DNA sequencing. Arch Dermatol 1998;134:963-7.

33 Tuan TL, Nichter LS. The molecular basis of keloid and hypertrophic scar formation. Mol Med Today 1998;4: 19-24.

34 Mercer WE, Shields MT, Lin D, Appella E, Ullrich SJ. Growth suppression induced by wild-type p53 protein is accompanied by selective down-regulation of proliferating-cell nuclear antigen expression. Proc Natl Acad Sci USA 1991;88:1958-62.

35 el-Deiry WS, Kern SE, Pientepol JA, Kinzler KW, Vogelstein B. Definition of a consensus binding site for p53. Nat Genet 1992;1:45-9.

36 Cho Y, Gorina S, Jeffrey PD, Pavletich NP. Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. Science 1994; 265:346-55.

37 Lane DP, Crawford LV. T antigen is bound to a host protein in SV-transformed cells. Nature 1979;278: 261-3.

38 Wrone-Smith T, Bergstrom J, Quevedo ME, Reddy V, Gutierrez-Steil C, Nickoloff BJ. Differential expression of cell survival and cell cycle regulatory proteins in cutaneous squamoproliferative lesions. J Dermatol Sci 1999;19:53-67.

39 Lane DP. Cancer. p53, guardian of the genome. Nature 1992;358:15-6.

40 Linke SP, Clarkin KC, Di Leonardo A, Tsou A, Wahl GM. A reversible, p53 dependent G0/G1 cell cycle arrest induced by ribonucleotide depletion in the absence of detectable DNA damage. Genes Dev 1996; 10:934-47.

41 Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. Cell 1997;88:593-602.

42 Nigro JM, Aldape KD, Hess SM, Tlsty TD. Cellular adhesion regulates p53 protein levels in primary human keratinocytes. Cancer Res 1997;57:3635-9.

43 Banasiak KJ, Haddad GG. Hypoxia-induced apoptosis: effects of hypoxia severity and role of p53 in neuronal cell death. Brain Res 1998;797:295-304.

44 Miyashita T, Krajewski S, Krajewska M, Wang HG, Lin HK, Liebermann DA, *et al*. Tumor suppressor p53 is a regulator of bcl-2 and bax gene expression in vitro and in vivo. Oncogene 1994;9:1799-805.

45 Dittmer D, Pati S, Zambetti G, Chu S, Teresky AK, Moore M, *et al*. Gain of function mutations in p53. Nat Genet 1993;4:42-6.

46 Milner J, Medcalf EA. Cotranslation of activated mutant p53 wild type drives the wild-type p53 protein into the mutant conformation. Cell 1991;65:765-74.

47 Malkin D, Li FP, Strong LC, Fraumeni JF Jr, Nelson CE, Kim DH, *et al*. Germ line p53 mutations in a familiar syndrome of breast cancer, sarcomas, and other neoplasms. Science 1990;250:1233-8.

48 Ueda H, Ullrich SJ, Gangemi JD, Kappel CA, Ngo L, Feitelson MA, *et al*. Functional inactivation but not structural mutation of p53 causes liver cancer. Nat Genet 1995;9:41-7.

49 Bold RJ, Termuhlen PM, McConkey DJ. Apoptosis, cancer and cancer therapy. Surg Oncol 1997;6: 133-42.

50 Dummer R, Bergh J, Karlsson Y, Horowitz JA, Mulder NH, Huinink DT, *et al*. Biological activity and safety of adenoviral vector-expressed wild-type p53 after intramural injection in melanoma and breast cancer patients with p53-overexpressing tumors. Cancer Gene Ther 2000;7:1069-76.

51 Ben-Hur H, Ben-Meir A, Hagay Z, Ben-Meir A, Berman V, Schwartsburd B, *et al*. Tumor-preventive effects of the soluble p53 antigen on chemically-induced skin cancer in mice. Anticancer Res 1998;18:4237-41.

Acta Dermatovenerol Croat 2003;11(4):231-235 REVIEW

Stomatodynia or Burning Mouth Syndrome

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SUMMARY We reviewed the literature on stomatodynia particularly to identify the factors associated with this annoying manifestation in order to better understand it and treat it. No consensus was found in the literature regarding etiological factors, associated morbidity, treatment, and definition of the burning mouth syndrome. This review aims at defining the disease, its characteristics, criteria for the diagnosis, and treatment.

KEY WORDS burning mouth syndrome; stomatodynia

INTRODUCTION

Stomatodynia or burning mouth syndrome is a relatively frequent disease characterized by intense feeling of burning or pain in the oral mucosa, mainly in the tongue, without any visible clinical changes in the oral cavity. The disorder is more common in women above 40 years of age.

CLINICAL CHARACTERISTICS

Stomatodynia, glossodynia (when only the tongue is affected), and burning mouth syndrome are some of the expressions used to describe pain symptoms and burning in the oral mucosa of normal aspect. The lack of unanimous opinion regarding the criteria for diagnosis makes the analysis of the studies in this condition very difficult. Many reports included patients with an altered oral mucosa, which invalidated the diagnosis of stomatodynia, because, in the opinion of the majority of the authors, the diagnosis of stomatodynia as disease must be excluded if there are detectable manifestations at oral physical examination.

The investigative study on etiological factors by Lamey and Lamb (1) showed that the most frequently affected area in the mouth is the tongue, although all other areas of the oral mucosa may also be involved. In their review of 98 cases of stomatodynia, Gorsky *et al* (2) found that the tongue was affected in 78% of the patients, either

solely or with other intraoral locations. Similar findings regarding the area of the affected mucosa were also reported by Grushka (3). Numerous factors have been reported as altered in such patients and consequently considered responsible for the appearance of the disease (4).

Stomatodynia is one of the most frequent reasons for consultation at the Oral Dermatology Outpatient Clinic of HUCFF-UFRJ, in Rio de Janeiro, and at the Stomatology Outpatient Clinic of the Complexo Hospitalar Santa Casa, in Porto Alegre, Brazil.

ASSOCIATED FACTORS

The most common factor implicated as a cause of stomatodynia has been the emotional state of the patient (5-10). There are also other factors, but many still without confirmation. The psychiatric manifestations related to anxiety, depression, and incapacity to adapt are found more frequently in patients with burning mouth syndrome, as demonstrated by psychological evaluation scales and tests (7,11-16). Other complaints regarding the oral area, such as dry mouth and metal taste, are also common, as well as extra-oral complaints, such as headache (17,18). The relief of burning mouth symptoms can be obtained by eating, sleeping, and various activities that distract the patient (3), which also speaks in favor of the importance of psychological aspect of the disease.

The search and identification of causes and factors involved in stomatodynia was a primary aim of several studies. Lamey *et al* (19) reported improvement of symptoms in 24 out of 28 patients after replacement therapy with vitamin B complex for 30 days. However, their results were not corroborated by those obtained by Hugeson and Thorstensson (20) and Grushka (3), who also investigated the effect of vitamin B complex replacement therapy in patients with low levels of these vitamins.

Some studies focused on microbiological and saliva aspects in patients with stomatodynia. The finding of *Candida* at the mycological examination is often indicated as a cause, even if oral candidosis is not present in any form. It is known, however, that *Candida* is found in the normal flora without pathological significance in up to 60% of healthy individuals (18,21-23). In subsequent studies, Lamey (24) suggested that saliva flow tests should be performed, because he found reduced flows in such patients in one of his previous studies (25). Other authors did not find any statistically significant difference in saliva flow between patients with stomatodynia and healthy subjects (26,27).

Improvement of associated factors, such as correction of poorly adapted prostheses, usually does not eliminate the symptoms. However, the replacement of odontological restoration material produced improvement when there was clinically evident allergy, which was not present when the mucosa was normal (1,28,29).

A single study that included patients with both stomatodynia and non-insulin dependent diabetes mellitus demonstrated the remission of the oral symptoms in all cases by treatment of diabetes (30). It seems that there are no other similar studies.

Xerostomia and hypofunction of salivary glands in older women are probably caused by other diseases and their treatment, and not by aging or postmenopause. Heft and Baum (31) and Ship *et al* (32) found no statistical difference in the activity of salivary glands related to age.

Tactile oral stimulation perception tests in patients with the burning mouth syndrome and healthy controls were performed by Lamey *et al* (33), with inconclusive results.

In another study, Grushka (34) established a reduction of painful sensitivity to high temperatures at the tip of the tongue in patients with stomatodynia. He showed that tactile sensations discriminatory of two points and the perception of thermal alteration were preserved, and that the same sensitivity was normal at the evaluation of the lower lip.

Heckmann *et al* (35) studied blood flow in the oral mucosa in patients with burning mouth syndrome using a Doppler laser flow meter. They found high vasoreactivity, mainly in the hard palate, and suggested further studies in the relation between blood flow and generation and/or maintenance of the pain.

Friedlander and Runyon (36) reported that claudication of the masticatory muscles and the tongue with pain and burning might develop during

temporal arteritis or might be its initial presentation symptom.

What seems to be unanimously agreed upon regarding stomatodynia is its association with the emotional state of a patient – many studies emphasized the anxiety and depression as prevailing factors. By reviewing 98 cases, Gorsky *et al* (2) observed that patients responded significantly well to the treatment with chlordiazepoxide, whereas Pokupec-Gruden *et al* (37) confirmed that depression, poor adaptability, and anxiety were significantly more present in patients with stomatodynia than in healthy subjects.

Nicholson *et al* (38) showed high prevalence of psychiatric morbidity in this syndrome, a fact already demonstrated by Rojo *et al* (39), who detected psychiatric changes in more than half of his 72 patients. Ali *et al* (28) and Eli *et al* (40) found high rates of psychiatric disturbances (40-50%) associated with the burning mouth syndrome, as well as Hampf *et al* (41), who also detected more cases of psychiatric disturbances in patients with orofacial disesthesia.

TREATMENT

The therapeutic result of stomatodynia is generally unsatisfactory. The greatest success is reached by use of medications aimed at the psychological alterations found in an individual patient, such as depression or anxiety. The duration of the treatment varies: some authors recommend a period of three to six months (42), whereas others prefer a longer treatment, i.e. between 12 and 18 months (43). Since patients are frequently concerned that stomatodynia could accompany the development of neoplastic disease, the physician must assure that the patient is familiar with the facts about the disease and that he or she understands that it does not have an organic or systemic cause (22,44). At the Oral Dermatology Outpatient Clinic of HUCFF-UFRJ in Rio de Janeiro, as well as at the Stomatology Out-Patient Clinic of the Santa Casa Hospital in Porto Alegre, the administration of pimozide at 1-2 mg/day has shown satisfactory results, with complete remission of symptoms in most patients. This drug, however, must be used with caution, due to its side effects (extrapyramidal symptoms), such as stiffness, agitation, and motor restlessness – a syndrome known as akathisia.

CONCLUSION

The oral cavity has undisputed relevance in interpersonal relationship since the earliest age (the mother-child relation) until old age. Oral functions range from the most simple and necessary for survival, such as breathing, eating, touching, and feeling, to the most elaborate, such as mimics and speech. In addition, we receive a wide spectrum of sensations from the oral area, from pain to pleasure. Maybe all these functions my reasonably explain why the oral cavity is an organ subject to apparently unexplainable or unjustifiable manifestations and why symptoms related to cancerophobia or a conflict, difficulty to adapt, or other emotional disturbances often set themselves in the mouth (1,22,44).

The search for organic changes to justify an affection of emotional prevalence has caused difficulty in the understanding of and approach to the disease, leading to wrong diagnoses and treatments. Additionally, reference to non-confirmed studies in recent publications has hampered the study of the disease.

Treatment with anti-depressive and anxiolytic medicaments has been the most effective therapy for stomatodynia (22,42-44). The physician has an important role in the exclusion of organic causes, assuring the patient that the disease has no internal cause, maintaining a good physician/patient relationship to obtain success in referring the patient to psychotherapy, and introducing anti-depressives or other adequate medications.

References

1 Lamey PJ, Lamb AB. Prospective study of aetiological factors in burning mouth syndrome. Br Med J 1988;296:1243-6.

2 Gorsky M, Silverman S Jr, Chinn H. Burning mouth syndrome: a review of 98 cases. J Oral Med 1987; 42:7-9.

3 Grushka M. Clinical features of burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63: 30-6.

4 Basker RM, Sturdee DW, Davenport JC. Patients with burning mouths. A clinical investigation of causative factors, including the climacteric and diabetes. Br Dent J 1978;145:9-16.

5 Coles RB. Glossodynia - a psychossomatic problem. Trans St John Hosp Dermatol Soc 1966;52:79-83.

6 Schoenberg B. Psychogenic aspects of the burning mouth. N Y State Dent J 1967;33:467-73.

7 Schoenberg B, Carr AC, Kutscher AH, Zegarelli EV. Chronic idiophatic orolingual pain. Psychogenesis of burning mouth. N Y State J Med 1971;71:1832-7.

8 Harris M, Davies G. Psychiatric disorders. In: Jones JH, Mason DK, editors. Oral manifestations of systemic diseases. Philadelphia(PA): WB Saunders; 1980. p. 447-8.

9 Brightman VJ. Oral symptoms without apparent physical abnormality. In: Lynch MA, editor. Burkett's oral medicine. 8th ed. Philadelphia (PA): JB Lippincott; 1984. p. 629-32.

10 Rogers RS III. Diseases of the tongue, lips and salivary glands. In: Lotti TM, Parish LC, Rogers RS III. Oral diseases: textbook and atlas. Heidelberg: Springer-Verlag; 1999. p. 219-37.

11 Main DM, Basker RM. Patients complaining of a burning mouth. Further experience in clinical assessment and management. Br Dent J 1983;154:206-11.

12 Grushka M, Sessle BJ, Miller R. Pain and personality profiles in burning mouth syndrome. Pain 1987;28: 155-67.

13 Van der Ploeg HM, Van der Wal N, Eijkman MA, Van der Waal I. Psychological aspects of patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1987;63:664-8.

14 Browning S, Hislop S, Scully C, Shirlaw P. The association between burning mouth syndrome and psychosocal disorders. Oral Surg Oral Med Oral Pathol 1987;64:171-4.

15 Lamb AB, Lamey PJ, Reeve PE. Burning mouth syndrome: psychological aspects. Br Dent J 1988;165: 256-60.

16 Lamey PJ, Lamb AB. The usefulness of the HAD scale in assessing anxiety and depression in patients with burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1989;67:390-2.

17 Van der Waal I. The burning mouth syndrome. Copenhagen: Munksgaard; 1990. p. 5-90.

18 Gorsky M, Silverman S Jr, Chinn H. Clinical characteristics and management outcome in the burning mouth syndrome. An open study of 130 patients. Oral Surg Oral Med Oral Pathol 1991;72: 192-5.

19 Lamey PJ, Hammond A, Allam BF, McIntosh WB. Vitamin status of patients with burning mouth syndrome and the response to replacement therapy. Br Dent J 1986;160:81-4.

20 Hugoson A, Thorstensson B. Vitamin B status and response to replacement therapy in patients with burning mouth syndrome. Acta Odontol Scand 1991;49:367-75.

21 Brawner DL, Cutler JE. Oral *Candida albicans* isolates from nonhospitalized normal carriers, immunocompetent hospitalized patients, and immunocompromised patients with or without acquired immunodeficiency syndrome. J Clin Microbiol 1989;27:1335-41.

22 Muzyka BC, De Rossi SS. A review of burning mouth syndrome. Cutis 1999;64:29-35.

23 Fotos PG, Vincent SD, Hellstein J. Oral candidosis. Clinical, historical, and therapeutic features of 100 cases. Oral Surg Oral Med Oral Pathol 1992;74:41-9.

24 Lamey PJ. Burning mouth syndrome. Dermatol Clin 1996;14:339-54.

25 Lamey PJ, Lamb AB. Lip component of burning mouth syndrome. Oral Surg Oral Med Oral Pathol 1994;78: 590-3.

26 Glick D, Ben-Aryeh H, Gutman D, Szargel R. Relation between idiopathic glossodynia and salivary flow rate and content. Int J Oral Surg 1976;5:161-5.

27 Yontchev E, Emilson CG. Salivary and microbial conditions in patients with orofacial discomfort complaints. Acta Odontol Scand 1986;44:215-9.

28 Ali A, Bates JF, Reynolds AJ, Walker DM. The burning mouth sensation related to the wearing of acrylic dentures: an investigation. Br Dent J 1986;161:444-7.

29 Dorey JL, Blasberg B, MacEntee MI, Conklin RJ. Oral mucosal disorders in denture wearers. J Prosthet Dent 1985;53:210-3.

30 Gibson J, Lamey PJ, Lewis M, Frier B. Oral manifestations of previously undiagnosed non-insulin dependent diabetes mellitus. J Oral Pathol Med 1990; 19:284-7.

31 Heft MW, Baum BJ. Unstimulated and stimulated parotid salivary flow rate in individuals of different ages. J Dent Res 1984;63:1182-5.

32 Ship JA, Nolan NE, Puckett SA. Longitudinal analysis of parotid and submandibular salivary flow rates in healthy, different-aged adults. J Gerontol A Biol Sci Med Sci 1995;50:M285-9.

33 Lamey PJ, Hobson RS, Orchardson R. Perception of stimulus size in patients with burning mouth syndrome. J Oral Pathol Med 1996;25:420-3.

34 Grushka M, Sessle BJ, Howley TP. Psychophysical assessment of tactile, pain and thermal sensory functions in burning mouth syndrome. Pain 1987;28: 169-84.

35 Heckmann SM, Heckmann JG, Hilz MJ, Popp M, Marthol H, Neundorfer B, *et al*. Oral mucosal blood flow in patients with burning mouth syndrome. Pain 2001;90:281-6.

36 Friedlander AH, Runyon C. Polymyalgia rheumatica and temporal arteritis. Oral Surg Oral Med Oral Pathol 1990;69:317-21.

37 Pokupec-Gruden JS, Cekic-Arambasin A, Gruden V. Psychogenic factors in the aetiology of stomatopyrosis. Coll Antropol 2000;24 Suppl 1:119-26.

38 Nicholson M, Wilkinson G, Field E, Longman L, Fitzgerald B. A pilot study: stability of psychiatric diagnoses over 6 months in burning mouth syndrome. J Psychosom Res 2000;49:1-2.

39 Rojo L, Silvestre FJ, Bagan JV, De Vicente T. Psychiatric morbidity in burning mouth syndrome. Psychiatric interview versus depression and anxiety scales. Oral Surg Oral Med Oral Pathol 1993;75:308-11.

40 Eli I, Kleinhauz M, Baht R, Littner M. Antecedents of burning mouth syndrome (glossodynia): recent life events vs. psychopathologic aspects. J Dent Res 1994;73:567-72.

41 Hampf G, Vikkula J, Ylipaavalniemi P, Aalberg V. Psychiatric disorders in orofacial dysaesthesia. Int J Oral Maxillofac Surg 1987;16:402-7.

42 Castera MJ. Stomatodynia and depressive syndrome [in French]. Chir Dent Fr 1991;61:43-5.

43 Grinspan D, Fernandez Blanco G, Allevato MA, Stengel FM. Burning mouth syndrome. Int J Dermatol 1995;34:483-7.

44 Neville BW, Damm DD, Allen CN, Bouquot JE. Facial pain and neuromuscular diseases. In: Neville BW, Damm DD, Allen CN, Bouquot JE. Oral and maxillofacial pathology. 2nd ed. Philadelphia (PA): WB Saunders; 2002. p. 741-62.

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Acta Dermatovenerol Croat 2003;11(4):236-246 REVIEW

Etiopathogenesis, Classification, and Current Trends in Treatment of Rosacea

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SUMMARY Rosacea is a common chronic dermatosis characterized by varying degrees of flushing, erythema, telangiectasia, edema, papules, pustules, ocular lesions, and phymas. Etiology and pathogenesis of rosacea are still unknown. Many possible causes have been described as inducing the disease or contributing to its manifestation, such as genetic predisposition, abnormal vascular reactivity, changes in vascular mediating mechanisms, *Helicobacter pylori* infection, *Demodex folliculorum* infestation, seborrhea, sunlight, hypertension, and psychogenic factors. However, none of these factors has been proved. Rosacea shows a wide spectrum of clinical presentations, which vary over time and with age. Successful management of rosacea requires careful patient evaluation and individualized therapy with appropriate variations and modifications, as the severity of the disorder fluctuates. In mild cases of rosacea, patients are instructed to avoid sun, to apply sun-protective creams, and to avoid facial irritants and other triggers that provoke symptoms. At later stage, drug therapy is often necessary. The disease commonly requires long-term treatment with topical or oral medicaments. Surgical correction may be required for rhinophyma and telangiectasia. We reviewed the current literature on the aspects of the pathogenesis, diagnostic criteria, and treatment options for rosacea.

KEY WORDS acne rosacea; facial dermatoses; *Helicobacter pylori*; mite infestations; rhinophyma

INTRODUCTION

Rosacea is a common chronic dermatosis of unknown etiology, currently considered a syndrome, or typology, encompassing various combinations of cutaneous signs, such as flushing, erythema, telangiectasia, edema, papules, pustules, ocular lesions, and rhinophyma. Hopefully, with the increase of our knowledge, the definition of rosacea may eventually be based on causality rather than on morphology alone (1). The disease occurs on the convexities of the face (cheeks, chin, nose, and central forehead). Less common sites include the retroauricular region, décolletage, upper aspect of the back, side of the neck, and scalp (1,2).

Rosacea affects both men and women. Although it may occur at any age, the onset typically begins at any time after age 30, and peaks between age 40 and 60 (1,2). Women are affected at a younger age and more often than men, although the grotesque tissue and sebaceous gland hyperplasia leading to rhinophyma occurs mostly in men (3). Rosacea has rarely been noted in children. In 1992,

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Drolet *et al* (4) described three children with rosacea, who responded well to traditional therapy, including systemic and topical antibiotics. Rosacea in childhood must be distinguished from other erythematous disorders, most commonly acne and perioral dermatitis.

Generally associated with people of Celtic or Scandinavian ancestry, rosacea has an inverse relationship with increasing epidermal pigmentation and is, therefore, uncommon in black people (3). The condition tends to be seasonal, worsening in the winter (cold and wind) and summer (sun) (5).

ETIOLOGY AND PATHOGENESIS

Etiology and pathogenesis of rosacea are still unknown (6,7). Although the etiology of disease is not fully understood, a genetic predisposition, changes in vascular mediating mechanisms, abnormal vascular reactivity, *Helicobacter (H.) pylori* infection, *Demodex (D.) folliculorum*, hypertension, sunlight, seborrhea, and psychogenic factors have been incriminated as causing factors. However, none of them has been proved.

Genetic Predisposition

The influence of heredity is debatable (8). Rosacea follows a clinical pattern, beginning and evolving in the genetically susceptible individual in response to exposure to different factors. Recently, many specific mediators of development of rosacea have been described (9). A primary genetic cause for rosacea has been suggested because single genes often control such mediators as enzymes, neuroendocrine transmitters, and cytokines, which are found in pathways present in rosacea (9). Recent research indicates that aberrations in vascular endothelial growth factor and angiogenesis may also be involved, as well as substance P, serotonin, bradykinin, catecholamines, histamine, neuropeptides, endorphins, gastrin, and cytokines (3).

Changes in Vascular Mediating Mechanisms

Cytokines, hormones, and neuropeptides communicate within the network made of the endocrine, nervous, and immune systems. The inflammatory reaction is likely a result of altered communication and/or reciprocal modulation between these mediators. In 2003, Pierard *et al* (10) reported about the possible modulatory role of somatostatin in the outcome of rosacea. They presented incidental findings related to the somatostatin treatment in diabetic patients suffering from rosacea. Four patients with papular type of rosacea who developed proliferative diabetic retinopathy were treated with laser photocoagulation combined with monthly 20-mg injections of the long-acting somatostatin-analogue, octreotide. Rosacea improved rapidly and even cleared without any recurrence in three of them. The observed beneficial effect might be attributed to inhibitory actions on the sebaceous gland, neovascularization, and/or inflammatory process (10).

Abnormal Vascular Reactivity

It is also likely that a flaw in the autonomic innervation of the cutaneous vasculature is the root cause of rosacea (3). Changes in the facial skin microvasculature may be quite prominent, with development of diffuse erythema and telangiectasia (10). The link between rosacea and migraine and between rosacea and perimenopause offers further evidence that a vascular abnormality could be an important underlying factor (3).

The Role of *Helicobacter pylori* in Rosacea

H. pylori is a Gram-negative flagellated bacterium that colonizes the gastric mucosa. It is now well recognized as an important cause of gastritis, gastric, and duodenal ulcers. It has also been reported as a possible cause of various dermatological disorders, such as chronic urticaria and atopic dermatitis. The frequent association of rosacea with gastrointestinal tract disorders suggests possible involvement of *H. pylori* in the etiopathogenesis of this dermatosis. Antibiotics that eradicate *H. pylori*, such as metronidazole or tetracyclines, are also very effective in the treatment of rosacea. Over the last few years, several studies based on serological testing, direct detection of *H. pylori* in the stomach, or response to eradication therapy have yielded controversial results concerning a potential relationship between rosacea and *H. pylori* infection (6).

H. pylori increases the synthesis of oxygen radicals, such as superoxide and proinflammatory cytokines. These cytokines have been shown to stimu-

late the synthesis of inflammatory species nitric oxide (NO). In 2002, Gurer *et al* (11) published the results of their study on the role of NO and its suspected association with *H. pylori* in rosacea. They found high percentage of seropositivity to *H. pylori,* but normal serum nitrate levels in their patients, which indicated that the inflammatory species NO had no role in the inflammatory mechanism of rosacea.

Szlachcic *et al* (12) studied 60 patients aged 30-70 years with visible cutaneous rosacea symptoms and the same number of their age- and sex-matched controls without skin diseases, but with dyspeptic symptoms similar to those present in rosacea and without endoscopic changes in gastroduodenal mucosa. They concluded that rosacea was a disorder with various gastrointestinal symptoms closely related to gastritis, especially involving the antral mucosa; that the eradication of *H. pylori* led to improvement of symptoms; that the lack of improvement of cutaneous symptoms in rosacea after eradication of *H. pylori* from the gastric mucosa could depend on bacteria in the oral cavity; and that rosacea could be considered as one of the extragastric symptoms of *H. pylori* infection, probably mediated by *H. pylori*-related cytotoxins and cytokines (12).

The exact pathogenic role of *H. pylori* in extradigestive diseases is still unclear. One of the hypothesis is that *H. pylori* leads to skin disorders, such as rosacea, by the induction of systemic inflammatory response mediated by direct and indirect production of various substances, including cytokines and vasoactive toxins (6). Extraintestinal pathologic manifestations may depend on infection with a particular strain of *H. pylori*. For example, type I is capable of producing cytotoxin-associated protein CagA, which is related to increased expression of interleukin 8 (IL-8). It has been shown that rosacea is associated with CagA-positive *H. pylori* and increased IL-8 and tumor necrosis factor alpha concentrations in most patients (6).

H. pylori is not the direct cause but may be an aggravating factor in the course of rosacea. The role of *H. pylori* infection is probably more important in the erythematous than in papular and glandular type of rosacea (13), which is why some of these patients may benefit from an eradication treatment. Eradication of *H. pylori* can be achieved with a triple therapy regimen – a drug able to diminish gastric secretion (i.e. omeprazole) and a combination of two antibiotics (a choice among amoxicillin, clarithromycin, azythromycin, and metronidazole).

Because metronidazole reduces rosacea, it is hardly surprising that this regimen might be helpful. The easiest way to shed light on this subject is to eradicate *H. pylori* infection without using metronidazole. Some findings in medical literature support hypothesis that *H. pylori* may be an aggravating factor in the course of rosacea and an eradication treatment, which may or may not include metronidazole, may reduce severity of the disease (14).

The Role of *Demodex folliculorum* in Rosacea

The exact pathogenic role of *D. folliculorum* in rosacea is still controversial (15). Whether pathogenetic or not, the local infestation with *D. folliculorum* seems to be important in the inflammatory reaction (16,17). This is confirmed by the fact that rosacea and other diseases accompanied with *Demodex* mites show improvement after the treatment with acaricides (18). However, in 2001, Georgala *et al* (19) reported that *Demodex* mites did not seem to be the cause of rosacea, although they might represent an important cofactor, especially in papulopustular rosacea. Their study included 92 consecutive patients with papulopustular rosacea and 92 age- and sex-matched controls in whom the prevalence and density of *D. folliculorum* were estimated by microscopic examination of the expressed follicular content. Histological examination and immunohistochemical study of the inflammatory infiltrate were performed in 10 subjects. Hair follicle infestation was associated with intense perifollicular infiltrate of predominantly (90-95%) CD4 helper/inducer T cells. They observed an increased number of macrophages and Langerhans cells only in subjects with positive *D. folliculorum* finding. Immunohistochemical findings in their study suggested the presence of delayed hypersensitivity reaction, possibly triggered by antigens of follicular origin and probably related to *D. folliculorum*, stimulating progression of the affection to papulopustular stage (19).

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Hypertension

Patients with hypertension may display flushing.

Sunlight

Sunlight might be a cofactor. Histologic studies have confirmed that almost all rosacea arises against the background of actinically damaged skin (2). Sun sensitivity is a frequent feature of rosacea in type I fair-skinned patients, who burn easily (8).

Seborrhea

Rosacea is considered to be a seborrheic disease. However, seborrhea is not a constantly present feature. Rosacea is not primarily a disease of sebaceous follicles, and in contrast to acne vulgaris, comedones are absent. If present, they have other origin, e.g., concomitant solar comedones (Favre-Racouchot disease) or contact acne (acne cosmetica). Nevertheless, rosacea may resemble acne (8). The rate of sebum excretion appears to be normal except in rhinophyma, where it is increased (3,7).

Psychogenic factors

Emotional stress may also precipitate worsening of rosacea.

Triggers Exacerbating Rosacea Symptoms

There are many incriminated triggers for worsening or exacerbation of rosacea symptoms. The most common are the following (3):

Exposure: anger, anxiety, embarrassment, sun, heat (from bath, hot tub, jacuzzi, sauna, shower), fever, humidity, cold, wind, menopausal hot flushes, and strenuous exercise.

Foods and beverages: alcohol, chili, curry, peppers, tomatoes, vinegar, coffee, chocolate, hot chocolate, and tea.

Irritants: alcohol containing cleansers, astringents, fragrance, menthol, peeling agents, perfume, shaving lotion, soap, sunscreen, and washcloths.

Medicaments: capsaicin, corticosteroids, doxorubicin, interferon, niacin, nifedipine, nitroglycerin, prostaglandin E, rifampicin, vancomycin, disulfiram, metronidazole, or chlorpropramide taken with alcohol.

CLINICAL FINDINGS

Early signs of rosacea may be discerned in young adults, but are often ignored. There may be a persistent dusky erythema, especially of the nose, as well as recurrent and persistent facial erythema ("flushers and blushers") (2). In many people, symptoms never progress beyond this premonitory phase as they fluctuate between normal skin and periodic erythema in a centro-facial or butterfly pattern. A history of acne can complicate diagnosis (3). It is important to discern the patients with acne who are flushers from those who are blushers, as they may develop rosacea later on. Such patients are a therapeutic challenge (8).

DIAGNOSTIC CRITERIA

Guidelines for the diagnosis of rosacea were adapted from those set by Wilkin J *et al* (1), within the standard classification of rosacea presented in the report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea (1). To establish the diagnosis of rosacea, one or more of the following primary features should be present: flushing (transient erythema), non-transient erythema, papules and pustules, nodules, and telangiectasia. Findings may also include one or more of the following secondary features: burning or stinging, plaque, dry appearance, edema (soft or solid non-pitting), ocular manifestations, peripheral location, and phymatous changes.

Rosacea Subtypes

The primary and secondary rosacea features described above often occur together. The most common patterns or groupings of signs are provisionally designated as specific subtypes of rosacea. Each subtype includes the fewest signs sufficient to make a diagnosis of the subtype, and patients may have characteristics of more than one rosacea subtype at the same time.

Subtype 1: Erythematotelangiectatic rosacea – flushing and persistent central facial erythema with or without telangiectasia.

Subtype 2: Papulopustular rosacea – persistent central facial erythema with transient, central facial papules or pustules, or both.

Subtype 3: Phymatous rosacea – thickening skin, irregular surface noduli, and enlargement, which may occur on the nose (rhinophyma), chin (gnatophyma), forehead (mentophyma), eyelids (blepharophyma), or ears (otophyma).

Subtype 4: Ocular rosacea – foreign body sensation in the eye, burning or stinging, dryness, itching, ocular photosensitivity, blurred vision, telangiectasia of the sclera or other parts of the eye, or periorbital edema.

Variants of Rosacea

Variants of rosacea, which do not represent morphologic patterns or combinations as seen in rosacea subtypes, may also occur. The example is *granulomatous rosacea*, characterized by non-inflammatory, hard brown, yellow, or red cutaneous papules or nodules of uniform size.

Entities Similar to Rosacea

The committee noted that certain disorders may have been prematurely identified as associated with rosacea or as a variant of rosacea. For the reasons of clarity, they should be recognized as separate entities.

Rosacea fulminans. Popularly known as pyoderma faciale, the classification of this disorder as a type of rosacea is premature. It is characterized by the sudden appearance of papules, pustules, and nodules, along with draining sinuses. The condition appears primarily in women in their twenties. Intense redness and edema also may be prominent.

Steroid-induced acneiform eruption. Steroid-induced acneiform eruption is not a variant of rosacea and can occur as an inflammatory response in any patient during or after chronic corticosteroid use (1,7,19). Trivial skin dermatoses, especially on the face, should not be treated with local corticosteroids (19).

Perioral dermatitis. Although rosacea papules may appear in the perioral area, perioral dermatitis without rosacea symptoms cannot be classified as a variant of rosacea. This disease is characterized by microvesicles, scaling, and peeling (1).

Demodicosis. Demodicosis is now believed to be a separate disease. These patients have typical follicular papules and pustules, especially on the lateral parts of the face and chin (1,17).

Haber syndrome. This syndrome is very uncommon genodermatosis, probably inherited in autosomal dominant pattern, with persistent rosacea-like facial eruption and keratotic truncal lesions (2).

Lupus miliaris disseminatus faciei. It is characterized by an eruption of discrete red-brown, dome-shaped papules on the medial and lateral areas of the face, and often extends on the neck and chin. The histopathologic characteristic of lupus miliaris disseminatus faciei is an epitheloid cell granuloma with central necrosis, which may also be found in granulomatous rosacea, whereas its clinical features and course are often similar to cutaneous maculopapular sarcoidosis. The pathogenesis of the disorder remains controversial. In the literature, lupus miliaris disseminatus faciei has been successively described as tuberculosis, sarcoidosis, or rosacea (20). We agree with some other authors (7,20) that lupus miliaris disseminatus is a distinctive rosacea-like eruption and not a granulomatous form of rosacea.

HISTOPATHOLOGY

Usually the clinical picture determines the diagnosis (7,8). Biopsy of the skin rarely assists in diagnosis of rosacea, although it may exclude other diagnoses under consideration (3). The histopathologic findings vary with the stage and type of the disease. Elastosis from photodamage is a constant feature and constitutes the terrain where rosacea emerges (8). In the early phase, only dilated blood vessels are seen. As the disease progresses, lymphectasia, actinic elastosis, edema, and perivascular and perifollicular lymphohistiocytic infiltrate appear. In the later stage, the follicles are more definitely involved with spongiosis, and dermal fibrosis and sebaceous gland hyperplasia are also found. The infundibula are widely dilated and run through the altered dermis; they are filed with debris and often contain *D. folliculorum* mites. In phymas, each of the components may predominate (2,7).

Epitheloid granulomas of the noncaseating type with multiple foreign-body multinucleated cells are histopathologic equivalent of lupoid rosacea (7,8).

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Immunofluorescence and immunohistochemical techniques have not contributed to the histopathologic identification of rosacea, or to an understanding of its pathogenesis. Immunoglobulins are often found, especially at the dermo-epidermal junction, but reflect mainly photodamage and chronic inflammation (8).

DIFFERENTIAL DIAGNOSIS

For patients in the earliest prodromal states with only intermittent flushing, possible diagnoses include emotional factors, use of certain pharmaceutical agents, and fluctuation of sex hormones.

Depending on the stage of rosacea under consideration, differential diagnosis includes a variety of miscellaneous skin diseases, such as acne vulgaris, carcinoid syndrome, demodicosis, dermatomyositis, dermatophyte infection, erysipelas, folliculitis, G-folliculitis, leukemia (leukemic infiltrates), lupus vulgaris, lymphoma (the leonine facies of cutaneous T-cell lymphoma), perioral dermatitis, photodermatitis, polymorphous light eruption, sarcoidosis, seborrheic dermatitis, steroid rosacea, and systemic lupus erythematosus (3). Since acne and rosacea are both very common, in some patients both diseases can be present simultaneously, with rosacea gradually replacing acne (2).

COURSE AND PROGNOSIS

Rosacea is unpredictable but potentially progressive and relapsing disease. Although periods of lesser or greater activity may occur, as well as temporary remissions and severe relapses, spontaneous remission is uncommon. The condition may last for years if it is left untreated, and gradually increases in severity (21).

CURRENT TRENDS IN THE TREATMENT OF ROSACEA

Management of rosacea consists of behavior modification to avoid triggers as well as pharmacologic and other medical therapy (3). Each phase of disease is likely to require different treatment. This includes (a) topical treatment, (b) oral therapy, (c) surgical treatment, and (d) other measures.

A. Topical Treatment

Topical treatment is selected according to the type of disease. Many topicals have been proposed, but they frequently irritate the skin and provoke vasodilatation, which may worsen rosacea symptoms. Also, a substantial number of patients with rosacea are sensitive and cannot tolerate many of the commercial vehicles (22). The clinician should find the product that the individual patient with rosacea tolerates the best (23).

Topical Antibiotics

How tetracycline and other antibiotics work in rosacea remains unknown. A local mechanism seems probable because rosacea responds to topical antibiotic therapy. An inhibition of chemotaxis of inflammatory cells and direct effect on vascular endothelium have also been proposed mechanisms of antibiotic action in rosacea (22). The clinician should inquire about the time of the year when exacerbations mostly occur as well as about the time of the year when symptoms of rosacea are fewest. Also, the patient should be aware that even after discontinuing the topical therapy, the use of nonirritating sunscreens and the avoidance of triggers that cause flushing or facial skin stinging and redness may still be very helpful (23). Topical antibiotics are usually effective in treatment of rosacea (2). There are four groups of broad-spectrum antibiotics in use today: metronidazole, tetracyclines, erythromycin, and clindamycin.

The papules and pustules of rosacea can be effectively treated with topical metronidazole (24), which remains the most popular topical agent. It is available as a 0.75%-cream, gel or lotion, and as 1% cream. Patients should apply preparations 5 minutes after gently cleansing the skin (3). Although data are limited, topical metronidazole seems to improve inflammatory lesions and erythema as effectively as oral tetracyclines, but like tetracyclines, it has no effect on telangiectasia. The effect of topical metronidazole preparations on rosacea symptoms is palliative, not curative, but preliminary data suggest that relapse rates after cessation of therapy are not worse than those after cessation of oral oxytetracyclines (25). Therefore, in patients with a preference for topical over oral therapy, the use of a topical metronidazole formulation must be taken in consideration (25). In 2001, Dahl et al (24)

compared the efficacy and safety of two commercially available topical metronidazole formulations: 0.75% metronidazole cream and 1% metronidazole cream. This multicentric, randomized, investigator-blind parallel group trial enrolled 72 patients with rosacea who also had 8-50 inflammatory facial lesions (pustules and papules) and moderately severe facial erythema. The patients were given the two formulations once a day for 12 weeks. There were no significant differences between the treatment groups in any of the efficacy parameters evaluated. Both drugs were well tolerated and there was no significant difference in the drug-related adverse events between the groups. This trial showed that both 0.75% and 1.0% metronidazole cream, when used once daily provided well-tolerated efficacious treatment of moderate to severe rosacea (24).

Topical clindamycin phosphate 1% in a lotion base or erythromycin in emulsion base are sometimes effective. In 1993, Wilkin *et al* (22) included 43 patients clinically diagnosed with rosacea in an investigator-blinded study. Their results showed that topical clindamycin in lotion might be a safe and effective alternative to oral tetracycline therapy in the treatment of rosacea, in addition to having compliance advantages (22).

Other Topicals

Azelaic acid, 20% cream, has been reported to reduce the severity of erythema (16). Topical imidazoles, such as ketoconazole, can also be chosen. Older creams, lotions, and pastes, which usually contain sulfur or ichthyol are minimally effective (2). Corticosteroids should never be used (19,26).

Massive infestations of *D. folliculorum* mites may sometimes aggravate rosacea. The mites may be satisfactorily controlled with lindane, crotamitone, permethrin, ivermectin, or benzoyl benzoate, applied once a day for 2-5 days. Intermittent schedules of application, including weekend doses every 2-3 weeks, can keep the mite population under control (8).

The fact that rosacea and other diseases due to *Demodex* mites show improvement after the treatment with acarides has led to investigations of many treatment alternatives. Thus, 5% permethrin cream used against human ectoparasites may be effective in papulopustular rosacea. Kocak *et al* (18) investigated the effectiveness of permethrin and metronidazole in a randomized placebo trial, which included 63 patients diagnosed with papulopustular rosacea on the basis of clinical and histological findings. They recorded the scores of erythema, telangiectasia, edema, and rhinophyma and the numbers of papules, pustules, inflammatory nodules, and *D. folliculorum*, and found that 5% permethrin cream was more effective than placebo and as effective as metronidazole 0.75% gel in resolving erythema and papules. In addition, permethrin was more effective against *D. folliculorum* than were metronidazole 0.75% gel or placebo. However, it had no effect on telangiectasia, rhinophyma, and pustules. Although side effects were detected, no local complication due to permethrin, metronidazole or placebo was observed. Their conclusion was that application of 5% permethrin cream twice daily for two months could be as effective and reliable as metronidazole in the treatment of rosacea and that the benefit could be even greater if permethrin was combined with other systemic and/or topical treatments (18). Their study supports the pathogenic role of *D. folliculorum* in rosacea.

Retinoic acid has shown beneficial effects on the vascular component of rosacea. However, the therapeutic response is delayed and side effects observed early in the treatment (skin dryness, erythema, burning, and stinging) result in temporary aggravation of lesions as well as patient's noncompliance.

Retinaldehyde, an intermediate between retinol and retinoic acid in natural metabolism of retinoids, is known to have a therapeutic activity close to that of retinoid acid and to be well tolerated by the skin (5). Suggested mechanisms of action of topical retinaldehyde may be their known beneficial action in photodamaged skin, which often accompanies rosacea. Another speculation is that retinaldehyde acts by masking the dermal vasculature by inducing the thickening of the overlying epidermal layer. Furthermore, retinaldehyde may also exert a more specific action on the vascular tissue, since it inhibits the vascular endothelial growth factor *in vitro*. Nevertheless, the implication of vascular endothelial growth factor in the pathogenesis of rosacea remains also to be clarified. In conclusion, retinalde-

hyde should be considered as part of the therapeutic arsenal to alleviate the vascular component of rosacea (5).

B. Oral Treatment

Oral treatment is indicated in subjects with moderate and severe rosacea. The two main groups of oral therapy in rosacea are antibiotics and retinoids.

Oral Antibiotics

The most agreeable feature of rosacea is that it generally responds well to oral antibiotics. Tetracycline, oxytetracycline, doxycycline, and minocycline are usually quite effective in controlling papulopustular rosacea and even reducing erythema (8). The above mentioned medications function as anti-inflammatory agents in patients with rosacea and possibly counteract neutrophil chemotaxis, macrophage activation, cytokine signaling, or activation of complement or protein kinase C (3). Tetracycline or oxytetracycline is the first choice of oral antibiotic treatment. It is important to start with full doses, i.e. 1.0-1.5 g tetracycline or oxytetracycline per day Appropriate alternatives are doxycycline or minocycline at daily dose of 100 mg. As soon as full control of papulopustules is achieved, usually after 2-3 weeks, maintenance doses of 250-500 mg tetracycline or oxytetracycline, or 50 mg minocycline or doxycycline per day are generally sufficient. The treatment usually lasts for 3-4 months. After that time it is usually possible to wean completely patients from the systemic agent and apply topical antibiotic, most commonly metronidazole. Some patients may become addicted to oral antibiotics and find ways to get them without prescription. The situation should be periodically controlled, since topical drugs may be sufficient during inactive phase of the disease (8). Tetracyclines in combination with corticosteroid or antibiotic eye drops and artificial tears also provide the best treatment for ocular rosacea, where they exert strong anti-inflammatory effect (2).

The next generally effective antibiotic in the treatment of the most types of moderate rosacea, including papulopustular and nodular stage, is metronidazole. It can be used in dosages of 250-500 mg daily, over a 2-6-week period (2,8). There is an antabuse-like effect, so alcohol consumption must be avoided. Because of this and many other side effects, long-term therapy is not possible. Systemic metronidazole is not approved for the treatment of rosacea in the USA and Germany (2). However, oral metronidazole should be considered a second-line drug to be tried when other methods have failed (8).

If stomach *H. pylori* infection can be documented, and especially if there are additional gastrointestinal signs or symptoms, then a course of therapy to eradicate this organism is well worth considering (2). Eradication of *H.pylori* can be achieved with a triple therapy regimen: a drug able to diminish gastric secretion (i.e. omeprazole 2x20 mg for 1.week, than 1x20 mg for 2-3 weeks) and a combination of two antibiotics (amoxicillin 2x1 g for 7 days, or clarithromycin 2x500 mg for 7 days, or azythromycin 1 g for 3 days, or metronidazole 2 x 500 mg for 7 days).

Retinoids

Isotretinoin is the treatment of choice for severe rosacea (rosacea conglobata and rosacea fulminans), applied in doses of 0.2-1.0 mg/kg daily (2) adjusted according to the response and side effects. Therapy lasts for 3-4 months, maximum 6 months, but careful consideration must be taken of the risk-benefit ratio (3). Long-term remission can often be achieved. Treatment smoothes the rest of the face, reduces sebaceous gland hyperplasia, lessens oiliness, and eliminates edema (2). Isotretinoin has teratogenic effects, and its use is contraindicated in women of childbearing age unless they have a negative pregnancy test and use effective contraception during and for one month after completing the therapy. We ask our patients to sign a written consent with explanation of possible side effect of retinoid therapy and we also administer contraception one month prior, during, and one month after retinoid therapy. Laboratory monitoring of SGOT, SGPT, cholesterol, and triglycerides is mandatory before the therapy and at monthly or bimonthly intervals (8).

Corticosteroids

Corticosteroids can be given before introduction of isotretinoin therapy in patients with rosacea conglobata and rosacea fulminans (2). Treatment starts with oral prednisolon, 1 mg/kg body weight per day, for one week. Then isotretinoin is added, at 0.2-0.5 (rarely 1.0) mg/kg body weight per day, with

a slow tapering of the corticosteroid over the next 2-3 weeks. Isotretinoin is continued until all inflammatory lesions have disappeared. This treatment modality may require 3-4 months. Draining abscess should not be incised. Concomitant treatment in the first 2 weeks may consist of warm compresses and topical application of a potent corticosteroid cream. This is the only indication for topical and systemic corticosteroid in the treatment of rosacea (8).

Clonidine

Currently, clonidine is the only drug available for the treatment of flushing (16). It is an alpha 2-adrenoreceptor agonist effective in lowering blood pressure and controlling some types of migraine and postmenopausal flushing. Stopping treatment may produce dangerous rise in blood pressure (27).

C. Surgical Treatment of Rosacea

Telangiectasia can be treated with electrocoagulation, various lasers, and intense pulsed light therapy (3).

Obliteration of ectactic vessels can be achieved by intravascular insertion of a fine diathermy needle or by light electrocoagulation of the surface. In expert hands, these physical modalities are very effective and practical. When ectases are numerous and large, the laser is the method of choice (8).

Rhinophyma is also a surgical problem. The excessive tissue can be shaved off with a blade or disposable razor, sanded away with a dermabrader, cut off with a hot loop, or vaporized with a CO_2 laser (2). In laser treatment, high absorption of the CO_2 laser wavelength in water is responsible for its low penetration depth in biological tissue. Shortening the tissue exposure time reduces the thermic side effects of laser radiation, such as carbonization and coagulation. Laser ablation of rhinophyma is a stress-minimizing procedure for the surgeon and the patient alike, as it is nearly bloodless and can be performed under local anesthesia. Cosmetically favorable re-epithelization of the laser-treated surfaces is achieved within a very short period of time (28). Some authors recommend treatment with isotretinoin 0.5-1.0 mg/kg daily for 4 weeks before and 4 weeks after the surgical procedure (2).

Intense pulsed light photorejuvenation represents a novel mode of treatment of photodamaged skin. A broad-spectrum flash lamp (500-1,200 nm) targets chromophores reversing pigmentation, vascular, and pilosebaceous aberrations. Both cytokine-mediated and thermally-induced deep dermal remodeling may be achieved by different polychromatic wavelengths. Inflammatory dermatosis, such as rosacea, may also be addressed. A structural approach to nonablative rejuvenation utilizing intense pulsed light is associated with high patient satisfaction and minimal adverse sequelae (29). Intense pulsed light provides superior and long-lasting results in patients whose primary manifestations include telangiectasia and erythema. Recent findings indicate this treatment is very promising for patients with papular and pustular subtypes of rosacea (3). Nodular lesions sometimes respond to *cryotheraphy* (2).

D. Other Measures

Appropriate therapy for rosacea often includes topical or oral preparations, but continued improvement of this condition hinges on a frank discussion between the physician and the patient regarding patient's lifestyle and its modification.

Establishing a reasonable treatment plan requires an understanding that rosacea occurs in a genetically susceptible person exposed to some triggering factors (3).

There is no specific rosacea diet (8). Patients must identify those triggers that provoke their symptoms. Alcohol is on the top of the list of such triggers. Topical irritants, astringents, and washcloths should also be avoided. Short, tepid baths should be given advantage over prolonged hot showers. Patients should avoid Jacuzzi, hot tubs, and saunas. Consuming coffee or tea rarely causes problems unless these beverages are too hot. A variety of drugs may precipitate worsening of rosacea. Niacin tablets are notorious for causing flushing. Whereas ultraviolet light may lead to a flare of rosacea, heat is more provocative factor. Exposure to excessive cold may be equally noxious. However, solar exposure during the colder months of the year rarely elicits problems. Winter outdoor activities often result in facial erythema. Unfortunately, avoiding these exacerbating factors does not guarantee freedom from further flares. Certain general advice seems prudent (3). Patients should be encouraged to use broad-spectrum sunscreens with

SPF of 30 or more, which provide protection against UV-B and UV-A (2,23), because rosacea is dermatosis aggravated by sunlight (30). For some patients, it may be hard to find a sunscreen that can be tolerated without burning or irritation (23). *Facial massage* can sometimes be useful in erythematous phase, as described by Sobye (2). The patient is encouraged to spend 2-3 minutes each evening massaging the cheeks, nose, and forehead to reduce edema. While controlled studies are not available, this harmless technique may be helpful and provides active participation of the patient in the treatment of the disease (2). The mechanism of action may be accelerated lymphatic drainage with reduction of edema (8). Rosacea may also have a significant impact on quality of life. Therefore, the application of *decorative cosmetics* is an effective, usually well-tolerated measure that might increase their quality of life (31).

Rosacea can cause severe emotional distress owing to its chronic course (8). The disorder is not physically threatening, but it often precipitates anxiety, depression, and social withdrawal (3). Therefore, compassion and understanding are essential part of treatment.

References

1 Wilkin J, Dahl M, Detmar M, Drake L, Feinstein A, Odom R, *et al*. Standard classification of rosacea: Report of the National rosacea society expert committee on the classification and staging of rosacea. J Am Acad Dermatol 2002;46:584-7.

2 Braun Falco O, Plewig G, Wolff HH, Burgdorf WH. Diseases of the sebaceous gland. In: Braun Falco O, Plewig G, Wolff HH, Burgdorf WH, editors. Dermatology. 2nd completely revised ed. Berlin, Heidelberg, New York (NY): Springer-Verlag; 2000. p. 1071-9.

3 Landow K. Untraveling the mistery of rosacea. Keys to getting the red out. Postgrad Med 2002;112:51-8.

4 Drolet B, Paller AS. Childhood rosacea. Pediatr Dermatol 1992;9:22-6.

5 Vienne MP, Ochando N, Borrel MT, Gall Y, Lauze C, Dupuy P. Retinaldehyde alleviates rosacea. Dermatology 1999;199:53-6.

6 Mayr-Kanhäuser S, Kranke B, Kaddu S, Müllegger R. Resolution of granulomatous rosacea after eradication of *Helicobacter pylori* with clarithromycin, metronidazole and pantoprazole. Eur J Gastronterol Hepatol 2001;13:1379-83.

7 Dobrić I, Basta-Juzbašić A, Skerlev M. The efficiency of tetracyclines in the treatment of rosacea with epitheloid granuloma [in Croatian]. Acta Med Iug 1989;43:127-36.

8 Plewig G, Kligman AM. Rosacea. In: Plewig G, Kligman AM. Acne and rosacea. 2nd completely revised ed. Berlin, Heidelberg: Springer-Verlag; 1993. p. 433-42.

9 Bamford JT. Rosacea: current thoughts on origin. Semin Cutan Med Surg 2001;20:199-206.

10 Piérard-Franchimont C, Quatresooz P, Piérard GE. Incidental control of rosacea by somatostatin. Dermatology 2003;206:249-51.

11 Gurer MA, Erel A, Erbas D, Caglar K, Atahan C. The seroprevalence of *Helicobacter pylori* and nitric oxide in acne rosacea, Int J Dermatol 2002;41:768-70.

12 Szlachcic A. The link between *Helicobacter pylori* infection and rosacea. J Eur Acad Dermatol Venereol 2002;16:328-33.

13 Son SW, Kim IH, Oh CH, Kim JG. The response of rosacea to eradication of *Helicobacter pylori*. Brit J Derm 1999;140:984-5.

14 Hirschmann JV. Does *Helicobacter pylori* have role in the pathogenesis of rosacea? [letter]. J Am Acad Dermatol 2000;42:537-8.

15 Škrlin J, Richter B, Basta-Juzbašić A, Matica B, Ivačić B, Cvrlje M, et al. Demodicosis and rosacea. Lancet 1991; 337:734.

16 Rebora A. The management of rosacea. Am J Clin Dermatol 2002;3:489-96.

17 Basta-Juzbašić A, Škrlin Šubić J, Ljubojević S. Demodex folliculorum in development of dermatitis rosaceiformis steroidica and rosacea-related diseases. Clin Dermatol 2002;20:179-82.

18 Koçak M, Yagli S, Vahapoglu G, Eksioglu M. Permethrin 5% cream versus metronidazole 0.75% gel for the treatment of papulopustular rosacea. Dermatology 2002;205:265-70.

19 Ljubojević S, Basta-Juzbašić A, Lipozenčić J. Steroid dermatitis resembling rosacea: aetiopathogenesis and treatment. J Eur Acad Dermatol Venereol 2002;16: 121-126.

20 Van de Scheur MR, van der Waal RI, Starink TM. Lupus miliaris disseminatus faciei: a distinctive rosacea-like syndrome and not a granulomatous form of rosacea. Dermatology 2003;206:120-3.

21 Utas S, Özbakir O, Turasan A, Utas C. Does *Helicobacter pylori* eradication treatment reduce the severity of rosacea? Does *Helicobacter pylori* have role in the pathogenesis of rosacea? Reply [letters]. J Am Acad Dermatol 2000;42:535-9.

22 Wilkin JK, DeWitt S. Treatment of rosacea: topical clindamycin versus oral tetracycline. Int J Dermatol 1993;32:65-7.

23 Wilkin JK. Use of topical products for maintaining remission in rosacea. Arch Dermatol 1999;135:79-80.

24 Dahl MV, Jarratt M., Kaplan D, Tuley MR, Baker MD. Once-daily topical metronidazole cream formulations

in the treatment of the papules and pustules of rosacea. J Am Acad Dermatol 2001;45:723-30.

25 McClellan KJ, Noble S. Topical metronidazole. A review of its use in rosacea. Am J Clin Dermatol 2000; 1:191-9.

26 Basta-Juzbašić A, Dobrić I. Influence of topical corticosteroids on the course and treatment of rosacea [in Croatian]. Liječ Vjesn 1989;111:89-93.

27 Yougson RM. Clonidin. In: Collins dictionary of medicine. 1st ed. New York (NY): Harper Collins Publishers; 1992. p. 135.

28 Jovanovic S, Sedlmaier B. CO2 laser theraphy for rhinophyma. Facial Plast Surg 1998;14:279-86.

29 Sadick NS, Weiss R. Intense pulsed-light photorejuvenation. Semin Cutan Med Surg 2002;21:280-7.

30 Tan JK, Girard C, Krol A, Murray HE, Papp KA, Poulin Y, et al. Randomized placebo-controlled trial of metronidazole 1% cream with sunscreen SPF 15 in treatment of rosacea. J Cutan Med Surg 2002;6:529-34.

31 Boehncke WH, Ochsendorf F, Paeslack I, Kaufmann R, Zollner TM. Decorative cosmetics improve the quality of life in patients with disfiguring diseases. Eur J Dermatol 2002;12:577-80.

Feller's Elsa Fluid and Elsa Beauty Cream (beginning of the 20th century).
From the collection of Assist. Prof. Stella Fatović-Ferenčić, MD, PhD.

Acta Dermatovenerol Croat 2003;11(4):247-250 REVIEW

Still Elusive Relationship between Atopic Dermatitis and Allergic Contact Dermatitis

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SUMMARY The relationship between atopic dermatitis (AD) and allergic contact dermatitis (ACD) has long been and continues to be an unsolved and frequently discussed issue. Whereas AD patients have traditionally been considered to have a decreased frequency of ACD, recent studies revealed that these individuals are more or equally likely to develop ACD. The aim of the present review was to determine whether the results of recent experimental studies and theoretical considerations might lead to a parallel shift in our concept on the causal relationship between AD and ACD. It has been shown that Th2 and Th1-type immune responses are not mutually exclusive, and that at least in AD a mixture of both Th2 and Th1 occurs and the interactions between them account for the clinical characteristics of the disease. This new concept on the immunopathomechanism of AD challenges our previous belief that the cytokine pattern of the affected skin is unsuitable for the development of delayed-type hypersensitivity. Since we do not know the exact quantitative balance between Th1 and Th2 reactions along a time axis, we cannot predict whether the cytokine pattern of AD patients favors or inhibits the development of ACD. What we do know with a greater degree of certainty, is that when the eczematous excoriated skin of AD patients, with its defective epidermal barrier (enhancing the penetration of many antigenic substances) is chronically exposed to skin care products and various sensitizing topical medications, it is more likely to develop a superimposed ACD.

KEY WORDS dermatitis, allergic contact; dermatitis, atopic; hypersensitivity, delayed; T lymphocytes

INTRODUCTION

The relationship between atopic dermatitis (AD) and allergic contact dermatitis (ACD) has long been and continues to be an unresolved and frequently discussed issue.

Recent epidemiological studies on the likelihood of patients with AD to develop ACD have brought about a change in our approach to this conundrum. AD patients had traditionally been considered to have a decreased frequency of ACD (1-4), but new findings have revealed a higher (5-7), or at least equal (8,9), rate of ACD occurrence in these patients.

The aim of the present review was to determine whether the results of recent experimental studies and theoretical considerations might lead to a parallel shift in our concept of the causal relationship between AD and ACD.

IMMUNOPATHOMECHANISM OF ALLERGIC CONTACT DERMATITIS

ACD is caused by dendritic cell (DC)-dependent T cell-mediated immune response. It has traditionally been distinctly divided into the sensitization (afferent) and the elicitation (efferent) phase.

Since the discovery of two subsets of T helper cells, type 1 (Th1) and type 2 (Th2), more than a decade ago (10,11), they have been implicated in the regulation of many immune responses, including that of ACD. ACD has traditionally been considered as mediated by hapten-specific CD4+ Th1 and CD8+ T cytotoxic 1 (Tc1) cells that mediate tissue damage through the release of pro-inflammatory cytokines and direct cytotoxicity (12). Type 2 cytokines, interleukin (IL)-4 and IL-10, which are regularly present in ACD, serve to down-regulate the reaction, rendering it a self-limiting response (13). Furthermore, as the antigen-induced hypersensitivity response progresses into chronicity, the local cytokine pattern shifts from the Th1-type to the Th2-type, a change which could represent natural evolutionary processes directed toward reducing the more deleterious Th1 response (14). A switch from Th1 to Th2 might also occur in the presence of an increasing antigen dose (15). IL-10 has been considered the most potent anti-inflammatory cytokine produced by various cell types, including T lymphocytes, monocytes, DC and the recently isolated CD4+ T cells, and T regulatory cells 1 (Tr1) (16,17).

In contrast, some researchers have shown that Th2 cytokines, particularly IL-4, do play a role in the elicitation phase of ACD, which is significantly compromized in IL-4-deficient mice (18,19). Current evidence seems to suggest that both Th1 and Th2 subtypes play a role in ACD, that the identity and dosage of the antigen is likely to control the equilibrium between types 1 and 2, and that Th1 predominates in most instances.

IMMUNOPATHOMECHANISM OF ATOPIC DERMATITIS

AD is considered an IgE-mediated, delayed-type hypersensitivity reaction. In this immunologic response, naive, allergen-specific T cells are preferentially induced to develop into T cells with a marker known as cutaneous lymphocyte antigen (CLA). These CLA-positive CD4+ T cells produce type 2 cytokines and migrate to the skin after encountering antigens in skin-draining lymph nodes. Type 2 T-cell cytokines promote the growth and activation of eosinophils (IL-5), a switch in the antibody isotype from IgM to IgE (IL-4 and IL-13), and a reduction in cell-mediated immunity (IL-10) (20,21). This generally accepted concept is one that has dominated the immunologic literature for years and has led to the very logical assumption that AD patients have a contrasting cytokine pattern with delayed-type hypersensitivity or type IV immune response as well as ACD, and thus show a lower tendency to and diminished ability to produce these reactions.

Recent studies that analyzed cytokine expression in skin biopsy samples from both affected and unaffected skin of AD patients (22-24) and, more importantly, sequential analysis of the skin biopsy samples from atopy patch-test sites in AD patients (25-27) provided important heretofore unavailable information that has led to a profound change in our previous concept of AD as being a prototype of a Th2-type response. The currently prevailing notion is that both the Th2 and Th1 cell types are involved in the pathomechanism of AD and that the response is two-phased in nature: the initial phase involves mostly Th2 cells producing IL-4 and activating macrophages and eosinophils, which, in turn, release IL-12, an activator of Th1 cell-mediated immunity. The activation of allergen-specific and -non-specific Th1 cells, which produce INFα, is responsible for the chronicity and severity of the disease. Actually, the pure acute form of AD is very rare: the typically observed appearances are those of a mixture of acute and chronic dermatitis. Specifically, the Th2- and Th1-type immune responses are not mutually exclusive, as it has been previously thought and, at least in AD, there is a mixture of both Th2 and Th1 and it is the interactions between the different Th-cell subsets that account for the clinical characteristics of the disease (28-31).

CONCLUSION

The above-described new concept on the immunopathomechanism of AD challenges our previous perception that the cytokine pattern of the affected skin is unsuitable for, or contrasting, the

development of delayed-type hypersensitivity. Since we do not know the exact quantitative balance between Th1 and Th2 reactions along a time axis, we cannot predict whether the cytokine pattern of AD patients favors or inhibits the development of ACD. What we do know with a greater degree of certainty is that when the eczematous excoriated skin of AD patients, with its defective epidermal barrier (enhancing the penetration of many antigenic substances), is chronically exposed to skin care products and various sensitizing topical medications, it is more likely to develop a superimposed ACD.

References

1 Jones H, Lewis C, McMarlin S. Allergic contact sensitivity in atopic dermatitis. Arch Dermatol 1973;107:217-22.

2 Angelini G, Meneghini C. Contact and bacterial allergy in children with atopic dermatitis. Contact Dermatitis 1977;3:163-7.

3 Rystedt I. Atopic background in patients with occupational hand eczema. Contact Dermatitis 1985;12: 247-54.

4 De Groot A. The frequency of contact allergy in atopic patients with dermatitis. Contact Dermatitis 1990;22: 273-7.

5 Lammintausta K, Kalimo K, Fagerlund V. Patch test reactions in atopic patients. Contact Dermatitis 1992; 26:234-40.

6 Lugović L, Lipozenčić J. Contact hypersensitivity in atopic dermatitis. Arh Hig Rada Toksikol 1997;48: 287-96.

7 Mortz C, Lauritsen J, Bindslev-Jensen C, Andersen K. Contact allergy and allergic contact dermatitis in adolescents: prevalence measures and associations. Acta Derm Venereol 2002;82:352-8.

8 Lever R, Forsyth A. Allergic and contact dermatitis in atopic dermatitis. Acta Derm Venereol Suppl (Stockh) 1992;176:95-8.

9 Sutthipisal N, McFadden J, Cronin E. Sensitization in atopic and non-atopic hairdressers with hand eczema. Contact Dermatitis 1993;29:206-9.

10 Mosmann T, Cherwinski H, Bond M, Giedlin M, Coffman R. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol 1986;136: 2348-57.

11 Cherwinski H, Schumacher J, Brown K, Mosmann T. Two types of mouse helper T cell clone. III. Further differences in lymphokine synthesis between Th1 and Th2 clones revealed by RNA hybridization, functionally monospecific bioassays, and monoclonal antibodies. J Exp Med 1987;166:1229-44.

12 Kimber L, Dearman R. Allergic contact dermatitis: the cellular effectors. Contact Dermatitis 2002;46:1-5.

13 Watanabe H, Unger M, Tuvel B, Wang B, Sauder D. Contact hypersensitivity: the mechanism of immune responses and T cell balance. J Interferon Cytokine Res 2002;22:407-12.

14 Kitagaki H, Ono N, Hayakawa K, Kitazawa T, Watanabe K, Shiohara T. Repeated elicitation of contact hypersensitivity induces a shift in cutaneous cytokine milieu from a T helper cell type 1 to a T helper cell type 2 profile. J Immunol 1997;159:2484-91.

15 Mosmann T, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol Today 1996;17: 138-46.

16 Cavani A, Nasorri F, Prezzi C, Sebastiani S, Albanesi C, Girolomoni G. Human CD4+ T lymphocytes with remarkable regulatory functions on dendritic cells and nickel-specific Th1 immune responses. J Invest Dermatol 2000;114:295-302.

17 Sebastiani S, Allavena P, Albanesi C, Nasorri F, Bianchi G, Traidl C, *et al*. Chemokine receptor expression and function in CD4+ T lymphocytes with regulatory activity. J Immunol 2001;166:996-1002.

18 Traidl C, Jugert F, Krieg T, Merk H, Hunzelmann N. Inhibition of allergic contact dermatitis to DNCB but not to oxazolone in interleukin-4-deficient mice. J Invest Dermatol 1999;112:476-82.

19 Yokozeki H, Ghoreishi M, Takagawa S, Takayama K, Satoh T, Katayama I, *et al*. Signal transducer and activator of transcription 6 is essential in the induction of contact hypersensitivity. J Exp Med 2000;191: 995-1004.

20 Leung D. The immunologic basis of atopic dermatitis. Clin Rev Allergy 1993;11:447-69.

21 Robert C, Kupper T. Inflammatory skin diseases, T cells, and immune surveillance. N Engl J Med 1999; 341:1817-28.

22 Hamid Q, Naseer T, Minshall E, Song M, Boguniewicz M, Leung D. In vivo expression of IL-12 and IL-13 in atopic dermatitis. J Allergy Clin Immunol 1996;98: 225-31.

23 Hamid Q, Boguniewicz M, Leung D. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. J Clin Invest 1994;94:870-6.

24 Grewe M, Gyufko K, Schopf E, Krutmann J. Lesional expression of interferon-gamma in atopic eczema. Lancet 1994;343:25-6.

25 Grewe M, Walther S, Gyufko K, Czech W, Schopf E, Krutmann J. Analysis of the cytokine pattern expressed in situ in inhalant allergen patch test reactions of atopic dermatitis patients. J Invest Dermatol 1995;105: 407-10.

26 Werfel T, Morita A, Grewe M, Renz H, Wahn U, Krutmann J, *et al*. Allergen specificity of skin-infiltrating T cells is not restricted to a type-2 cytokine pattern in

chronic skin lesions of atopic dermatitis. J Invest Dermatol 1996;107:871-6.

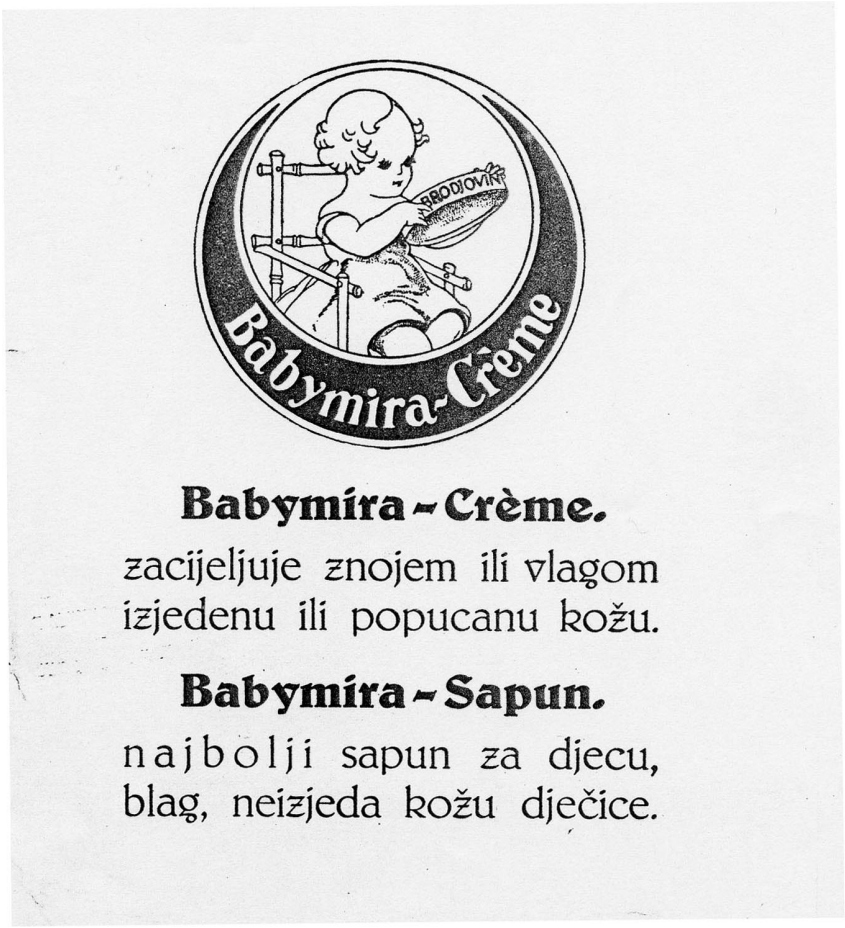
27 Thepen T, Langeveld-Wildschut E, Bihari I, van Wichen DF, van Reijsen FC, Mudde GC, *et al*. Biphasic response against aeroallergen in atopic dermatitis showing a switch from an initial TH2 response to a TH! response in situ: an immunocytochemical study. J Allergy Clin Immunol 1996;97:828-37.

28 Leung D, Bieber T. Atopic dermatitis. Lancet 2003; 361:151-60.

29 Ring J, Darsow U, Behrendt H. Atopic eczema and allergy. Curr Allergy Rep 2001;1:39-43.

30 Grewe M, Bruijnzeel-Koomen CA, Schopf E, Thepen T, Langeveld-Wildschut AG, Ruzicka T, *et al*. A role for Th1 and Th2 cells in the immunopathogenesis of atopic dermatitis. Immunol Today 1998;19:359-61.

31 Galli E, Cicconi R, Rossi P, Casati A, Brunetti E, Mancino G. Atopic dermatitis: molecular mechanisms, clinical aspects and new therapeutic approaches. Curr Mol Med 2003;3:127-38.



Babymira-Cream for diaper rash and Bebymira soap, the best soap for baby's skin.
From the collection of Assist. Prof. Stella Fatović-Ferenčić, MD, PhD.

News and Comments

Some Thoughts on Bostonian Spirit of Cosmopolitan Dermatology – Dedicated to «Harvard Team» of Professor Thomas Bernard Fitzpatrick

In spite of the risk of being, maybe, accused for "overpassing" my competences if I mention anything associated with Professor Thomas Bernard Fitzpatrick, I feel I should write some of my thoughts on the occasion of the recent loss that was felt when Professor Fitzpatrick left the Scene. During my stay at Harvard in 1991, 1995 and, very shortly in 2002, I had an extreme privilege to collaborate with some of my colleagues and, I am sure I may say so, friends from the Department of Dermatology of the Harvard Medical School in Boston, USA, all of them friends and close co-workers of Prof. Fitzpatrick. Spending some "dermatologically intensive" months with them, especially with Dr Richard A. Johnson, Prof. Jeffrey S. Dover, and Prof. Kenneth Arndt, I have definitely realized that there was no "Bostonian or American Dermatology", there was one and only Dermatology, cosmopolitan and progressive. That was definitely the idea and the spirit of Professor Fitzpatrick who ran very intriguing Rounds at Massachusetts General Hospital at that time. Like me, there were a few other colleagues visiting Harvard Department of Dermatology, as well, from different parts of the world. We were all not only encouraged to discuss, but to participate very actively in the every day activities; it was the part of our routine and permanent commitment. Very seldom would Prof. Fitzpatrick forget to ask each of us, from the youngest to the most experienced member of the dermatological community, to give our opinion regarding different dermatological issues. It was a great privilege, not so much practiced in Europe at that time; on the other hand, it was the exciting commitment at the same time.

After a few weeks of working with my Harvard Dermatology friends, I was offered a very challenging task – to author a Chapter on Human Herpesvirus 6 infections, including Exanthema Subitum for the Forth Edition of the Fitzpatrick's Textbook, Dermatology in General Medicine, a well renowned "Bible" for dermatologists. I almost could not believe I was given such a chance and honour, and I am still most grateful to Professor Fitzpatrick. However, my special thanks go to Drs Johnson and Dover, great dermatologists and great personalities, who made all that possible. Their wish to fulfill the high standard in Dermatology has never "surpassed" their human approach. I believe this is also a part of Bostonian cosmopolitan spirit of Harvard Dermatology. Doctor Johnson, a great expert in "Infective Dermatology" is also "to blame" for giving me a chance to be a co-author of the chapter regarding the same issue in the next (fifth) edition of the Fitzpatrick's Textbook. The whole atmosphere regarding preparations for that manuscript, taking place in the "intellectual headquarters" of the Textbook, at Dick' Johnson's house, at Otis Place in the old part of Boston downtown, was fully creative and rather stimulating. On that occasion, I also had a chance to meet Ms. Patricia K. Novak, a technical secretary and a unique woman who made enormous contributions to the success of the first four editions. Unfortunately, Pat died during the preparations of the fifth edition, but the standards of excellence of production she had set continued to live.

In the preface of the first edition of the Fitzpatrick's Textbook Dermatology in General Medicine, the editors stated their conviction that

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Figure. Prof. Fitzpatrick's "Harvard team" and the international co-workers (from the left): Dr Jeffrey S. Dover, Dr Tanya Dover, Dr Mihael Skerlev, Dr Richard A. Johnson, Dr Charles Taylor, and Ms. Patricia K. Novak. July 1991, Boston, USA.

dermatology was relevant and important to general medicine. Since that time, in the mid-1960s, Dermatology in General Medicine has flourished as a textbook through all the subsequent editions, each one bringing new ideas and introducing new areas of knowledge. The excellence of this Textbook is, everyone should believe, to be continued not only in the most recent, 6th edition, but also in the 7th, 8th, 9th, and all editions that will certainly follow. This excellence would, I am sure, reflect the humanistic and cosmopolitan spirit of the Professor Fitzpatrick's Harvard team and of all the successors and friends throughout the whole World.

Assist. Prof. Mihael Skerlev, MD, PhD

References

1 Freedberg IM. Preface. In: Freedberg IM, Eisen AZ, Wolff K, Austen FK, Goldsmith LA, Katz SI, Fitzpatrick TB, editors. Fitzpatrick's dermatology in general medicine. 5th ed. New York (NY): McGraw-Hill Inc.; 1999. p. XXXI.

2 Fitzpatrick TB, Johnson RA, Polano MK, Suurmond D, Wolff K. Color atlas and synopsis of clinical dermatology. Common and serious diseases. 2nd ed. New York (NY): McGraw-Hill Inc.; 1994.

3 Urioste S, Skerlev M, Johnson RA. Human herpesvirus 6 and 7 infections and exanthem subitum (roseola infantum or sixth disease). In: Freedberg IM, Eisen AZ, Wolff K, Austen FK, Goldsmith LA, Katz SI, Fitzpatrick TB, editors. Fitzpatrick's dermatology in general medicine. 5th ed. New York (NY): McGraw Hill Inc.; 1999. p. 2463-7.

4 Skerlev M, Johnson RA. Exanthema subitum. In: Fitzpatrick TB, Eisen AZ, Wolff K, Austen FK, Goldsmith LA, Katz SI, Fitzpatrick TB, editors. Dermatology in general medicine. 4th ed. New York (NY): McGraw-Hill Inc.; 1993.

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Referent Center of the Ministry of Health for Contact Allergy

In April 2003, the Department of Dermatology and Venerology, Zagreb University Hospital Center and School of Medicine, Zagreb, Croatia, has been proclaimed the Referent Center for Contact Allergy by the Ministry of Health of the Republic of Croatia. The golden plate of the Referent Center was given to Policlinic for Allergy, Clinical Immunology and Professional Skin Diseases, due to the engagement of Prof. Jasna Lipozenčić (Fig. 1).

It is an honor for the whole Department and especially for the team working at the Policlinic for the last 20 years (Fig. 2).

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

Figure 1. Golden plate.

Figure 2. The team at the Referent center of the Ministry of health for contact allergy.

International Symposium

UPDATE ON ATOPIC ECZEMA/DERMATITIS SYNDROME

Hotel Croatia, Cavtat/Dubrovnik, Croatia
April 25-28, 2004
www.cybermed.hr/4dermkh

Second Program and Call for Abstracts

Acta Dermatovenerol Croat
2003;11(4):251-264

Under the auspices of the Croatian Academy of Medical Sciences

International Symposium

UPDATE ON ATOPIC ECZEMA/DERMATITIS SYNDROME

organized by

International League of Dermatological Societies

in cooperation with

Section Dermatology of the European Academy of Allergy and Clinical Immunology (EAACI)

and

Croatian Dermatovenerological Society of the Croatian Medical Association

Hotel Croatia, Cavtat/Dubrovnik, Croatia
April 25-28, 2004
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SECOND PROGRAM AND CALL FOR ABSTRACTS

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Presidents:

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C. Bindslev-Jensen (Odensee)

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U. Wahn (Berlin), R. Wolf (Rechovot), T. Zuberbier (Berlin)

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Target Audience

Dermatologists, pediatricians, allergists, and immunologist are invited to participate with their colleagues from basic and clinical research and pharmaceutical industry in a discussion forum on early diagnosis of atopic eczema/dermatitis syndrome, with an emphasis on future developments of diagnosis, management, and prevention of the syndrome.

Atopic eczema/dermatitis syndrome strategies: The relevance of the diagnosis of allergy in atopic dermatitis and research in the pediatric allergy/dermatology will be presented by prominent lecturers.

Dear Colleagues,

International League of Dermatological Societies and Section Dermatology of the European Academy of Allergology and Clinical Immunology (EAACI) in cooperation with Croatian Dermatovenerological Society organizes a symposium Update on atopic eczema/dermatitis syndrome, which will take place in Cavtat/Dubrovnik. Cavtat, near Dubrovnik, is the pearl of south Adriatic Coast and considered one of the sunniest places in Europe, with unique world cultural heritage under the auspices of UNESCO. The scientific program of the Symposium is well balanced and tailored to the current needs of clinicians and basic scientists with a special interest in atopic eczema/dermatitis syndrome.

TOPICS

1. PROGRESSION IN ATOPIC DERMATITIS

~ B. Wüttrich (Zürich): The atopic eczema/dermatitis syndrome: classification, natural course, and immunological differences between IgE-and non-IgE-associated AEDS

~ K. Thestrup-Pedersen, M. Deleuran (Aarhus): Atopic dermatitis T cells

~ S. Pastore, G. Girolomoni (Roma): Keratinocytes contribute to inflammatory circuits in atopic dermatitis

~ T. Novak (Bonn): The role of dentritic cells in atopic dermatitis

~ C. Bindslev-Jensen (Odensee): Atopic dermatitis can be allergic–but when?

~ T. Diepgen (Heidelberg): The natural history of atopic dermatitis

~ S. Seidenari, F. Giusti (Modena): Intrinsic vs. extrinsic atopic dermatitis: diagnostic definition and prevalence

~ T. Zuberbier (Berlin): The role of mast cells in atopic dermatitis

2. CURRENT APPROACH TO ALLERGY

~ A. Kapp (Hanover): Neuroimmunological interactions in atopic dermatitis

~ T. Reunala (Tampere): Cutaneous route sensitization with natural rubber latex elicits Th2 inflammation in lung

~ I. Dobrić (Zagreb): Micromorphology of atopic dermatitis

~ T. Werfel (Hanover): Antigen-specificities and functions of T-lymphocytes in AEDS

~ R. Blaser (Davos): Mechanism of atopic eczema

~ J. Lipozenčić (Zagreb): Overview on etiopathogenesis of atopic dermatitis

~ S. Murat-Sušić (Zagreb): Serum eosinophilic cationic protein in children with atopic dermatitis

3. PRO AND CONTRA IMMUNOLOGIC BASIS OF ATOPIC DERMATITIS

~ J. Ring (Munich): IgE vs. non IgE-related atopic dermatitis

~ D. Bobek, J. Lipozenčić, O. Badovinac (Zagreb): Association between CD30 expression and atopic dermatitis

~ R. Marks (Melbourne): Studies on the frequency and causation of atopic eczema in Australia

~ G. Novelli (Rome): Insight into genetics of atopic dermatitis: future approaches and directions

~ T. Ruzicka (Düsseldorf): New developments in atopic eczema

~ L. Lugović, J. Lipozenčić (Zagreb): Immunologic factors involved in atopic dermatitis

4. ATOPY PATCH TESTING IN ATOPIC ECZEMA/DERMATITIS SYNDROME

~ K. Turjanmaa (Tampere): What's new in atopy patch test

~ S. Seidenari, F. Giusti (Modena): Results of patch and prick testing with egg, milk and peanut in patients with atopic dermatitis

~ M. Tengvall Linder (Stockholm): Atopy patch test with house dust mite allergen

5. PREVENTION OF TRIGGER FACTORS

~ R. Marks (Melbourne): Public and professional education programs on atopic dermatitis: a community based approach to prevention and reduction of severity

~ M. Šitum (Zagreb): Psychiatric factors in exacerbation of atopic dermatitis

~ H. Nakayama (Tokyo): The role of house dust mites on atopic dermatitis

~ R. Wolf (Rechovot): Soaps and shampoos in health and disease

~ H. Behrendt (Munich): Impact of airborne pollen, temperature and humidity on severity of atopic dermatitis in children

~ J.C. Szepietowski (Wroclaw): Itching in atopic dermatitis

~ F. Gruber, M. Kaštelan, L. Prpić Massari (Rijeka): Treatment of pruritus in atopic dermatitis patients

~ R. Wolf (Rechovot): Contact dermatitis in children and atopic dermatitis

~ A. Basta-Juzbašić (Zagreb): Rosacea and atopic dermatitis

~ V. Barišić-Druško, N. Šustić, I. Ručević (Osijek): The frequency of atopic dermatitis among psoriatics

6. DIAGNOSTIC STATE OF THE ART IN ATOPIC DERMATITIS

~ V. Milavec-Puretić, M. Rudolf, J. Lipozenčić, B. Malenica (Zagreb): Use of CAST-ELISA test in the diagnosis of atopic dermatitis

~ S. Ljubojević, J. Lipozenčić, V. Milavec-Puretić (Zagreb): Hypersensitivity to food additives in adult atopic patients

7. MANAGEMENT OF ATOPIC DERMATITIS

~ U. Darsow (Munich): Atopic dermatitis: new treatment strategies to control “the itch”

~ G. Girolomoni (Roma): The anti-inflammatory actions of antihistamines

~ G. A. Vena (Bari): Evaluation of a new sequential treatment with fusidic acid in atopic dermatitis patients

~ J. Lipozenčić, R. Wolf (Zagreb, Rechovot): What’s new in management of atopic dermatitis

~ S. Murat-Sušić (Zagreb): Management of atopic dermatitis in infancy

~ A. Pašić (Zagreb): The light in atopic dermatitis treatment

~ E. Fedenko, N. Ilina, I. Gushchin (Moscow): Russian experience of managing of atopic dermatitis patients

~ E. Fedenko, O. Elissioutina, N. Lapshin (Moscow): *Staphilococcus aureus* allergovaccine for diagnostics and treatment of atopic dermatitis

8. NEW DRUGS FOR ATOPIC DERMATITIS

~ T. Luger (Münster): Efficacy and safety challenge with pimecrolimus

~ G. Trevisan, F. Kokelj (Trieste): Tacrolimus in the treatment of atopic dermatitis: our experience

~ E. Berardesca (Roma): Combined therapy in atopic dermatitis

~ N. Lapshin, T. Latysheva, O. Elissioutina (Moscow): Clinical safety of phototherapy and pimecrolimus cream in atopic dermatitis patients

9. MODALITIES FOR IMMUNOTHERAPY

~ V. Milavec-Puretić, J. Lipozenčić, S. Ljubojević (Zagreb): Immunotherapy in atopic dermatitis patient: our experience

10. FREE COMMUNICATIONS

11. DIA CLINIC

POSTERS

1. S. Seidenari, F. Giusti (Modena): Reproducibility of atopy patch tests with aeroallergens and food allergens
2. S. Seidenari, F. Giusti (Modena): Atopy patch tests with dermatophagoides in patients without atopic dermatitis
3. S. Ljubojević, A. Pašić, J. Lipozenčić, I. Dobrić (Zagreb): A case of atopic dermatitis with sudden appearance of acquired vulgar ichthyosis
4. B. Vincetić, J. Lipozenčić, S. Ljubojević (Zagreb): Preventive measurement of pH-value in cosmetic dermatitis patients
5. L. Lugović, J. Lipozenčić (Zagreb): Concomitant respiratory allergy in atopic dermatitis

SYMPOSIUM VENUE

Hotel Croatia, Cavtat, Croatia, April 25-28, 2004

ACCOMMODATION AND REGISTRATION FEE

Technical Secretariat: Travel agency Spektar Holidays d.o.o.

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OFFICIAL LANGUAGE

English

REGISTRATION FEES

	Payment before February 2, 2003	Payment after February 2, 2003	Payment on site
Participants	200 EUR	250 EUR	300 EUR
Residents, retirees, and accompanying persons	100 EUR	100 EUR	100 EUR

Registration fee for participants and residents includes symposium material, admission to scientific sessions, opening ceremony and welcome reception, coffee breaks, and free entrance to exhibition.

Registration fee for accompanying persons includes welcome cocktail, coffee breaks, opening ceremony, and free entrance to exhibition.

SCIENTIFIC INFORMATION

The Scientific Program consists of Plenary lectures, Lectures, Satellite Symposia, Free Communications, and Posters. The main topics of the Symposium are highlights in atopic eczema/dermatitis syndrome. A number of distinguished scientists have been asked to present their lectures related to the main Symposium topic. The time allotted for each presentation is 8-20 minutes (15-20 minutes for plenary and 8-15 minutes for other lectures). The speakers are kindly requested to adhere strictly to the time schedule.

TECHNICAL EXHIBITION

Pharmaceutical companies, manufacturers of technical equipment, and publishers are invited to display their products at the exhibition organized within the Symposium.

ABSTRACT SUBMISSION

The Scientific Committee invites participants to submit their abstracts for consideration and inclusion in the program.

Abstracts must be submitted in English. All abstracts must be typed, left justified using 12 point, Times New Roman font. All headings and text must be on one page and within the margins of a 14.0 x 12.7 cm rectangle.

The title of the abstract must be in 12 point, Times New Roman font, left justified in bold capital letters, and extend for not more than two lines. The use of abbreviations in the title is not allowed.

The author's family names preceded by initials of the first names (e.g. J. Smith) must left justified below the title. The presenter's name must be underlined. The institution where the work originated, city, and country must be italicized, left justified below the author's names.

Paragraphs should not be indented and there should be no blank space between them.

Submission of abstracts by e-mail is preferable. If the abstract cannot be sent by e-mail, please send three hard copies and the electronic version of the abstract on a floppy.

Authors will have received notification on acceptance or rejection of abstracts by the end of February 2004.

Closing date for abstract submission: February 2, 2004

All abstracts will be published in the journal Acta Dermatovenerologica Croatica (Index Medicus/Medline).

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Why Cavtat as a congress venue?

Cavtat is a small town in the farthest south of the Croatian Adriatic coast. It has developed from the ancient Epidaurus built on the slopes of two peninsulas: Rat and Sustjepan. It owes its development to the geographical position in the southern Dalmatia with the fertile valley of Konavle in its hinterland. It is from that valley that the town was supplied with fresh water by a roman aqueduct. The archaeological research of the roman sanctuaries, necropolis, thermae and the shipwreck sites, have not yet given a complete picture of that roman settlement from the beginning of new era. The monuments from the time of early Christianity are the Mithra's sanctuaries. They date from the beginning of the era, representing the struggle between good and evil in the image of god Mithra, all represented in relief. The downfall of the Western Roman Empire and the invasion of Avars and Slavs caused the fall of Epidaurus as a seat of a diocese and its destruction. The legend says that the refugees from Epidaurus fled to the protected settlement of Laus – Lave – Ragusa, from which originates Dubrovnik. For centuries Cavtat was connected to Dubrovnik by administration, trade, and the freedom-loving spirit of the Dubrovnik Republic. It was a port where people from Konavle had their administrative and juridical control, where they traded in various goods, and where the masterminds like Baltazar Bogišić, Vlaho Bukovac, and Frano Supilo were born.

There are more than 5 miles (7 km) of sandbanks, clean sea water, sand beaches and bays, fine new hotels of high and luxury class, and all this has made Cavtat one of the most sought after and visited tourist resorts in the Dubrovnik area.

Special charm of this old city lies in the buildings that have remained from the times of the old Dubrovnik Republic.

How to reach Cavtat?

Cavtat is at the very south of the Republic of Croatia – 18 kilometers from Dubrovnik and only 6 kilometers from Dubrovnik International Airport. There are frequent direct flights to Dubrovnik International Airport from major European cities.

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Croatian Dermatovenerological Society of the Croatian Medical Association

and

Department of Dermatology and Venerology
"Sestre Milosrdnice" University Hospital
Zagreb, Croatia

in cooperation with

the European Society of Dermatology and Psychiatry (ESDP)

Organize

1st Croatian Congress of

PSYCHODERMATOLOGY

Cavtat/Dubrovnik, Hotel Croatia

September 23-26, 2004

Dear Colleagues,

On behalf of the Croatian Dermatovenerological Society we are pleased to invite you to participate at the 1st Croatian Congress of Psychodermatology, with great contribution of international guests, which will be held in Cavtat, September 23-26, 2004.

The accent will be put on the cooperation and teamwork of dermatologists, psychiatrists, and psychologists in recognizing and helping patients with skin disorders considered as psychosomatic dermatoses and patients with significant psychological disturbances influenced by dermatological disorders.

The Congress will gather many experts in the field of psychodermatology from Europe and Croatia.

The program consists of lectures, symposia, workshops, free communications, and poster sessions.

We are honored to welcome you in the beautiful town of Cavtat!

Main topics

– **Chronic skin disorders** (psoriasis vulgaris, dermatitis atopica, acne vulgaris, and alopecia areata) **and quality of life**

– **Cutaneous associations of psychiatric disorders** (dysmorphophobia and delusions) *and self-inflicted dermatoses* (dermatitis artefacta, neurotic excoriations, and trichotillomania)

– **Psychiatric and psychological aspect of dermatological disorders**

– **Liaison Clinic** (psychiatric and psychological approach to dermatological patients)

– **Psychotropic drugs and psychotherapy in dermatology**

– **Psychoneuroimmunology – skin, immune system, and psyche**

Official Language

English and Croatian.

Congress Committee:

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Vice President

Head Doctor Lenka Oremović, MD

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Invited Speakers

Cristopher Bridget (UK), Linda Papadopoulos (UK), Jacek C. Szepietowski (Poland), Rudolf Gregurek (Croatia), Eduard Klain (Croatia), Daniele Innocenzi (Italia)

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Abstract Submission

The Scientific Board invites authors to submit abstracts for consideration and inclusion in the program.

Abstracts must be submitted in English. All abstracts must be typed, left justified using 12 point Times New Roman font. All headings and text must be contained within the margins of a 15 x 13 cm rectangle. The abstracts should be submitted to the Scientific Secretary by March 30, 2004.

Abstracts should be sent to the Scientific Secretariat by e-mail or snail-mail on a floppy disc (Word document, Word for Windows).

Detailed information and abstract submission will be available as of December 8, 2003 at *www.kbsm.hr/congress-psychoderm*.

Scientific Information

The scientific program consists of lectures, symposia, workshops, free communications, and poster sessions. The time allotted for each presentation is 7-10 minutes, for lectures by invited speakers 15-20 minutes.

Registration Fee and Accommodation

Registration fee

Registration fee for participants:

before March 30, 2003	200 EUR
after March 30, 2003	250 EUR
on site	250 EUR

Registration fee for residents, retirees, and accompanying persons: 50 EUR

Accommodation

Organizing Committee has arranged the accommodation in the Hotel «Croatia» through Technical Secretariat – Spektar Holidays d.o.o., Sanja Vukov-Colić, Congress Department Manager

Bank account

For payment in Kunas: Spektar Holidays Zagrebačka banka, 2360000-1101441297

For payment in EUR: Spektar Holidays Zagrebačka Banka, SWIFT ZABA 2x2500-1553224

Impressions From "The First Russian Congress of Dermatovenereologists", St. Petersburg, September 23-26, 2003, and Visit to Moscow

The first Russian Congress of Dermatovenereologists took place in St. Petersburg, September 23-26, 2003, and gathered about 250 specialists in dermatology and venereology from Russia and fewer number of their colleagues from abroad. The Congress was organized by Department of Medical Organization of Ministry of Russia; Central Scientific Dermatovenereology Institute of Ministry of Russia, Cathedra for Dermatovenereology of Military Academy in St. Petersburg, and All Russian general organization "Russian Society of Dermatovenereology". Besenski žal castle of Tavricesko was chosen for the Congress venue (Fig. 1).

The main topics were as follows: dermatocosmetology and esthetic medicine; dermatooncology; pediatric dermatology; instrumental methods and physiotherapy in dermatovenereology; infective and parasitic diseases; mycoses: diagnosis, therapy, and prophylaxis; occupational diseases; and current diagnosis and therapy of dermatoses. The oral presentations were divided in 18 sessions, 9 symposiums, and two round-table discussions. Among international presenters, there were Diane Rouso, Keat Redcliff, Jana Hercogova, Torello Lotti, James Bingham, Michael Waugh,Peter Kohl, Lars Braathen, Pierre Morell, and Franco Kokelj. I was honored to be the only active participant from Croatia and a coauthor of "Clinical examination with Afloderm in different dermatoses" with Prof. Kungurov, director of Ural dermatovenereology and immunology (Figs 2-4).

Belupo Ltd. Pharmaceuticals and Cosmetics, Moscow office, sponsored the First Russian Congress of Dermatovenereologists and my participation. The director Mr Ruzicka, MS gave an excellent presentation of Croatian dermatovenereology and Belupo.

It was very instructive for me to be there. I met many of my friends, Prof. Gomberg, Prof. Kungurov, Prof. Skripkin, Prof. J. Hercogova, Prof. T. Lotti, Prof. M. Waugh, and Prof. Sokolovsky, all lecturers at the International Symposium "Update on Atopic Eczema/Dermatitis Syndrome" that would take place in Cavtat, Croatia, in April 2004.

The disadvantage of the Congress for non-Russian participants was the fact that only Russian language was in use and the slides were in Cyrillic, which made the lectures difficult to follow. The Abstract book was also written in Russian. Hopefully, at the next congress, which is planned for 2004 in Novosibirsk, Russian will not be the only official language.

What to say about two wonderful cities I visited - St. Petersburg and Moscow?

St. Petersburg, this grandiose, mysterious, and charming city, the youngest among European capitals, is on the threshold of its 300th anniversary. The new capital of the great country became the "Gateway to Europe" and had a decisive role in the transformation of Russia into a great European and world empire. The northern capital on the Neva River was constructed as a model European city but with a Russian scope. It attracted thousands of serf craftsmen, builders, dozens of Russian and foreign architects, painters, sculptors, and scien-

Figure 1. Besenski žal castle of Tavricesko.

tists. The city is closely linked with Peter the Great's reformers and the personality of the Tsar, himself a reformer. Some believe it is the triumph of Peter's genius, this city that opened up the new horizons of the Russian history, a model of beauty and rationalism, an ideal city. In an instant, St. Petersburg became the subject of many myths and legends, it was praised in elevated verse and prose, and represented in graphics and paintings. Powerful, gorgeous, and majestic Neva River, its canals, and granite embankments, arcades of magnificent bridges miraculously transfigure the city. Luxurious suburban gale residencies, estates and cottages, and small satellite towns encircle St. Petersburg. The image of St. Petersburg, the city of social revolts and uprisings, of great literature and great music is first of all associated with its architecture. Monumental grandeur and austere nobleness, beautiful panoramic views, the union of water and stone conquer the travelers to Northern Palmyra. The city is by all means distinguished by the remarkable integrity of its architecture, proportion, and harmony.

St. Petersburg is among cities that lend a special spirit to the culture they belong to and create. Its unique role in Russian and universal culture was realized hundreds of years ago; its mystery still excites us, even now on the threshold of its 300th anniversary.

Moscow is the other really amazing city, which is not too much to say from cultural and historic point of view.

Ancient Russian frescos and icons, old and modern portraits, landscapes, miniatures, sculpture and graphical works, watercolors and drawings are exhibited in Moscow museums and Galleries. Moscow offers most up-to-date technology for the businessperson. Modern conference centers, advanced communication networks, and wide range of financial services make all facets of doing business easy.

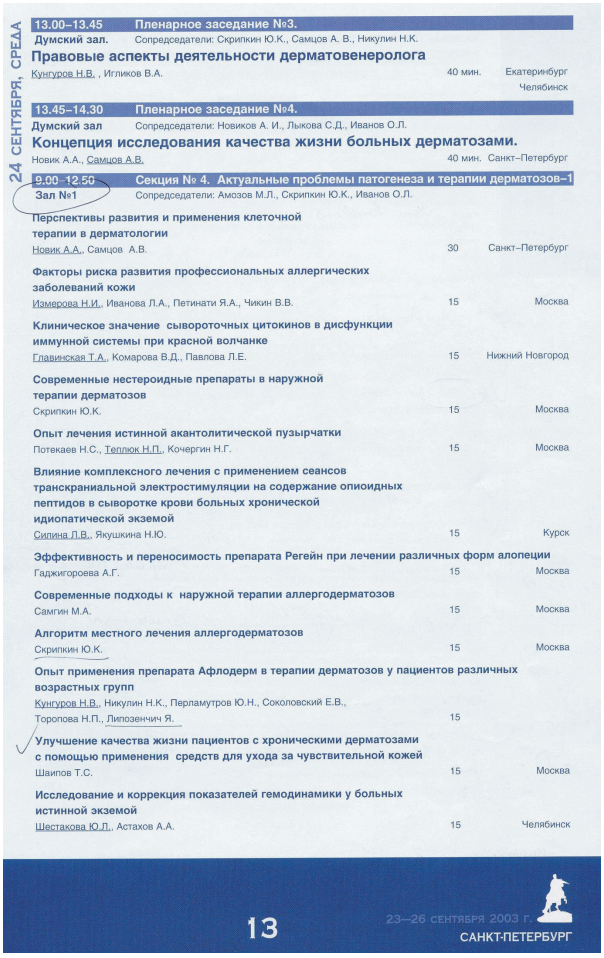
The city was founded on the 4th of April 1147, when Yuri Dolgorukiy invited prince Soyatoslav of Novgorod Seversky to Moscow. In the first half of the 14th century, during the rule of Ivan Kalita began the heyday of Moscow. It became the spiritual center of Russia: in 1326 the metropolitan seat was transferred to Moscow from the capital city of Vladimir. The same year saw the construction of the first stone Assumption Cathedral in Moscow. In the middle of the 15th century, after the fall of Constantinople, Moscow proclaimed itself the Third Rome – the earthy protector of the Orthodox Church. By the end of the 16th century four fortified walls had already surrounded Moscow. The first fortification ring is the Kremlin on the Borovitsky Hill. The city was burned to ashes several times, devastated by invasions. Tyrants and imposters ruled the city, riots

Figure 2. International participation.

were ruthlessly suppressed, but Moscow survived.

Many medieval churches and monasteries have been preserved to our days. There are the ensembles of the Kremlin, Zaryadye, Kitaygorod, the Church of the All Saints in Kulishki, the Church of St. Trifon in Naprudnaye, the Church of the Nativity of the Virgin in Putinka, the Church of the Resurrection in Kadasky, and many more. A number of medieval dwelling houses and public buildings exist in Moscow, like the Printing Court, the homestead of Averky Kirillov, or the Loom and the Pharmaceutical Court.

In the 18th century Moscow was ruled by Peter the Great. The first monuments and signs of the


24 СЕНТЯБРЯ, СРЕДА

13.00–13.45 Пленарное заседание №3.
Думский зал. Сопредседатели: Скрипкин Ю.К., Самцов А. В., Никулин Н.К.
Правовые аспекты деятельности дерматовенеролога
Кунгуров Н.В. , Игликов В.А. 40 мин. Екатеринбург Челябинск

13.45–14.30 Пленарное заседание №4.
Думский зал Сопредседатели: Новиков А. И., Лыкова С.Д., Иванов О.Л.
Концепция исследования качества жизни больных дерматозами.
Новик А.А., Самцов А.В. 40 мин. Санкт–Петербург

9.00–12.50 Секция № 4. Актуальные проблемы патогенеза и терапии дерматозов–1
Зал №1 Сопредседатели: Амозов М.Л., Скрипкин Ю.К., Иванов О.Л.

Перспективы развития и применения клеточной терапии в дерматологии
Новик А.А., Самцов А.В. 30 Санкт–Петербург

Факторы риска развития профессиональных аллергических заболеваний кожи
Измерова Н.И., Иванова Л.А., Петинати Я.А., Чикин В.В. 15 Москва

Клиническое значение сывороточных цитокинов в дисфункции иммунной системы при красной волчанке
Главинская Т.А., Комарова В.Д., Павлова Л.Е. 15 Нижний Новгород

Современные нестероидные препараты в наружной терапии дерматозов
Скрипкин Ю.К. 15 Москва

Опыт лечения истинной акантолитической пузырчатки
Потекаев Н.С., Теплюк Н.П., Кочергин Н.Г. 15 Москва

Влияние комплексного лечения с применением сеансов транскраниальной электростимуляции на содержание опиоидных пептидов в сыворотке крови больных хронической идиопатической экземой
Силина Л.В., Якушкина Н.Ю. 15 Курск

Эффективность и переносимость препарата Регейн при лечении различных форм алопеции
Гаджигороева А.Г. 15 Москва

Современные подходы к наружной терапии аллергодерматозов
Самгин М.А. 15 Москва

Алгоритм местного лечения аллергодерматозов
Скрипкин Ю.К. 15 Москва

Опыт применения препарата Афлодерм в терапии дерматозов у пациентов различных возрастных групп
Кунгуров Н.В., Никулин Н.К., Перламутров Ю.Н., Соколовский Е.В., Торопова Н.П., Липозенчич Я. 15

Улучшение качества жизни пациентов с хроническими дерматозами с помощью применения средств для ухода за чувствительной кожей
Шаипов Т.С. 15 Москва

Исследование и коррекция показателей гемодинамики у больных истинной экземой
Шестакова Ю.Л., Астахов А.А. 15 Челябинск

13
23–26 СЕНТЯБРЯ 2003 Г.
САНКТ-ПЕТЕРБУРГ

Figure 3. My active participation in the Congress (encircled)

new century were the Sukharev and Menshivkov towers, the Botanical Garden, Slavonic-Greak-Latin Academy, the German suburb, and schools from Europe. Architect Bazbenov built "Pashkov house" opposite to Kremlin, and Kazakov the Kremlin Senate, the Moscow University, the Galitsin hospital, the Noble Assembly with its famous Hall of Columns, and numerous country estates.

In 1812, Moscow was burned, but its reconstruction gave life to magnificent architectural monuments and superb ensembles: Bolshoi Theater and Manege by architect Beauvois, county estates, and rich town residences. The Glorious victory in the Patriotic war of 1812 and the awareness of the national dignity ushered Russia in a new epoch: of Russian literature and music, the awakening of Russian philosophy and the renaissance of Russian spirituality. Moscow is the home of Puschkin's family happiness, the spiritual drama of Gogol, the birthplace of Dostoevsky and Solovyev, the university of Lermontov, Tuetchev and Turgenev, the city where Tolstoy and Chekhov, Tchaikovsky and Rubinstein lived and worked. At the end of the 19th century, after almost five decades of construction, there emerged the main cathedral of Russia – the Cathedral of Christ the Savoir commemorating the military fear of the Russian army in 1812. Other cathedrals are linked with the destinies of the famous people. The Cathedral of "Big Ascension" keeps the memory of Puskhin's wedding with Natalya Gomkarova, the Church of Simeon, the Stylites in Povarskaya Street, of Gogol's last prayers.

The end of the 19th – beginning of the 20th century in Moscow is associated with the Treatykov Gallery, Mamontov's opera, Stanislavsky Art Theater under patronage of Savoa Morosov, the art collections the Schukins and Balbruskin, the paintings of Scryabin, literately and philosophy salons, and the Museum of Fine Arts.

The age of Modern, the Silver age of Russia culture was in search of renewal and fusion with life. In November 1917 Moscow was the scene of fierce battles before it surrendered to the revolution.

In March 1918, Bolshevik government moved from Petersburg to Moscow and it again became the capital of the state. Million of people's lives and hundreds of churches and civil building were destroyed, as well as the Cathedral of Christ of Savoir, the Kazan cathedral, the Sukhner tower, the Resurrection gates, Simanov and Strastnoy monasteries.

But Moscow remained the city of writers, Pasternack and Bulgarkov, and poets Jesenin and Mayakovsky.

Figure 4. Prof. Sofia Likova, MD, PhD (left) and Prof. Jasna Lipozenčić, MD, PhD (right).

The 1930s saw the beginning of the first socialist city: the gigantic Palace of Soviets was to replace the Cathedral of Christ the Savoir; monotonous blocks of multi-storied buildings were to be built instead of private homes.

In 1941 Moscow become the first city to defeat Hitler's Germany. Marshal Zhukov on horseback at the Victory Parade in 1945 became the great image.

The nine centuries have gone by. The history of the city in the austere and magnificent Kremlin, in Red Square – the altar of Russia, in picturesque boulevards, estates, Moscow skyscrapers and in the metro, its underground museum, in the churches and monasteries. The Moscow is nowadays a modern European capital with the national original character of the ancient Russian capital.

Prof. Jasna Lipozenčić, MD, PhD

Croatian Dermatovenereologists Visit the Pierre Fabre Laboratories

During the 6-day study journey (September 13-18, 2003) organized by Oktal-Pharma, Croatia, ten Croatian dermatovenereologists visited the Pierre Fabre Laboratories in South France (Fig. 1), where they were introduced to the scientific research programs and products of Pierre Fabre Laboratories. After two years of collaboration between Oktal-Pharma and a French pharmaceutical company Pierre Fabre, we have finally got the chance to visit the place where one of the leading pharmaceutical firms in France and the leading manufacturer of dermatologically tested cosmetics in the world has been born. There are several Pierre Fabre Dermo-Cosmetique laboratories in four different cities: Laboratoires Dermatologiques Avéne, Ducray et Laboratoires Pierre Fabre Dermatologic; Conservatoire Botanique Pierre Fabre in Cambounet/Le Sor; Toulouse-Institute de Recherche Pierre Fabre, Hotel-Dieu Saint Jacques; and Castres – "Les cauquillous" – Lavaur Cedex (Figs. 2 and 3).

Figure 1. Croatian dermatovenereologists visit to Domaine du Carla.

Figure 2. Pierre Fabre in Castres.

Pierre Fabre, who founded the company 77 years ago, regularly arrives at work every day and independently runs his company. After World War II when he completed his studies in pharmacy, his parents bought him a drugstore in his hometown Castres, in the southwest France. Deep interest in science led young Pierre Fabre into the area of

Figure 3. Galenic laboratory in Avene.

pharmacognostic research. In 1961, he founded the Pierre Fabre Laboratory, which started with a production of its first phytotherapeutical agent for treatment of venous insufficiency, which is still available at the market. After this first success, business ambitions of Pierre Fabre were not to be stopped. During the following years, his research extended into the area of immunology and oncology; Klorane, a French cosmetic company, was bought; Pierre Fabre Research Institute was founded; and the first daughter companies established in Spain, Italy, and Germany. The collaboration with Japanese firm Shiseido has been very important for the business of production of dermatologically tested cosmetics, as it was the purchase of a thermal water spring in Avéne, where a 250 years old thermal spa was restored.

The Pierre Fabre Group developed immensely over a period of 40 years, making today a successful business in France and all over the world through three main activities: pharmaceuticals production, homeopathic production, and dermatologically tested cosmetic production.

After taking over the spring and spa in Avéne in south France in 1975, the Group has carried out numerous clinical studies, proving the unique characteristics of Avéne thermal water, i.e. its anti-inflammatory, soothing, and anti-irritation effects on the sensitive skin. This research has resulted in a production of a wide range of dermatologically tested cosmetic products containing carefully chosen and purified ingredients. Avéne line of products is recommended by dermatologists throughout Europe, and has been available in Croatian pharmacies for two years now.

Today, Avéne thermal spa is a modern facility embedded in well-preserved environment of south France, offering treatment to around 2,000 patients with exclusively dermatologic problems, such as atopic dermatitis and psoriasis, every year. The treatment process is supervised by a specialist in dermatology, and includes baths, showers, dressings with Avéne product line, and drinking of water drawn from the spring (Fig. 4).

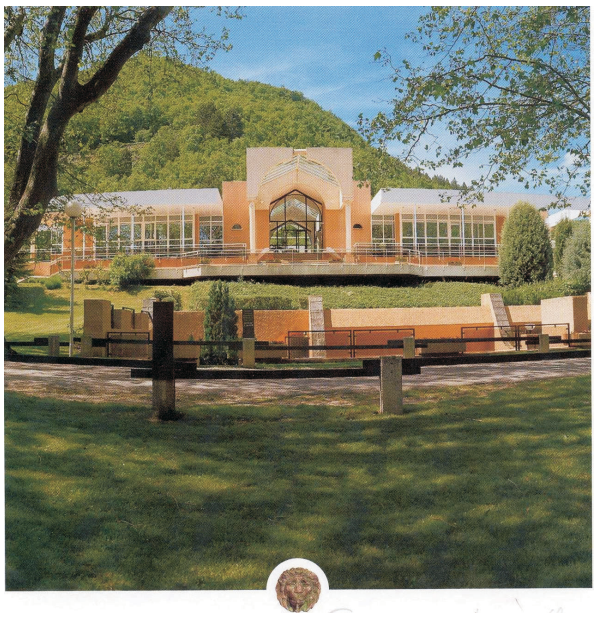


Figure 4. Avene Therme.

Environment protection, love for his native soil, investment in people and the region as well as a special attention paid to the manufacture of Avéne products from raw material to a final product adorn the character of this businessman whose firm has become one of the main economic mainstays of the region.

The fascinating fact is that Pierre Fabre Avéne thermal water product is distributed throughout the world, with 60% of production intended only for Japan. Pierre Fabre line consists of more than 1,000 of different products. Nearly 1,000 researchers are involved in pharmaceutical innovation at the Pierre Fabre Research Institute. The Pierre Fabre Medicaments makes 52% of production activity, Fabre Dermo-Cosmetique 36%, homeopathy-phy-

totherapy products 10%, and other products 2%. Pierre Fabre Research in Immunology Centre Saint-Julien-en-Genevois has four priority areas of research: central nervous system, oncology, cardiovascular diseases, and immunology.

The visit to the Pierre Fabre Laboratories was very well organized and the Croatian dermatovenereologists have returned home with a wonderful experience to remember.

Melita Škvorc, MD

Prof. Jasna Lipozenčić, MD, PhD

International Symposium "Current State on Psoriasis and Naphthalanotherepy", Ivanić Grad, September 19, 2003

I "Naftalan" Special Hospital for Medical Rehabilitation in Ivanić Grad, Croatia (Fig. 1), hosted a whole day International Symposium "Current State on Psoriasis and Naphthalanotherapy" (Fig. 2). «Naftalan» Special Hospital for Medical Rehabilitation, organized bus transportation from Zagreb to Ivanić Grad for members of Croatian Dermatovenereological Society. There were 127 participants. Pero Vržogić, MD, director of the «Naftalan», organized the refreshment and lunch for all participants.

At the beginning, Dr. Pero Vržogić welcomed all participants, especially Prof. Trevisan with colleague Kokelj, MD (Figs. 3 and 4). Prof. Lipozenčić cordially welcomed the guests from Italy, Prof. Wolf, doyens of Croatian dermatovenereology, all professors, presidents of dermatovenereologic departments in Croatia, members of four Croatian Dermatovenereological Society Branches, and all pharmaceutical exhibitors. Prof. Lipozenčić proposed this traditional Symposium on psoriasis to be organized for Italian and Croatian dermatovenereologists every year. Prof. Trevisan agreed with this proposal and next Symposium on psoriasis will be organized in Trieste in 2004, and the following one in Ivanić Grad or Zagreb in 2005.

Main topics of the Symposium were as follows: Immunologic basis of psoriasis; Genetic factors in manifestation of psoriasis; Immunohistochemical diagnosis in prognosis of psoriasis; Combined ultraviolet B (UVB) light and naphthalan therapy; PUVA therapy – our experience; Coexistence of psoriasis and bullous pemphigoid; New therapeutic option in psoriasis management; Effect of naphtha-

Figure 1. Naftalan special hospital for medical rehabilitation in Ivanić Grad.

Figure 2. Participants of International Symposium in "Napftalan".

Figure 3. P. Vržogić, MD (left) and Prof. Trevisan (right).

Figure 4. Participants of International Symposium "Current State on Psoriasis and Naphthalanotherapy".

lan on epidermal proliferation activity and lymphocyte count; Psoriasis treatment – yesterday, today, and tomorrow; Naphthalan in atopic dermatitis management; Heliomarinotherapy; and Other therapeutic options in treatment of psoriasis". Prof. Giusto Trevisan and Franco Kokelj, MD, from Trieste University gave a very instructive lecture "PUVA therapy – our experience". At the end of their presentation the audience was invited to the 5th Alpe-Adria-Danube Symposium on psoriasis, which was held in Bibione Therme, Italy, November 7-8, 2003. Each presentation was followed by a fruitful discussion.

In conclusion of the International Symposium, Prof. Lipozenčić informed the participants that all lectures from "Current State on Psoriasis and Naphthalanotherapy" symposium will be published as a Supplement to *Acta Dermatovenerologica Croatica* (ADC) titled "Psoriasis for Clinician". All Symposium participants have been invited to send their manuscripts on psoriasis and naphthalanotherapy to the ADC Editorial Board.

For physicians who are interested in the problem of psoriasis but were not able to join us in Ivanić Grad, here follow the main conclusions of the Symposium.

Psoriasis is genetic and autoimmune disease, with histocompatibility genes, polymorphism, and genetic disequilibrium playing a crucial role in the development of the disease. HLA-C region is especially important for the development of guttata psoriasis. Candidate loci in psoriasis are PSORS 1-8. In addition to hyperproliferation of keratinocytes, inflammatory infiltrate in psoriasis is also a dominant sign. Combined therapy, rotational, sequential therapy in remission phase, transitional and maintenance phases are important in the treatment of psoriasis. Maximum dose of cyclosporine should be given in "clearing" phase, followed by administration of acitretin in transitional phase with decreasing dose of cyclosporine and long-term acitretin therapy in maintenance phase. Phototherapy or PUVA are additional treatment methods in maintenance phase. Combined PUVA+calciportiol is an effective treatment modality, with less adverse reactions. Immunohistochemistry is imperative in diagnosis, especially in prognosis of psoriasis. Coexistence of psoriasis and bullous pemphigoid is not so rare and must be taken into consideration. Historical review of therapeutic formulations and methods used in the treatment of psoriasis from arsen, mercury, tars, Göckermann method, crisarobin, antranil (cignolin→Ingram method), nitrogen mustard, to new therapeutic options is useful today as it will be in the future. New agents for the treatment of psoriasis – alefacept, etanercept, and efalizumab – seem very promising. A report on naphthalanotherapy in 15 patients with atopic dermatitis showed that this treatment modality yielded good treatment results in all relevant parameters.

Finally, highlights on current state on psoriasis, as given on this Symposium, also included naphthalanotherapy as a very good treatment option for psoriasis and atopic dermatitis.

Pero Vržogić, MD

Acta Dermatovenerol Croat
2003;11(4):265-277

Highlights of the First World Congress on Work-Related and Environmental Allergy, Helsinki, Finland, July 9-12, 2003

The First World Congress on Work-related and Environmental Allergy (WOREAL) together with the Fourth International Symposium on Irritant Contact Dermatitis and the Seventh International NIVA Course on Work-related Respiratory Hypersensitivity was held in a beautiful capital of Finland, Helsinki.

Around 200 participants from all over the world gathered in that city, together with the many leading scientists and specialists in occupational diseases and asthma. Helsinki is place that offers an exciting vacation as well as relaxing retreat in beautiful natural surrounding. However, all interesting and useful lectures and symposia gave us new data on irritant and allergic contact dermatitis and environmental and occupation diseases.

The Congress was divided into 16 symposia, 4 plenary sessions, 4 free communications lectures, and a Poster discussion session.

Department of Dermatology and Venerology, Zagreb University Hospital Center, participated with the poster presentation on wet cement chemical burns, written by Radoš J. and colleagues, and presented by S. Ljubojević. After the discussion about our work on the poster presentation session, it was concluded that although the cement worker knew the side effects of wet cement, there should be clearly stated warnings about its, sometimes fatal side effects, especially for the individuals that come in contact with it only occasionally.

Dr Schwantz form Germany spoke about education programs in the prevention of irritant contact dermatitis. According to views, there are three lines of prevention: a) primary prevention that is directed to the avoidance of occupational skin diseases; b) secondary prevention that aims at early recognition an intervention; and tertiary prevention, which tries to limit sequelae of occupational skin diseases that have already occurred in an individual.

Lots of speakers agreed that the most common causes of all occupation diseases are detergents, rubber and rubber chemicals, plastic chemicals, oils and lubricants, including metalworking fluids, cement, concrete, and others.

There were many lectures on how to prevent occupational contact dermatitis, but no definite answer was given. There should be more research into the causes and prevention of occupational diseases, mainly contact dermatitis, based on epidemiological, clinical, and laboratory data.

Most cases of occupational rhinits are caused by organic material but some chemicals can cause some. Dr Hytönen concluded that provocation tests could confirm causality between the disease and work exposure.

Professor Turjanmaa gave an outstanding lecture on problems in clinical praxis of latex allergy. Although the latex allergy has become a well-understood entity during the last decade, life-threatening reactions, as well as contact allergy are often reported in the literature. For prevention, the use of low-protein, non-powered latex gloves has been widely adopted in health care.

Professor Maibach explained sensitive skin syndrome within different concepts: irritant dermatitis syndrome, allergic and photoalleregic dermatitis, contact urticaria syndrome, and chemical acne.

Dr Seaton from Scotland discussed weather dietary factors influence asthma. He concluded that intake of food containing vitamin E influences risks of asthma and in utero responses to allergens. Maternal allergy and early administration of antibiotics to the child stood out as influential factors.

Dr Susitaival from Finland revealed a new standardized tool for HE-surveys, complied by a Nordic group of experts (*www.ami.dk/nosq*).

At the end of the Congress, Professor Rycroft gave an outstanding and useful lecture on management of work-related chronic hand dermatitis.

The welcome reception was held in the beautiful City Hall and the City Major wished us a warm welcome to “his” beautiful city. Young British artists in the very acoustic and magnificent Temppeliau-

kion church held the great concert, which was a surprise gift from the Congress organizers. Gala dinner took place on Soumenlinna Island, one of the most attractive and popular leisure sites in Helsinki and precious gem on the UNESCO's World Heritage List.

One of the best allergists, Lasse Kanerva, had his 60th birthday, and professor Maibach thanked him for the great contribution in the field of the contact dermatitis, especially environmental and occupational diseases. He recently published an outstanding handbook of occupational dermatology that contains a new therapeutical and diagnostic approach to those impairing diseases that effect the quality of life.

The next WOREAL will be organized by the Department of Dermatology, Fredrich Schiller University, Jena, and it will take place in July next year in Jena, Weimar, Germany. Again, the meeting will be combined with an International Symposium on Irritant Contact dermatitis (ISICD).

Suzana Ljubojević, MD, MS

Report from the European Union of Medical Specialists Section and European Board of Dermatology and Venereology Meeting, Barcelona, October 18, 2003

Autumn meeting of Section of Dermatology-Venereology of the European Union of Medical Specialists (UEMS, Union Europeenne des Medecins Specialistes) was held after the Closing Ceremony of the 12th Congress of the European Academy of Dermatology and Venereology in Barcelona, on October 18, 2003.

UEMS is a non-profit organization, which started being active in 1958 and established its Specialist Sections in 1962. The main goals of this organization are promotion of the highest level of training of the medical specialists, advancement of medical practice and health care within the European Union (EU), and promotion of free movement of specialists within the EU countries. Full active members of the UEMS are specialist organizations from EU countries or signatory countries of the European Economic Area agreement, whereas associate members are member countries of the Council of Europe that belong neither to EU nor to the European Free Trade Association (EFTA). Croatia, represented by Prof. Jasna Lipozenčić and Branka Marinović, MD, has been an associated member of the UEMS Dermatology-Venereology Section since 2000.

At the beginning of the Autumn meeting, president of the UEMS Prof. Gollnick reported on the main topics that were worked out during 2003: foundation process of a Multidisciplinary Joint Committee of Immune-mediated Diseases, the revision of the curriculum teaching questionnaire, and the revision of the continuos professional development questionnaire. These questionnaries are filled out by full and associated members of UEMS, and returned to the UEMS, which then provides an overview of actual situation of teaching curriculum as well as of continuous professional development. Data about the situation in Croatia, as given by its representatives, have been included in reports since 2001.

In the last few years, the UEMS Dermatology-Venereology and Pathology Sections worked together on further coordination of dermatopathology in Europe. Aim of the UEMS Dermatology Section was to obtain the right to process, read, and sign dermatohistological slides. For this purpose, two-year additional full-time training in dermatopathology or at an pathology institution would be mandatory, followed by an examination before a joint commission. Prof. Gollnick also reported about his contacts with Prof. Kerl, president of the

European Society of Dermatopathology, regarding the board certificate in dermatopathology. The first meeting and examination procedure before the Board composed of world known dermatopathologist and pathologist will take place in Frankfurt on December 5, 2003.

With a goal of promotion of harmonization and improvement of the quality of specialist medical care within the countries participating in the UEMS, Central UEMS organization has created four Charters: Charter on Training of Medical Specialists in the European Community; Charter on Continuing Medical Education in the European Union; Charter on Quality Assurance, and Charter on the Visitation of Training. Charters are available online at *www.uems.be/derm-ven.htm.*

The task of the delegates in the UEMS Section Dermatology-Venereology is to bring these Charters to the attention of their national organizations and to assist with the implementation of the Charters in European countries.

Branka Marinović, MD, PhD

Report from the 19th Congress "Progress in Allergology, Immunology and Dermatology" in Davos, September 17-20, 2003

The Congress was organized by Professors J. Ring and S. Borelli mainly for participants from three countries: Germany, Austria, and Switzerland. The plenary lecture "What can we learn from skin mosaics?" was presented by Prof. R. Happle from Marburg. The main topics of the Congress were as follows: Allergy and Skin; Asthma and Occupational asthma; Anaphylaxis; Clinical Allergology; and New Therapies in Allergology and Immunology. There were also symposia on mycology and occupational asthma and epidemiology of the occupational dermatoses; workshops on hyposensitization and principals in allergology; and small group seminars on occupational problems. Prof. D. Nowak presented interesting data on occupational asthma, Prof. A. Kapp gave a very instructive talk on pathophysiology and current trends in the treatment of urticaria, Prof. Th. Bieber introduced the novelties in immunologic role of the Langerhans cells in atopic patients, Prof. U. Müller held a lecture on anaphylactic reactions, T.L. Diepgen on epidemiology of occupational diseases, and Prof. D. Abeck on pediatric dermatology. Every morning, there were Patients Dia-Clinic presentations, a very original and interesting part of the program. We also visited AlexanderHaus Klinik in Davos and saw pediatric and adult patients with psoriasis, atopic dermatitis, and asthma. Two very nicely organized programs included dinner, dance, and offered opportunity for a lot of contacts, which all participants enjoyed. The product exhibition area was well organized and interesting as always.

As every year before, Congress in Davos has again been well organized, offering great presentations and opportunity to exchange knowledge and learn about the novelties in the fields of allergology, immunology and dermatology.

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

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The 6th Alpe Adria Symposium on Psoriasis in Bibione, Italy, November 7-8, 2003

The 6th Alpe Adria Symposium on Psoriasis was held under the patronage of Italian Society of Dermatology and Venereology (SIDEV), Regione Autonoma Friuli Venezia Giulia, Ospedali Riunita di Trieste, and Azienda Sanitaria Territoriale di Trieste in Savoy Beach Hotel in Bibione Thermae, November 7-8, 2003. This is a traditional meeting on psoriasis, which is held every two years.

There were 130 registered delegates from 8 countries, with eight active participants from Croatian Dermatovenerological Society.

Presidents Prof. G. Trevisan, Dr. G. Chieregato, and Dr. P. Sedena and General Secretary Dr. M. Kokelj organized a very successful Symposium. The Italian and Croatian dermatovenereologists have decided that the Meeting on psoriasis be held every year from now on because the new trends in the diagnosis and treatment of psoriasis emerge every year. Thus, the next meeting will be organized by Prof. Trevisan in Trieste in 2004 and it will take place together with Lyme disease Symposium, whereas the meeting in 2005 will be organized by Prof. J. Lipozenčić, in Croatia (Fig. 1).

Figure 1. Prof. G. Trevisan and Prof. J. Lipozenčić during 6th Alpe Adria Symposium on Psoriasis, Bibione, November 7-8, 2003.

Figure 2. Secretary of the 6th Alpe Adria Symposium on Psoriasis, Bibione, November 7-8, 2003.

The Meeting in Bibione was very fruitful in respect of news in the field of immunology. Colleagues from Rijeka presented their research in keratinocyte growth factor, interleukin-10 promoter, adhesion molecules, and Fasl molecule in chronic plaque psoriasis, psoriasis, and pruritus. News about therapy included “Tomesa” photo-balneotherapy, balneotherapy for psoriasis at Bibione, and biologicals in the treatment of psoriasis, especially Infliximab and Alefacet. Well received were the presentations by dermatovenereologists from Croatia whose contribution was, in Prof. Trevisan‘s opinion determinant for the success of this symposium: effects of naphthalan on epidermal proliferation in psoriasis, epidemiology and triggers of psoriasis in Eastern Croatia, psoriasis and AIDS, and practical considerations in psoriasis therapy. Judging by the excellent attendance of all scientific sessions and reported satisfaction of participants with the organization and choice of topics, we may say that this was a very successful meeting (Fig. 2).

Prof. Jasna Lipozenčić, MD, PhD

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Visit to Uriage Termal Station

Within the context of cooperation of BIORGA Ltd., Paris, and FORMASANA Ltd., Zagreb (importer of dermo-cosmetics URIAGE and BIORGA for Croatia), dermatovenereologists from Croatia paid a visit to URIAGE dermatological laboratory in June 12-16, 2003. During these few days, our host introduced us not only to *Uriage les Bains* (Fig. 1) and URIAGE dermatological laboratory, but also to historical, cultural, and gastronomical values of that part of France.

Uriage les Bains enjoy a privileged geographic location, with the Spa located just outside Grenoble (8 km).

At the foot of the Belledonne Range, not far from the summits of Chamrousse, this area is one of the most majestic sites in the French Alps. Located in the Vaulnaveys Valley at an altitude of 400 meters, in a magnificent 200-hectare park, Uriage is a haven of calm and greenery.

Uriage's patron is the goddess Hygeia, daughter of the god of medicine. The ruins of the Roman baths testify to the great importance formerly attached to the therapeutic virtues of hot springs. Roman soldiers came here specially to speed the healing of their wounds.

Jules Vulfranc Gerdy, intern and graduate from the Paris Hospitals (*Hospital Saint Louis*), published a thesis in 1838 entitled "Skin diseases cured by Uriage Spa water ". He confirmed the therapeutic virtues of the water, conferred by its unique physical and chemical properties. Dermatologically beneficent effects of the Spa were confirmed under Napoleon III, when the facilities were built. The leading celebrities of the Belle Époque flocked to Uriage to take waters and rub shoulders.

Today, 7,000 people enjoy the waters at *Uriage les Bains* every year. The Spa is famous for the treatment of inflammatory and pruriginous dermatoses (all forms of psoriasis, psoriasis complicated by rheumatism, atopic dermatitis, chronic or recurrent subacute eczemas, seborrheic dermatitis, prurigo, refractory lichen planus, and many others). Isotonic and anti-inflammatory, healing, anti-irritant, and filmogenic properties of Uriage Spa water make it effective in the treatment of inflammatory and pruriginous skin conditions. Perfect isotonicity of Uriage water makes it extremely well tolerated by the most sensitive skin. Dr. Doyon, the founder of the French review *Annales de Dermatologie*, has practiced at *Uriage les Bains* for more than 50 years. Inaugurated in 1977, the Hydrology et Rheumatology Hospital of *Uriage les Bains*, connected to the Chair of Hydrology at Grenoble University Hospital, houses a French Hydrotherapy Research Institute.

Unique and Naturally Isotonic Water

For more than 75 years, Uriage spa water has been passing through the crystalline rocks and sands of the Belledonne Range, a vast natural filter that enriches it with exceptional mineral salts and trace elements. This absolutely clear water, untouched by air or pollution, gushes forth from a depth of 80 meters. For centuries, the spring has invariably supplied 400,000 liters of warm water (27° C) every day, with a physiological pH. Subjected to regular tests by approved laboratories like the Institute Pasteur, its physical and chemical properties and its bacteriological purity are constantly guaranteed.

Uriage Spa water has osmolarity (275 mosm/L) identical to that of blood plasma. This perfect isotonicity preserves the osmotic equilibrium of the skin, prevents the loss of mineral elements, and is perfectly tolerated by the most sensitive skin. It is also the only spa water that can be sprayed and left to act without buffering.

Figure 1. Uriage les Bains

With a dry residue of 11 g/L, Uriage water has the highest content of mineral salts and trace elements of all spa waters used in dermatology. Professor Landry of INSERM has showed that the inhibiting effect of Uriage water on histamine release is linked to its high calcium content (600 mg/L). This study, carried out on human skin mastocytes, explains why the local application of spa water is good for inflammatory dermatoses. Zinc (160 μg/L) and copper (75 μg/L) are involved in the synthesis of collagen and elastin, and hence play an important role in healing mechanisms. Manganese (154 μg/L) protects the cells from oxidative stress by activating manganese dismutase superoxide, thus preventing the formation of free radicals. Its high content of silicon (42 mg/L), a key factor in the skin architecture and elasticity, makes it an excellent skin softener. Its composition, which is similar to NMF, gives it optimal moisturizing power on the stratum corneum. The moisturizing rate in the superficial layers of the epidermis increases as early as one hour after application.

All Uriage products benefit from a high concentration of spa water. Uriage offers a complete skin care product range, which is remarkably well-tolerated and has extremely pleasant texture, to improve the suppleness, the comfort, and the physiological equilibrium of the most sensitive skins.

Ljiljana Škrinjar, MD

Bartulić ointment for nasal disinfection and Bartulić ointments for the treatment of mosquito bites.
From the collection of Assist. Prof. Stella Fatović-Ferenčić, MD, PhD.

Marko Polo´s Diary

Stella Fatović-Ferenčić, ESHDV representative of Croatia

The Wellcome Library & Institute, The Royal Society of Medicine, and The Medical Society of London, June 3-11, 2003

My flight by Rayan Air from Graz to London went smoothly and soon I landed at Stansted airport. The Wellcome Institute and Library is a dream of any scientist, and for medical historians, a desired place for frequent returns. It was the purpose of my visit to London this time. It preserves the records of medicine, past and present, to foster and facilitate understanding of medicine, its history and its impact on society. The Institute's collections cover works on numerous areas that have impacted on the human life. At Wellcome I got a small office with a computer at my disposal, a closet for my belongings and material. What more could one wish for? I transformed myself into a scholar immediately and enjoyed it fully. On Wednesday after introducing myself to the History of medicine staff at the Centre, I was invited to a conference on geriatric medicine. Many prominent medical historians gathered and participated in discussions. In the afternoon I went to the Wellcome Library at Euston Road again and spotted a print reference to Girolamo Fracastoro's poem and the history of syphilis that I intend to use for the lecture I was invited to give next year at Royal Society of Medicine. The next day I had an appointment with Professor Ma Kan-wen, originally from Beijing, but for years now at Wellcome. We agreed on plans for the spring conference that would take place in Beijing next year, and it was a pleasure to learn from the modesty and wisdom so typical of Chinese people, which Professor Ma radiated. The following days flew by while I searched for William Bagg's portrait and literature essential for the book *Skin in Water Colours in preparation*. With a kind help of Dr. Anthony Griffiths, Honorary Librarian of the Royal Society of Medicine, I saw water colors on skin conditions painted and signed by Thomas Bateman (1778-1821), Robert Willan's pupil and follower. Willan was, by the way, elected "dermatologist of the millennium" on February 23, 1999, at a session of the Royal Society of Medicine on account of his eminent merits for dermatology. The Royal Society of Medicine has developed over many decades into a famous institution with thousands of Fellows. It has many sections, a vast library, and a photography section. Eager to look into the wealthy British medical tradition, I also paid a visit to the Medical Society of London founded by Fothergill and Lettsom in 1773. I recalled that this society was a particular favorite of Lord Lister, as it was shown by his bequest to them of the pick of his medical library, as well as his oration on the value of antiseptic treatment of wounds delivered in 1891. An amazing place to visit, indeed.

On serendipity and the neo-Gothic castle in Strawberry Hill

On Sunday I made a research break and took a train to Strawberry Hill. It was a chilly gray day and it started raining when I arrived to the outskirts of London in Twickenham. A small but extraordinary castle in neo-Gothic style was redesigned later by Horace Walpole (1717-1797), 4th Earl of Orford. The

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moment I entered the caste filled with art, curiosities, rare books, and the Yale edition of Walpole's 10,000 letters, my exasperation for picking such a lousy day for a trip immediately disappeared. Never had the neo-Gothic style in architecture been so thoroughly revived as at Strawberry Hill, but for me to be in the place where the concept of *serendipity* was born 250 years ago had also an additional importance. As I would write later in the commentary for the *Journal of Investigative Dermatology* together with my coauthor and mentor, serendipity is a synthetic capacity, which is not based on science alone and perhaps we can see it as a symbol of a process not fully perceptible, yet. Louis Pasteur had written that chance favors the prepared mind and I must admit that within the mystery walls of the Gothic castle this thought seemed even more convincing. I felt like being in a timeless space intertwined with magic, imagination, reality, art, and science. Suddenly or serendipitously, it became more clear to me. Not only problem-based learning will get us closer to new discoveries. We need much more than that! We need the whole world in all its glistening magic in our minds.

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The world is waiting, sretan vam put !

stella@hazu.hr

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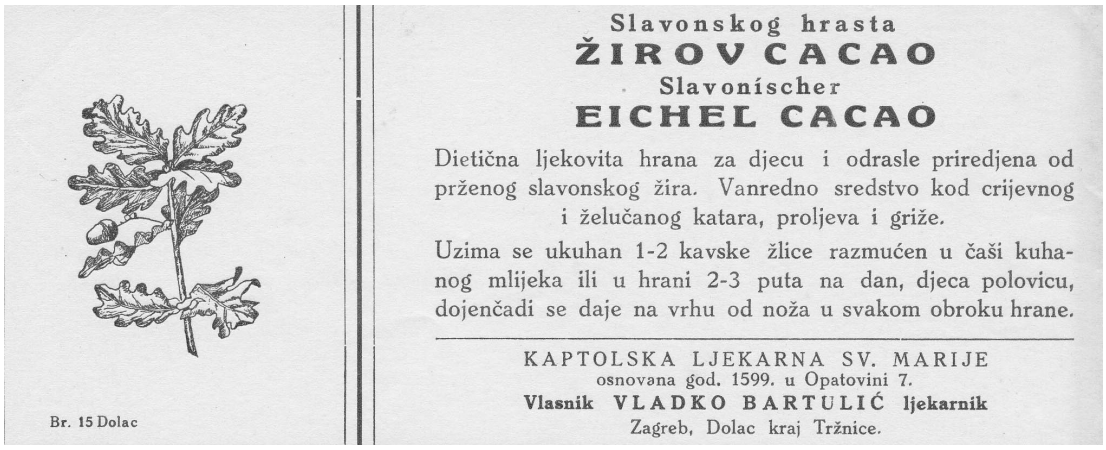

Acorn cacao – healing diet for children and adults against diarrhea.
From the collection of Assist. Prof. Stella Fatović-Ferenčić, MD, PhD.

Dear Editor,

As the member of the Editorial Board and a fellow editor from a larger journal, I follow the life of the *Acta Dermatovenerologica Croatica* with great interest and sympathy. I was most delighted to witness the inclusion of the journal into MEDLINE bibliographic database – it was a well-deserved international acknowledgment I. Of course, the inclusion in MEDLINE is not the ultimate goal, it is a stimulation to keep up the quality of the journal. A very important step in this direction is the new layout of the journal, which makes it modern, engaging, clear, and easy to read.

What advice can I give you as the member of the Editorial Board for the future? I wanted to give an evidence-based answer, so I looked at the issues published this year. I came up with rather disturbing data. In the first 2003 issue, the journal devoted 40 pages to articles, but there was only a single original scientific article (out of 7 published, including the editorial). More than 40% of the journal pages (29 pages) were devoted to the information on meetings, meeting abstracts, news, columns, and instructions for authors. In the second issue, the there were even more pages dedicated to non-scientific contributions: 18 pages were given to articles, including a single (short) original scientific article (out of 4 published); whereas 35 pages (more than 60%) contained information on meetings, meeting abstracts, news, columns, and instruction for authors. In the last issue, there were 40 pages for articles, featuring again a single original scientific article (out of 6 published), and 20 pages for information on meetings, obituaries, news, columns, and instructions for authors.

These data clearly suggest that the *ADC* needs to publish more reports on original scientific research if it wants to keep its quality and increase international visibility and recognition. If not, it would turn into a local bulletin (and is actually not far from it, considering the number of pages devoted to reports from meetings!).

I also have to object to publishing articles with clear commercial orientation, such as the review on naphthalan in the last issue (Vržogić P, Ostrogović Z, Alajbeg A. Naphthalan - a natural medicinal product. Acta Dermatovenerol Croat. 2003;11(3): 178-84). It was written by the employees of the Naphthalan Special Hospital and promoted the use of this medicinal agent. Publishing an original scientific research on a potentially beneficial agent (Vržogić P, Jakić-Razumović J, Pašić A. Effect of naphthalan on epidermal proliferation activity ad CD3, CD4, ad CD8 lymphocyte count. Acta Dermatovenerol Croat. 2003;11(2):65-69), is very appropriate, but objective and neutral reviewer(s) would have added to the quality of the review on this topic. Also, at this stage of knowledge about naphthalan (the authors of the review cited many clinical studies on this potential medicinal agent), one would expect to see reports of clinical (randomized, double-blind) trials and not only descriptions of case series!

So, with congratulations for the job well done and with best wishes for the coming year, I advise the editors to work even more on attracting high-quality research articles – *ADC* inclusion in MEDLINE database is a definite incentive for potential authors!

With best wishes,

Ana Marušić, MD, PhD

Professor of Anatomy,

Zagreb University School of Medicine

Editor in Chief, *Croatian Medical Journal*

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Letter to the Editor

To the ADC Editorial Office:

"The ADC really looks terrific and I enjoy looking at it!"

Jeffrey D. Bernhard, MD

Editor of the Journal of the
American Academy of Dermatology

Comment of the ADC Editorial Office:

"It is pleasure to get such opinion of the great Editor of the most prestige dermatological journal in the world! We hope, in the future, to get "Letter to the Editor" from Jeffrey D. Bernhard.

Figure 1. Prof . J. Lipozenčić, Prof. J. Bernhard, Assist. Prof. S. Fatović-Ferenčić, (from the left), Malta, March 26, 2003

ANNOUNCEMENTS

4th Congress of Slovak Society of Aesthetic and Cosmetic Dermatology with International Participation - Dermaparty 2003, December 5-6, 2003, Hotel Carlton, Bratislava, Slovakia. Contact: *progresswbb@dodo.sk*

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; *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.

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

2nd EADV International Spring Symposium, Budapest, Hungary, April 29-May 1, 2004. Contact: info@eadvbudapest2004.com; *www.eadvbudapest2004.com*

31st Annual Joint Meeting of Society for Cutaneous Ultrastructure Research and European Society for Dermatopathology, Rome, Italy, May 6-8, 2004. Contact: Assist. Prof. Friedrich Breier, *brf@der.kh1.magwien.gv.at*

9th International Congress of Dermatology, Beijing, China, May 19-22, 2004. Contact: ICD2004 Secretariat, International Department, Chinese Medical Association, 42 Dongsi Xidajie, Beijing 100710, China; *ICD2004@chinamed.com.cn*; *www.chinamed.com.cn/dermatology*

International Symposium "Frontiers in Allergy and Autoimmunity", Mainz, Germany, May 21-22, 2004. Contact: *Anja.Oberlaender@uni-mainz.de*

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*

7th Congress of the European Society of Contact Dermatitis, Copenhagen, Denmark, June 6-8, 2004. Contact: Liss@ics.dk; *www.iscd2004.info*

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; *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; *info@congresscare.com*, *www.congresscare.com*

10th 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*

19th Continuing Medical Education Course for Practical Dermatology and Venerology, Munich, Germany, July 25-30, 2004. Contact: *www.fortbildungswoche.de*

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

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

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

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

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

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*

Spring Symposium of the European Academy of Dermatology and Venerology, Sofia, Bulgaria, 2005. Contact: Bulgarian Dermatological Society; *dermven@bg.com*

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

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

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

IV IACD (International Academy of Cosmetic Dermatology) World Congress, Paris, France, July 3-5, 2005. Contact: iacd2005@mci-group.com; *www.iacd-paris2005.com*

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

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

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