REVIEW ARTICLE

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Topical Use of Dexpanthenol in Skin Disorders

Fritz Ebner,[1] *Andreas Heller,*[2] *Frank Rippke*[2] and *Irene Tausch*[3]

1 Technical University of Munich, Allershausen, Germany
2 Beiersdorf AG, Hamburg, Germany
3 Daily Care Clinic, Preetz, Germany

Contents

Abstract

Pantothenic acid is essential to normal epithelial function. It is a component of coenzyme A, which serves as a cofactor for a variety of enzyme-catalyzed reactions that are important in the metabolism of carbohydrates, fatty acids, proteins, gluconeogenesis, sterols, steroid hormones, and porphyrins. The topical use of dexpanthenol, the stable alcoholic analog of pantothenic acid, is based on good skin penetration and high local concentrations of dexpanthenol when administered in an adequate vehicle, such as water-in-oil emulsions. Topical dexpanthenol acts like a moisturizer, improving stratum corneum hydration, reducing transepidermal water loss and maintaining skin softness and elasticity. Activation of fibroblast proliferation, which is of relevance in wound healing, has been observed both *in vitro* and *in vivo* with dexpanthenol. Accelerated re-epithelization in wound healing, monitored by means of the transepidermal water loss as an indicator of the intact epidermal barrier function, has also been seen. Dexpanthenol has been shown to have an anti-inflammatory effect on experimental ultraviolet-induced erythema.

Beneficial effects of dexpanthenol have been observed in patients who have undergone skin transplantation or scar treatment, or therapy for burn injuries and different dermatoses. The stimulation of epithelization, granulation and mitigation of itching were the most prominent effects of formulations containing dexpanthenol. In double-blind placebo-controlled clinical trials, dexpanthenol was evaluated for its efficacy in improving wound healing. Epidermal wounds treated with dexpanthenol emulsion showed a reduction in erythema, and more elastic and solid tissue regeneration. Monitoring of transepidermal water loss showed a significant acceleration of epidermal regeneration as a result of dexpanthenol therapy, as compared with the vehicle. In an irritation model, pretreatment with dexpanthenol cream resulted in significantly less damage to the stratum corneum barrier, compared with no pretreatment. Adjuvant skin care with dexpanthenol considerably improved the symptoms of skin irritation, such as dryness of the skin, roughness, scaling, pruritus, erythema, erosion/fissures, over 3 to 4 weeks. Usually, the topical administration of dexpanthenol preparations is well tolerated, with minimal risk of skin irritancy or sensitization.

Dexpanthenol (CAS No. 81-13-0) is an alcoholic analog of pantothenic acid, a member of the B complex vitamins (vitamin B_5).[1,2] Dexpanthenol is enzymatically oxidized to pantothenic acid, which is distributed into the tissues, mainly as coenzyme A. Pantothenic acid is optically active, only the dextrorotatory isomer has biologic activity. Dexpanthenol is freely soluble in water and alcohol, practically insoluble in fats, and it is the most stable form of pantothenic acid in liquids. Dexpanthenol is used topically as an ointment, emulsion, or solution, at concentrations of 2 to 5%, as an adjunct in the treatment of various skin and mucosal lesions. Topical formulations marketed in Europe usually contain 5% concentration, US Food and Drug Administration–approved dexpanthenol preparations, for topical use to relieve itching or promote healing of various dermatoses, contain 2% dexpanthenol. In addition to the use of dexpanthenol in topical formulations, dexpanthenol can be administered systemically; 250 to 500mg of dexpanthenol has been given to adults.

Clinical investigations have highlighted the beneficial use of dexpanthenol preparations in the treatment of various pathological conditions. This review discusses the uses of topical dexpanthenol in the treatment of skin conditions; there are a number of other indications for which dexpanthenol is also marketed, in particular:

- For topical use as an adjuvant in corneal or conjunctival lesions of the eye, or in mucosal lesions of the nose
- For systemic use in postoperative enteroparesis
- In the burning feet syndrome
- The vitamin is included in multivitamin preparations, and in enteral and parenteral alimentation.

Although pantothenic acid is essential as a nutrient, the daily requirement is not known in detail. Accordingly, the recommendations of the Committee on Dietary Allowances are provisional, indicating a range of intakes. For adults, this is 4 to 7mg daily. In view of the widespread distribution of pantothenic acid, deficiency is unlikely to occur.[3] Dietary deficiency of pantothenic acid has not been clinically identified in humans, except in association with other deficiency states. The symptoms of experimental pantothenic acid–deficiency were somnolence, fatigue, headache, paresthesia of the hands and feet followed by hyperreflexia and muscular weakness, cardiovascular instability, gastrointestinal complaints, changes in disposition, and increased susceptibility to infections. Infertility, spontaneous abortion, neonatal death, growth retardation, adrenocortical dysfunction, sudden death, and abnormal skin were also observed.[1,4]

1. The Physiological Basis of Pantothenic Acid Activity

Elucidation of the biochemical function for the vitamin began in 1947 when Lipmann and co-workers showed that the acetylation of sulfanilamide required a cofactor that contained pantothenic acid. Pantothenic acid has no specific effects when it is administered to animals or healthy human beings.[1] According to standard textbooks, pantothenic acid is a component of coenzyme A, which serves as a cofactor for enzyme-catalyzed reactions, such as transfer of acetyl groups; fragments of various lengths react with the sulfhydryl group of coenzyme A. These reactions are important in the metabolism of carbohydrates, gluconeogenesis, degradation of fatty acids, as well as in the synthesis of sterols, steroid hormones, or porphyrins. As a component of the acyl carrier protein, pantothenate is involved in fatty acid synthesis. Coenzyme A also participates in the modification of proteins, such as N-terminal acetylation, acetylation of internal amino acids, and fatty acid acylation, thereby influencing the localization, stability, or activity of the proteins. Coenzyme A is not transported across cell membranes, however pantothenic acid is.[5] Special attention is paid to pantothenic acid within the frame of biosynthesis of acetylcholine, as the final step in the synthesis of acetylcholine involves the transfer of an acetyl group from acetylcoenzyme A to choline. Decrease in acetylcholine content would result in decreased peristalsis.

2. Dermatological Effects

Pantothenic acid appears to be essential to normal epithelial function, subsequent to its role in metabolic processes. Several aspects of the topical activity of dexpanthenol have been studied as outlined in the following.

Topical dexpanthenol acts like a moisturizer, maintaining skin softness and elasticity.[4,6] This activity may be based on the hygroscopic properties of dexpanthenol. Dexpanthenol in skincare products may also act as a humectant, but its exact mechanism of action is not yet fully understood.[7] In a randomized, double-blind, placebo-controlled study the effect of topical dexpanthenol, formulated in two different lipophilic vehicles, on the epidermal barrier function was studied *in vivo*.[8] Treatment with dexpanthenol for 7 days improved stratum corneum hydration and reduced transepidermal water loss. The active treatment was different from the vehicle control on both measures.

Dexpanthenol is added to various cosmetic products, e.g. after-sun formulations and preparations for baby care, for its anti-inflammatory activity.[9] However, the results of experimental and clinical studies are ambiguous; 4.2% panthenol ointment had

no protective efficacy on the formation and development of inflammation, subsequent to ultraviolet (UV) radiation,[10] and dexpanthenol cream had no beneficial effect during radiotherapy.[11] By contrast, dexpanthenol-loaded nano-sized particles were significantly superior to placebo, with regard to the anti-inflammatory effect on experimental UV-induced erythema in a dose-dependent manner (5% = 0.5% > 0.05% dexpanthenol).[12] Anti-inflammatory effects on UV erythema in the guinea pig were also proven, using a heparin-allantoin-dexpanthenol ointment.[13]

Proliferation of fibroblasts is an important factor in wound healing; activation of fibroblast proliferation was observed both *in vitro* and *in vivo*.[14,15] *In vitro* experiments with dexpanthenol have demonstrated proliferation of human fibroblasts. This effect may correlate with an improvement of the firmness of aponeurotic membrane.[16] The influence of dexpanthenol ointment (0.5 to 10%) on human gingival fibroblasts *in vitro* has been described.[14] The mitotic index increased at all concentrations tested, however, the most prominent effect was obtained at the lowest concentration (0.5%); the highest concentration of the ointment exerted the lowest effect. The addition of dexpanthenol ointment had no effects on the cell morphology *in vitro*. However, several other *in vitro* studies on human fibroblasts have demonstrated that the incubation of the cultures with pantothenic acid, or its derivatives, enhances proliferation, cell migration, attachment of fibroblasts, and collagen synthesis.[4,5]

In murine fibroblast cell–cultures, dexpanthenol showed wound-healing activity by activating fibroblast cells and exerting cytoprotective activity, as measured by the total number of cells, cells in mitosis, the percentages of fusiform, polygonal, round, and vacuole-containing cells and the number of intracellular collagen granules.[17] An *in vivo* study in a suction-blister model demonstrated that emulsions containing 5% dexpanthenol accelerated wound healing.[18] The results were obtained by adding dexpanthenol to different vehicles which have an intrinsic effect on wound healing, and by comparing the healing rate of the formulation, with and without dexpanthenol. An acceleration of wound-healing by dexpanthenol was documented (5% dexpanthenol by a factor of 1.52 *vs* the vehicle).[18] Another study, conducted in rabbits, demonstrated that pre- and postoperative treatment with pantothenic acid increased the fibroblast content of the scar tissue, and also increased aponeurotic resistance.[5]

Several further *in vivo* experiments demonstrated the acceleration of wound healing by dexpanthenol. Panthenol sticks (5 to 10% dexpanthenol) containing 15% glycerol and panthenol ointment (5% dexpanthenol), proved to be effective in stimulating wound-healing in rats following the production of lesions using concentrated HCl acid.[15] Similarly, improved healing was also found in mucosa, e.g. in the event of gastric ulcer.[19] The topical administration of dexpanthenol to injured horse or guinea-pig skin stimulated cell mitosis.[4] It appears that the topical administration of dexpanthenol (5.4% emulsion) after burn injuries in guinea pigs not only improved re-epithelialization, but may also have prevented the loss of water.[4]

3. Absorption

In contrast to pantothenic acid, dexpanthenol is well absorbed through the skin and is rapidly converted to pantothenic acid. Absorption of dexpanthenol after its topical administration was shown in experiments using [^{3}H]-labeled dexpanthenol.[4,19] The concentration of pantothenic acid ranged between 3 and 9 µg/g of fresh tissue in the control rats; it was increased, up to 40 µg/g of tissue, after repeated administration of 20mg dexpanthenol. Percutaneous absorption of [^{3}H]-labeled dexpanthenol was studied *in vivo* with excised human skin.[20] Accordingly, dexpanthenol penetrates into the viable epidermis. Reduced absorption was found after administration of dexpanthenol in olive oil, in comparison to the ointment, highlighting the relevance of the vehicle.[20] The role of the penetration properties of dexpanthenol in different vehicles was further evaluated in a perfused skin udder model. Both the rate and extent of penetration was much higher from a water/oil vehicle, than from a oil/water formulation.[21]

Human studies also demonstrated an increased concentration of pantothenic acid in the hair, hair roots, nails and the skin epidermis and corium, after topical administration.[4,20]

4. Clinical Experience

Dexpanthenol has been used in the treatment of wounds and in skin care for decades, particularly in Europe.[4,9,13,22-26] According to Eggensperger,[4] the beneficial effects of dexpanthenol have been demonstrated in patients who have undergone skin transplantation or scar treatment, or have been treated for burn injuries or different dermatoses. The stimulation of epithelization, granulation and mitigation of itching were the most prominent effects of dexpanthenol formulations. Other effects, e.g. reduction of local blood-flow, have also been demonstrated. Dexpanthenol ointment has also been shown to be effective in the treatment of diaper dermatitis. Moosmann[25] noted an acceleration of epithelization associated with dexpanthenol therapy in wound healing. The latter may be the reason for the use of dexpanthenol in leg ulcers,[27,28] or anal fissures.[29] More recent studies are detailed in sections 4.1 to 4.3.

4.1 Skin Injury

Dexpanthenol, at concentrations of 2 to 5%, stimulates the regeneration of injured human skin.[5,30,31] The efficacy of dexpanthenol in wound-healing, using a water-in-oil-emulsion, was reported in a double-blind clinical trial.[5] Dexpanthenol was evaluated using ultrasound and histological techniques for its efficacy in improving wound healing in 15 adult male participants. Four standardized epidermal shave wounds were produced in all participants. Three wounds were each treated daily for 5 days with: a water-in-oil emulsion with 5% dexpanthenol, the corresponding emulsion without dexpanthenol, or a first aid cream; the fourth wound served as an untreated control. Erythema, wound closure, wound volume, and viscoelasticity were assessed. The epidermal wounds treated with the dexpanthenol emulsion showed a reduction in erythema and had more elastic and solid tissue regeneration. Histologically, in 10 of the 15 participants, dexpanthenol was effective in stimulating the healing process.

In a further randomized, placebo-controlled, double-blind study, the skin regenerating properties of a topical preparation containing 5% dexpanthenol was tested *in vivo*, employing the human epidermal suction-blister model.[30] Twenty volunteers with healthy skin were included in the study. Dexpanthenol and placebo, as well as a 0.9% saline solution serving as control, were applied under occlusion on the epidermal defects for 5 days. The process of epithelization was monitored via transepidermal water loss (TEWL) over the study period of 6 days. TEWL serves as an indicator of the intact epidermal barrier function. A statistically significant acceleration of the epidermal regeneration was observed for the dexpanthenol preparation, as compared with both placebo ($p < 0.05$) and the untreated control ($p < 0.0004$), see figure 1. These results showed that the tested preparation, containing 5% dexpanthenol, promoted the regeneration of the epidermal barrier, compared with placebo, and that this difference in effect was statistically significant. Skin irritation, or other adverse effects, were not observed throughout the study period. Comparable to the aforementioned study, epidermal regeneration was also observed in the human suction-blister model employing 3% dexpanthenol formulations.[31]

4.2 Irritated Skin

The protective and conditioning properties of a hand care system, consisting of a cleansing oil and an intensive-care cream (water-in-oil emulsion containing 5% dexpanthenol), were evaluated in an irritation model.[32] Sodium lauryl sulfate 2% was used to induce irritation in participants with atopic eczema in a

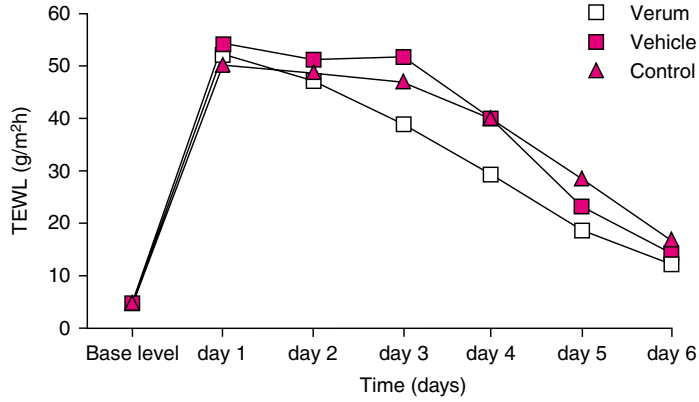

Fig. 1. Epithelial regeneration, as measured by the transepidermal water loss (TEWL), in a suction-blister model under treatment with 5% dexpanthenol cream (pH5 Eucerin®[1] Hand Intensive Care), its vehicle, or 0.9% saline solution (control). Twenty volunteers were treated for 6 days (reprinted from Presto et al.,[30] with permission of Blackwell Wissenschafts-Verlag).

lesion-free interval. Pretreatment with the cream resulted in significantly less damage to the stratum corneum barrier, compared with no pretreatment (TEWL: $p < 0.0056$; pH values: $p < 0.001$), see figure 2. Significantly fewer severe skin reactions were observed in the pretreated areas ($p < 0.04$). 37 patients with mild-to-moderately severe atopic hand eczema used the hand care system over a period of 3 weeks. Four patients dropped out: two patients discontinued the study in the first week due to a general worsening of skin condition; one patient discontinued the study due to a worsening condition, only in the area of the hand; and one patient dropped out for personal reasons. In 33 of 37 patients the exclusive use of the hand care system over a treatment period of 3 weeks was sufficient as a treatment of hand eczema. In 24 patients an improvement in the hands was seen, and in another nine patients the skin condition was stabilized. Using corneometry, a significant and lasting increase in skin moisture was noted on day 8 ($p < 0.0001$). Positive ratings of skin-care properties and dermal tolerability were noted by approximately 90% of the patients.

Medical professionals are at a high risk of irritant or allergic contact dermatitis. Rippke et al.[33] investigated the degree of skin-stress in 262 healthcare professionals, and the prevalence of their skin disorders. Furthermore, the efficacy, skin compatibility and application properties of the hand-care system mentioned above were investigated in a practical use setting. The occupational skin-stress was rated as being severe in nearly 38% of all medical professionals. Many (31.3%) of the participants had severely dry skin, while 17% reported dermatological diseases, par-

1 Use of tradenames is for product identification only and does not imply endorsement.

ticularly of the hands. The xerotic or eczematous symptoms present at the start of the investigation showed a highly significant improvement after 3 to 4 weeks of use, and 79% of participants rated their skin condition as improved or normalized at the final visit. Skin tolerability proved to be good or very good in 95% of cases, and the cosmetic properties were also mostly judged as good or very good.

In a multicenter study, 483 patients requiring adjuvant skin care received dexpanthenol in topical formulations.[34] Most patients had atopic dermatitis (41.8%), ichthyosis (19.7%), psoriasis (9.3%), or contact dermatitis (9.3%). All symptoms (dryness of the skin, roughness, scaling, pruritus, erythema, erosion/fissure) improved considerably over 3 to 4 weeks, see figure 3. All symptoms improved by >80%, in the case of dryness of the skin and desquamation, improvement was as high as >90%. Local irritation was observed in 1.9% of the cases only, and the cosmetic properties of the dexpanthenol formulations were rated as good or very good by >90% of the patients.

4.3 Other Indications

Beneficial effects of topical formulations containing dexpanthenol were reported in the daily care of scars, following burns and skin transplantation.[35] Improvement of scar quality after different skin lesions, was also found in clinical trials with topical long-term administration of formulations containing heparin, allantoin collagen and dexpanthenol.[36]

Dexpanthenol is a component of topical preparations for the treatment of sports injuries and venous diseases. Dexpanthenol is also added for an improved percutaneous absorption of other active ingredients (carrier-function).[37] Comparatively good results were obtained in clinical trials with the use of dexpanthenol-containing topical preparations, in combination with heparin.[24,38,39]

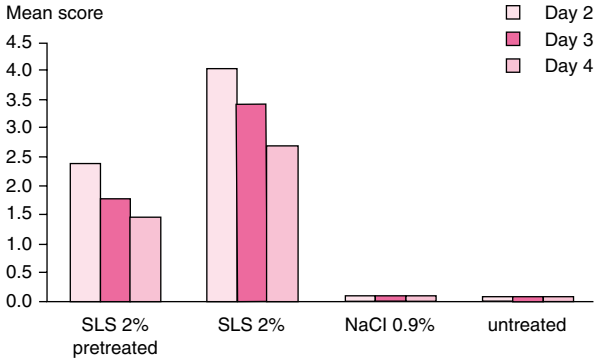

Fig. 2. Visual assessment of skin reaction after irritation with 2% sodium lauryl sulfate (SLS) or 0.9% saline solution (NaCl 0.9%; control) with, or without, pretreatment with 5% dexpanthenol cream (pH5 Eucerin® Hand Intensive Care), or no treatment in 19 participants on days 2 to 4. Erythema scores were measured on a 6-point scale: 0 = negative; 1 = slight, diffuse or partial; 2 = marked, sharply delimited; 3 = severe without infiltrate; 4 = severe with infiltrate; 5 = severe with infiltrate and vesiculation or epidermal defects, (reprinted from Bielfeldt et al.,[32] with permission of ECV Editio Cantor Verlag).

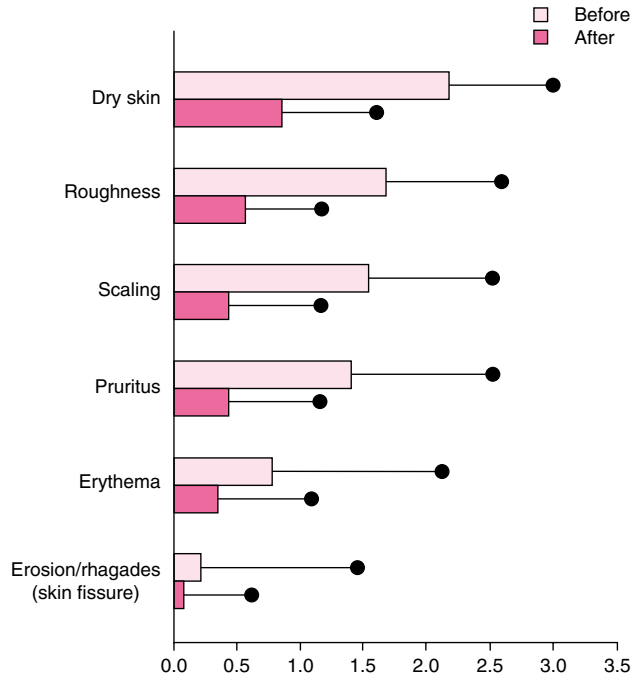

Fig. 3. Improvement of symptoms under the adjuvant treatment with 3% dexpanthenol preparations (pH5 Eucerin® Creams and Lotions) in a group of 483 patients. Symptom scores were measured on a 5-point scale: 0 = negative; 1 = slight, diffuse or partial; 2 = marked, sharply delimited; 3 = severe without infiltrate; 4 = severe with infiltrate, (reprinted from Bahmer et al.,[34] with permission of Urban & Vogel Medien und Medizin Verlagsgesellschaft).

A pilot study in five elderly women with aging skin, using oil-in-water emulsion of retinol (vitamin A), tocopherol (vitamin E), urea and panthenol, showed significant clinical and histological improvement of the treated skin areas.[40]

Positive clinical experience was reported after the treatment of dry eyes with dexpanthenol (30 mg/ml),[41] and after the treatment of corneal erosions with 5% panthenol eye ointment, or panthenol ophthalmic gel.[42]

5. Safety

In general, dexpanthenol may be classified as atoxic.[19] Nevertheless, adverse reactions have been reported in single cases. Allergic or irritative reactions to dexpanthenol have been seen.[43-51] A single case of contact urticaria from panthenol, and a case of hand eczema as a result of ingestion of oral pantothenic acid, in a patient sensitized to dexpanthenol, have been reported.[52] Dexpanthenol is mentioned among the agents potentially involved in type IV-allergy reactions associated with formulations intended

for ocular therapy.[53] Positive reaction to dexpanthenol on patch testing supported this conclusion. Additional indication for this was found in lymphocyte-transformation tests, using dexpanthenol-modified microsomes.[44] Altogether, regarding the widespread use of dexpanthenol, contact allergy to dexpanthenol appears to be very rare.[48] The Code of Federal Regulations regarded dexpanthenol as a substance generally recognized as safe (GRAS status).[23]

6. Conclusion

The available evidence supports the efficacy and excellent safety profile of dexpanthenol when administered topically in a variety of dermatological disorders. These include: skin abrasions, petty injuries, chronic ulcers, decubital ulcers, anal fissures, skin transplantation, nonsevere burns, diaper dermatitis, epithelial lesions and the prevention and treatment of breast fissures or skin irritations.

Recent evidence documents the efficacy of dexpanthenol in experimental models of skin injuries, such as the suction-blister model where improved and accelerated wound healing was observed.[5,30] TEWL, a highly selective and noninvasive parameter of re-epithelization,[54] has been found to be significantly affected by dexpanthenol, indicating dexpanthenol is effective in stimulating wound healing. Similar to the beneficial effect on skin regeneration, the local use of dexpanthenol was highly effective in the treatment or prevention of skin irritancy.[32-34]

The effects of dexpanthenol are considered to be of clinical relevance, both in the treatment and prevention of these dermatological disorders that have been shown to be accessible to treatment. The short-term results in wound healing, and the long-term efficacy in the treatment or prevention of skin irritancy, suggest the clinical value of this therapeutic approach.**2**

Acknowledgments

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2 After this paper had been accepted for publication two further studies which may be of interest in the present context came to our knowledge.[55,56] In an evaluation of oil-in-water emulsions containing dexpanthenol (0, 2, 5%) on skin hydration and pH for 4 weeks the concentration-dependent moisturizing potential of the vitamin was demonstrated.[55] Likewise, a hydrophilic emulsion with 0, 2.5 or 5% dexpanthenol was effective with regard to hydration and anti-inflammatory efficacy in the repetitive washing test.[56]

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Correspondence and offprints: Dr *Fritz Ebner*, Abt-Joseph-Str.2, Allershausen, D-85391 Germany.
E-mail: fritz.ebner@t-online.de