

Azelaic Acid Bibliography

1978 - 2004

Table of contents

1.	CLINICAL SECTION	3
1.1	Acne	3
1.1.1	Clinical studies and reviews on Azelaic acid	3
1.1.2	General reviews on acne-therapy including Azelaic acid	10
1.2	Rosacea	23
1.2.1	Clinical studies and reviews on Azelaic acid	23
1.2.2	General reviews on rosacea-therapy including Azelaic acid	26
1.3	Pigmentation disorders	27
2.	PHARMACOLOGY AND PHARMACOKINETICS	37
2.1	Pharmacology and mechanism of action	37
2.1.1	Acne and rosacea	37
2.1.2	Pigmentation and tumor cells	46
2.2	Kinetics and metabolism	52
3.	CHEMISTRY	57
4.	MISCELLANEOUS	58

The references are listed by topics and the time of publication. Abstracts are added, if available.

1. Clinical Section

1.1 Acne

1.1.1 Clinical studies and reviews on Azelaic acid

Draelos Z D. What's in a Formulation?. Cosmetic Dermatology, 2003, Vol/Iss/Pg. 16/11 (56-58)

In dermatology, we tend to focus more on the active ingredient than the formulation, because we think, "a cream is a cream and a gel is a gel." This may not necessarily be the case. Often, the active ingredient is only part of the true value of a topical medication. The vehicle may account for 50% to 75% of the ability of the topical to achieve efficacy. Remember, the formulation is the key to efficacy.

Shemer A, Weiss G, Amichai B, Kaplan B, Trau H. Azelic acid (20%) cream in the treatment of acne vulgaris (6). Journal of the European Academy of Dermatology and Venereology, 2002, Vol/Iss/Pg. 16/2 (178-179)

Juettner C, (Juttner C). Behandlung mit Minocyclin plus Azelainsaeure bei schwerer rezidivierender Acne papulopustulosa. Haut 12, 1: 12-13 (2001)

Rulcova J TI: Azelaic acid in the treatment of acne vulgaris TT: AZELAINOVA KYSELINA V LECBE ACNE VULGARIS. Cesko-Slovenska Dermatologie 76, 1: 21-24 (2001)

The author summarizes pharmacological and therapeutic properties of natural azelaic acid, which is a C9-dicarboxylic acid (HOOC-(CH₂)₇-COOH). It was first used in hyperpigmentation as it suppresses the action of tyrosinase and other oxidoreductases in mitochondria of active melanocytes. During this treatment accidentally a positive effect also in concurrent acneous lesions was found. Multiple studies of patients with different types of acne confirmed this therapeutic effect. Azelaic acid in a 20% concentration is the active substance in Skinoren cream. By its local application for 3 - 6 months important pharmacological properties were confirmed, i.e. its comedolytic, antibacterial and anti-inflammatory effect. Microscopic and electronoptic examination of the epidermis revealed a reduction of the number and size of keratohyaline granules and bundles of tonofilaments in the stratum corneum and weakening of the corneal layer in the region of the acroinfundibulum. By selective action on protein synthesis of keratinocytes azelaic acid reduces filagrin synthesis and thus acts against the impaired cornification. Inhibited growth of aerobic and anaerobic microbes is due to suppression of bacterial protein synthesis by azelaic acid which leads to antibacterial action - primarily bactericidal action. After two months of Skinoren application the intrafollicular growth of *Propionibacterium acnes* is reduced by 97.7% and of *Staphylococcus epidermidis* by 99%. Another favourable property of azelaic acid is that it does not produce resistance of these bacteria. In addition to an anti-inflammatory effect via elimination of bacteria azelaic acid suppresses the inflammation also directly by inhibiting the formation of reactive forms of oxygen which when released into tissue exerts an inflammatory action. Skinoren is effective monotherapy in acne comedonica and acne papulopustulosa grade I and II. In serious forms of acne (acne papulopustulosa grade III and IV and acne conglobata) it is an important supplementary factor of systemic treatment with antibiotics, antiandrogens and isotretinoin. Positive factors include good tolerance of the drug, safety, the possibility of long-term administration without toxicity or cumulation of the drug in the organism, a zero risk during pregnancy and lactation. No teratogenic and mutagenic effects are known. If necessary, Skinoren can be combined with other locally and systematically administered drugs.

Webster G TI: Combination azelaic acid therapy for acne vulgaris Journal of the American Academy of Dermatology 2000 43: 47-50

Ozkan M, Durmaz G, Sabuncu I, Saracoglu N, Akgun Y, Urer S M TI: Clinical efficacy of topical clindamycin phosphate and azelaic acid on acne vulgaris and emergence of resistant coagulase-negative staphylococci. Turkish Journal of Medical Sciences, 2000, Vol/Iss/Pg. 30/5 (483-487)

In this study, the uses of topical clindamycin phosphate and azelaic acid were compared from point of clinical efficacy and emergence of resistant coagulase-negative staphylococci (CNS). Each group contained 20 patients. Pre- and post-treatment acne grades and comparison of two groups were evaluated by using the Wilcoxon and Spearman statistical techniques. The sensitivity of CNS to azelaic acid and to clindamycin phosphate were searched by microbroth dilution technique. Azelaic acid was found more effective in reducing acne grade. Eleven CNS strains were found resistant to clindamycin phosphate before treatment. After 8 weeks of therapy with topical clindamycin phosphate 18 of 20 CNS strains were resistant to this agent. No difference was detected for the MIC (minimal inhibitory concentration) values of CNS before and after topical azelaic acid treatment.

Das neue 3-S-Therapiekonzept. Mit drei Komponenten vereint gegen Akne Haut 11, 3: 106-107 (2000)

Rulcova J TI: Results of treatment with azelaic acid as monotherapy and in combination with acnetherapeutic agents in patients with acne vulgaris TT: VYSLEDKY LECBY AZELAINOVOU KYSELINOU V MONOTERAPII A V KOMBINACI S AKNETERAPEUTIKY U PACIENTU S ACNE VULGARIS Cesko-Slovenska Dermatologie, 2000, Vol/Iss/Pg. 75/6 (274-279)

The authors evaluated in a group of 106 patients (47 women and 59 men, mean age 26 years) with different types of acne (acne comedonica, acne papulopustulosa grade I-IV and acne conglobata) the results of therapy with azelaic acid (Skinoren cream) used as monotherapy or in combination with other drugs for external use or systemic drugs. The type of selected therapy in different subjects depended on the extent and severity of the disease. After 3 and 6 months the number of non-inflammatory and inflammatory lesions was assessed, and based on the results, recovery, partial improvement or no improvement were evaluated. The results are presented in tables and graphs. In the group of 22 patients with acne comedonica and acne papulopustulosa grade I and II treated by Skinoren cream in the course of 6-month therapy 77% patients recovered, partial improvement was recorded in 18 % patients, one patient (5%) did not improved. Combined therapy with azelaic acid (Skinoren cream and tretinoin (Retin A 0.05% cream) was used in 7 patients. 21 patients were treated with Skinoren cream) and Eclaran 5% gel (benzoyl peroxide). To a group of 29 patients a combination of Skinoren cream and Zineryt solution was administered (4% erythromycin with 1.2% zinc acetate). In patients with very severe and severe types of acne (acne papulopustulosa grade III and IV and acne conglobata) combined treatment with Skinoren cream and a systemic drug was used. Eleven female patients of the group took a hormonal antiandrogenic preparation, Diane-35 tablets and 16 female patients had treatment with Roaccutan capsules (isoretinoin).

Pierard G E, Arrese J E, Claessens N, Greimers R, Pierard Franchimont C, Bacterial resistances during anti-acne antibiotherapy. How to abate the risk Revue Medicale de Liege {REV-MED-LIEGE}, 1999, 54: 100-104

The treatment of moderate to severe acne often relies on antibiotherapy in order to eradicate as much as possible microorganisms such as Propionibacterium spp colonizing the sebaceous follicles. In recent years, bacterial resistances against specific antibiotics have emerged. Both the antibiotic and its administration modalities must be considered in order to control the risk. With regard to this conundrum, minocycline is a medication of choice among the diverse anti-acneic therapies.

Spellman MC, Pincus SH. Efficacy and safety of azelaic acid and glycolic acid combination therapy compared with tretinoin therapy for acne. Clin Ther. 1998 Jul-Aug;20(4):711-21.

We conducted a 12-week, multicenter, randomized, double-masked, parallel-group study of the efficacy, safety, and tolerability of azelaic acid 20% cream and glycolic acid lotion compared with tretinoin 0.025% cream and a vehicle lotion to treat mild-to-moderate facial acne vulgaris. Patients treated with azelaic/glycolic acid experienced a significantly greater reduction in the number of papules, as well as a greater reduction in the number of inflammatory lesions, than those treated with tretinoin. Overall global improvement was approximately 25% in both groups. In the physician evaluations, treatment with azelaic/glycolic acid was found to cause significantly less dryness, scaling, and erythema than tretinoin.

Patients also reported significantly less dryness, redness, and peeling with azelaic/glycolic acid. Significantly more patients in the azelaic/glycolic acid group than the tretinoin group reported that they felt attractive. The combination of azelaic acid and glycolic acid is a useful alternative to tretinoin, being at least as efficacious as the latter, while offering a superior tolerability and patient approval profile.

Samtsov A V, Shimanovsky N L TI: The use of Skinoren for the treatment of acne vulgaris, Vestnik-Dermatologii-i-Venerologii, 1998, 0: 39-41

The aim of this study was to assess therapeutic efficiency of Skinoren in patients with acne vulgaris. It is concluded that pathogenetic therapy with this preparation has advantages over other products used for the pharmacotherapy of this pathology.

Gibson JR. Azelaic acid 20% cream (AZELEX) and the medical management of acne vulgaris. Dermatol Nurs. 1997 Oct;9(5):339-44. (Review)

Azelaic acid 20% cream (AZELEX) is a novel anti-acne agent with antimicrobial activity and keratinization-normalizing properties. In acne it is broadly comparable in efficacy to 0.05% tretinoin, 5% benzoyl peroxide, and 2% erythromycin, but is less irritating than tretinoin and benzoyl peroxide.

Aksakal A B, Koruyucu M, Onder M, Oztas M O, Gurer M A TI: A comparative study of metronidazole 1% cream versus azelaic acid 20% cream in the treatment of acne GAZI-MED-J, 1997, 8: 144-147

In acne vulgaris, a variety of therapies with different mechanisms of action are available. This study, which aims to compare the efficacy and skin tolerance of metronidazole cream and azelaic acid (AZA) cream in the treatment of moderate to severe acne, appears to be the first of its kind. Methods: Forty patients with only moderate to severe acne participated in this randomized, comparative study. In this study, according to the Allen Smith Scale, 15 patients were grade 8; 11 patients grade 6; and 14 patients were grade 4 acne. Twenty of them were treated with the AZA 20% cream and the other twenty patients were treated with the metronidazole cream 1% for three months. Results: The results of this study showed that the AZA cream is more effective than the metronidazole cream in reducing counts of inflamed and non-inflamed lesions of acne ($p < 0.001$). Conclusion: In moderate and severe acne, it is a waste of time to use only metronidazole cream topically.

DUNLAP F E, MALONEY J M, LEVY S TI: AN INVESTIGATOR-BLIND, RANDOMIZED STUDY COMPARING A 3-PERCENT ERYTHROMYCIN 5-PERCENT BENZOYL PEROXIDE COMBINATION IN GEL VERSUS 20-PERCENT AZELAIC ACID CREAM IN THE TREATMENT OF ACNE-VULGARIS JOURNAL-OF-INVESTIGATIVE-DERMATOLOGY, 1997, 108: 126,

144 Evaluable patients with acne vulgaris were randomized to topical treatment with 3% erythromycin/5% benzoyl peroxide in a gel vehicle or 20% azelaic acid cream. The results of the study showed significant differences favoring 3% erythromycin/5% benzoyl peroxide over 20% azelaic acid. (conference abstract). 150 Male and female patients (aged 13-30 yr) with acne vulgaris (Grades II or III, Pillsbury classification) were randomized to topical treatment with 3% erythromycin/5% benzoyl peroxide in a gel vehicle or 20% azelaic acid cream applied b.i.d. for 8 wk. On each visit (baseline and wk 2, 4, and 8), the physician counted the number of comedones and inflammatory lesions (papules/pustules). Global evaluations assessing the overall effectiveness of treatment, compared to baseline, were done by the physician at each follow-up. 144 Patients were considered evaluable for efficacy (69 erythromycin /benzoyl peroxide, 65 azelaic acid). The results showed significant differences favoring 3% erythromycin/5% benzoyl peroxide over 20% azelaic acid for the following parameters: 1) reduction in inflammatory lesions (papules/pustules) at each follow-up evaluation (wk 2, 4 and endpoint); 2) reduction in comedones at wk 2 and 4; 3) improvement in overall acne condition at each follow-up evaluation (wk 2, 4 and endpoint), as measured by Physician Global Evaluations. (DAC).

Kakita L S TI: Azelaic acid in the treatment of acne, rosacea, and hyperpigmentary skin diseases TODAY-S-THER-TRENDS, 1997, 14: 251-266

Topical 20% azelaic acid cream (Azelex registered trade mark) is the first new prescription agent to be approved in the past 10 years for the treatment of mild to moderate inflammatory acne vulgaris, and is also

effective in treating rosacea and hyperpigmentary skin disorders. A highly favorable safety and patient tolerability profile, with an incidence of adverse events comparable to vehicle cream alone, gives azelaic acid distinct advantages over many other therapies employed in treating these varied dermatologic conditions. Azelaic acid cream is comparable in antiacne efficacy to topical benzoyl peroxide 5% gel, tretinoin 0.05% cream, erythromycin 2% cream, and oral tetracycline in mild to moderate acne. The lack of adverse effects and absence of drug interactions may make azelaic acid an attractive treatment option for many rosacea patients. In the treatment of melasma and other hyperpigmentary disorders, azelaic acid (unlike hydroquinone) does not depigment normal skin, and in efficacy is superior to 2%, and comparable to 4%, hydroquinone.

Mackrides PS, et al. Azelaic acid therapy for acne. Am Fam Physician. 1996 Dec;54(8):2457-9. (Review)

Azelaic acid is another option for the topical treatment of mild to moderate inflammatory acne vulgaris. It offers effectiveness similar to that of other agents without the systemic side effects of oral antibiotics or the allergic sensitization of topical benzoyl peroxide and with less irritation than tretinoin. Azelaic acid is less expensive than certain other prescription acne preparations, but it is much more expensive than nonprescription benzoyl peroxide preparations. Whether it is safe and effective when used in combination with other agents is not known.

[No authors listed] Azelaic acid-a new topical drug for acne. Med Lett Drugs Ther. 1996 Jun 7;38(976):52-3.

Lowe NJ. New approaches in dermatology: a clinical profile of azelaic acid. Cutis. 1996 Jan;57 (1 Suppl):7.

Graupe K, Cunliffe WJ, Gollnick HP, Zaumseil RP. Efficacy and safety of topical azelaic acid (20 percent cream): an overview of results from European clinical trials and experimental reports. Cutis. 1996 Jan;57(1 Suppl):20-35.

Azelaic acid cream (20 percent) is a new topical treatment for acne with an additional therapeutic potential in rosacea and hyperpigmentation disorders. Azelaic acid (AzA; HOOC-(CH₂)⁷-COOH) is a naturally occurring compound that interferes with acne pathogenesis by virtue of its antikeratinizing, antibacterial, and anti-inflammatory properties. Vehicle-controlled studies have verified that AzA exercises a significant and clinically relevant effect on both non-inflammatory and inflammatory acne lesions. Comparisons with clinically proven therapies have shown that 20 percent AzA cream is an effective monotherapy in mild to moderate forms of acne, with an overall efficacy comparable to that of tretinoin (0.05 percent), benzoyl peroxide (5 percent), and topical erythromycin (2 percent). In the treatment of moderate to severe acne, 20 percent AzA cream may be favorably combined with minocycline (90 percent good and excellent results), and may contribute towards reducing recurrences following discontinuation of systemic therapy (maintenance therapy with AzA cream). Particular advantages of AzA therapy include its favorable safety and side effect profile. It is non-teratogenic, is not associated with systemic adverse events or photodynamic reactions, exhibits excellent local tolerability, and does not induce resistance in *Propionibacterium* acnes.

Gibson JR. Rationale for the development of new topical treatments for acne vulgaris. Cutis. 1996 Jan;57(1 Suppl):13-9.

The development of new topical anti-acne therapies reflects the need for medications that address the requirements and concerns of an increasingly mature and demanding acne patient population. Some of the topical agents currently under investigation in the United States include several alpha-hydroxy acids (AHAs), the retinoids tazarotene and adapalene, and azelaic acid. All of these agents appear to exert their effect on acne through some effect on the process of keratinization and/or the thickness of the stratum corneum. Azelaic acid also has significant antimicrobial activity relevant to its efficacy in acne vulgaris. While azelaic acid has already been used successfully in many parts of the world for several years, the potential roles of the new retinoids in acne therapy are just beginning to be clarified. The properties of

AHAs suggest that they may also be of value in the treatment of acne, but further systematic evaluation is needed.

Farag A, Ananieva L TI: Acne vulgaris: Ultrastructure changes after treatment with 20% azelaic acid. J-DERMATOL-TREAT, 1995, 6: 151-154

Transmission electron microscopy (TEM) was used to clarify the effect of topically applied 20% azelaic acid (AA) on acne vulgaris lesions. Twenty male acne patients were included in this study. A punch biopsy was taken from each patient before treatment and from five of the treated patients. After 2 months of treatment with 20% AA, the pattern of follicular keratinization was markedly altered. In particular, there was a reduced thickness of the horny layer, a mild decrease in tonofilaments and a marked reduction in the number and size of keratohyaline granules. Enlargement of perinuclear rough endoplasmic reticulum (RER) and swollen mitochondria were frequently observed. A reduction in the dermal inflammatory infiltrates was frequently identified. Very few bacteria were detected in the lumen. These findings confirm the antikeratinizing effects of 20% AA on acne vulgaris lesions.

Cunliffe W J. The Clinical Efficacy of Azelaic Acid in the Treatment of Acne. Rev. Contemp. Pharmacother. 1993; 4: 433-439

Azelaic acid, a relatively new treatment for mild-to-moderate acne vulgaris, affects both *P. acnes* population and comedone formation, resulting in a reduction of both inflamed and non-inflamed lesions. Comparative studies clearly show azelaic acid to be better than placebo and similar to standard topical therapies such as retinoic acid which works predominantly against non-inflamed lesions, and benzoyl peroxide and topical erythromycin which are reputed to be more effective on inflamed lesions. The data of a 6-months study showed azelaic acid and oral tetracycline to be of similar efficacy. Not surprisingly, topical azelaic acid is not as effective as oral isotretinoin. The rate of onset of benefit of azelaic acid is gradual, with most studies showing an improvement of the order of 60% in both inflamed and non-inflamed lesions by the end of 6 months treatment. One of the major benefits of azelaic acid relates to its favourable adverse event profile. Most topical therapies for acne produce a significant degree of erythema and irritation and these side effects can be a significant clinical problem; azelaic acid, on the other hand, produces less erythema, scaling and itching than is noted with benzoyl peroxide or topical retinoic acid. A further benefit over certain topical preparations, such as benzoyl peroxide, is that it does not bleach clothes, and in contrast to antibiotics it will not be associated with the development of bacterial resistance. Azelaic acid is a useful addition to the armamentarium of topical therapies for mild-to-moderate acne.

Nguyen QH, et al. Azelaic acid: pharmacokinetic and pharmacodynamic properties and its therapeutic role in hyperpigmentary disorders and acne. Int J Dermatol. 1995 Feb;34(2):75-84.

Berova N, Nikolova A, Kratchanov C, Popova M, Hypoallergic cosmetic emulsion with azelaic acid for prophylaxy and treatment of acne vulgaris Journal of Applied Cosmetology 12,3: 51-55 (1994)

Acne vulgaris with its many clinical forms is the commonest skin disease among young people, which is very resistant and dysmorphicophobic and represents a big problem for the patients as well as for their physicians doctors. The authors produced an hypoallergenic cosmetic emulsion on the base of natural ingredients, without special preservatives: apple pectin as emulgator, sunflower oil and 10% and 20% Azelaic acid. These two different concentrations for two purposes: prophylaxis and therapy. The clinical results from its application in a 100 of patients with different forms of Acne, show a general favorable effect: (90%), 54% very good and 36% good. The distribution of the positive influence in the different forms of Acne is as follows: 100% in Acne comedonica; 65% in Acne papulo-postulosa and 36% in Acne nodulocystica. The tolerability of the emulsion is perfect. The hypoallergic emulsion with Azelaic acid is a new original effective and well tolerated cosmetic product for prophylaxis and treatment of Acne vulgaris, especially for sensitive patients and comedonic and papulo-pustular forms.

[No authors listed] Azelaic acid--a new topical treatment for acne. Drug Ther Bull. 1993 Jun 21;31(13):50-2.

Ortonne JP, Lacour JP. Evaluation de la phototoxicite de l'acide azelaique par la methode de Kaibet et Kligman modifiee. *Nouv Dermatol* 1992; 2: 490-495.

Graupe K, Zaumseil R.P. Skinoren - a new local therapeutic agent for the treatment of acne vulgaris. in : *Jahrbuch der Dermatologie* 1991/92, pp 159-169; Biermann Verlag, FRG

Skinoren is a topical therapeutic agent for treating acne containing 20 % azelaic acid in an O/W-emulsion. Azelaic acid, HOOC-(CH₂)⁷-COOH modulates terminal processes in infundibular keratinization (filaggrin), acts antibacterially against intrafollicular P. acnes (inhibition of protein synthesis), and inhibits the formation of reactive, pro-inflammatory oxygen species in neutrophils and may thus interfere with both the non-inflammatory and inflammatory phase in the pathogenesis of acne. In controlled clinical investigations with >2000 patients Skinoren led to significant reductions not only in the number of comedones (mean: 79 %), papules and pustules (means 79-84 %), but also in the number of nodular lesions. Overall, the clinical efficacy of the azelaic acid cream was comparable to 0.05 % tretinoin in comedonal acne, to 5 % benzoylperoxide and 2% erythromycin in papulopustular acne (grade I-III), and matched oral tetracycline (0.5-1 gld) in papulopustular and nodular types of acne; the rates of good to excellent results ranged from 60-82%. Particular advantages of Skinoren therapy include its broad indication spectrum, the lack of teratogenicity and toxicity, superior local tolerance, lack of systemic adverse reactions, photosensitization and, in addition, the fact that it does not induce bacterial resistance.

Gollnick H.

Azelaic acid for keratinization disorders. *Med Monatsschr Pharm.* 1991 Dec;14(12):370-1.

Fitton A, Goa. Azelaic acid. A review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. *Drugs.* 1991 May;41(5):780-98.

[No authors listed] Azelaic Acid- a new application in acne therapy. Expert's exchange. Berlin, 18-20 January 1991. *Hautarzt.* 1991 Mar;42(3 Suppl):1-8. (German)

Troccoli T, et al. Topical therapeutic action of azelaic acid in polymorphous acne. *G Ital Dermatol Venereol.* 1989 Oct;124(10):485-91. (Italian)

Thirty patients of either sex (23 M, 7 F) ranging in age between 16 and 36 years, affected of acne vulgaris, were given 20% azelaic acid cream over a period of 6 months. The product, very well tolerated, was significantly and substantially effective for all types of acne, especially for the deep lesions, i.e. nodules and cysts. The rates of improvement obtained indicate that azelaic acid can interfere with various aetiopathogenetic process of acne.

Colonna SM. Validity of azelaic acid in the therapy of acne. Long-term clinical results. *G Ital Dermatol Venereol.* 1989 Oct;124(10):479-84. (Italian)

Giannotti B. National and international clinical experiences with azelaic acid cream in the treatment of comedo acne *G Ital Dermatol Venereol.* 1989 Oct;124(10):471-7. (Italian)

20% azelaic acid cream was compared clinically with its vehicle in a 3-month double-blind study of 92 patients with moderate inflammatory acne. It was found that the azelaic acid treatment significantly reduced inflamed and non-inflamed lesions and yielded clinically relevant improvement rates. Its action was significantly more effective than its vehicle. In the study of comedo acne, 20% azelaic acid cream was equally effective as 0.05% tretinoin cream in reducing the number of comedones and with respect to overall response. However azelaic acid cream was better tolerated, causing fewer local side effects than the tretinoin.

Cavicchini S, et al [National and international experiences with azelaic acid cream in the treatment of papulo-pustular acne]. G Ital Dermatol Venereol. 1989 Oct;124(10):465-70. (Italian)

In a series of investigation using 20% azelaic acid as a therapy for acne, it was found that the treatment, compared with most common therapies (benzoylperoxide, oral tetracycline) significantly reduced inflamed lesions in papulo-pustular acne. The rates of improvement obtained indicate that topical azelaic acid treatment can be considered an effective therapy for papulo-pustular acne and it compares well with other agents. Azelaic acid cream shows a progressive and significant beneficial effect and its action is more pronounced in long-term treatment.

Nazzaro-Porro M, et al. Azelaic acid in the treatment of acne. G Ital Dermatol Venereol. 1989 Apr;124(4):175-84.

This review is an update of the literature accumulated over the past 6 years following the original observation that topically applied azelaic acid, a non-toxic C9 dicarboxylic acid, has a beneficial therapeutic effect on acne vulgaris. These studies have shown that azelaic acid has a modulating influence on the process of keratinization, and that it acts as a keratolytic and anti-comedogenic agent. There is evidence that it inhibits mitochondrial and microsomal oxido-reductases, including 5-alpha-reductase, and that it may interfere with the process of sebogenesis. It has a spectrum of antimicrobial activity, both in vitro and in vivo, against aerobic microorganisms and is effective against the anaerobic *Propionibacterium* acnes. Extensive multi-centre clinical trials have established that topical azelaic acid (a 20% cream) is an effective treatment for all types of acne. It compares well with other agents, such as topical tretinoin or benzoylperoxide, or oral tetracycline. It is non-irritant, and does not give rise to allergic or photo-toxic reactions. Its use is not associated with teratogenicity, possible endocrine unbalance, or the disadvantages of antibiotic treatment. It can be applied for long periods, in recurrences, and as maintenance "spot" therapy against individual lesions.

Hjorth N, et al Azelaic acid for the treatment of acne. A clinical comparison with oral tetracycline. Acta Derm Venereol Suppl (Stockh). 1989;143:45-8.

Cavicchini S, et al. Long-term treatment of acne with 20% azelaic acid cream. Acta Derm Venereol Suppl (Stockh). 1989;143:40-4.

Preliminary clinical studies (2) proved the effectiveness of topical azelaic acid (AZA) in the treatment of acne vulgaris. During the period of 1982-86 we carried out two studies with 20% AZA cream in patients with acne to determine its clinical indications and therapeutic schedules. The first, open study was of 100 unselected patients of either sex, while a second group of 30 patients formed a part of a larger (309 patients) multicentre single-blind comparison of topical AZA vs. 5% benzoylperoxide (BPO) gel for the treatment of papulopustular acne. The rates of improvement obtained indicate that topical AZA can be considered an effective therapy chiefly for papulo-pustular acne, with a very good local tolerance.

Katsambas A, Graupe K, Stratigos J. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris. Comparison with vehicle and topical tretinoin. Acta Derm Venereol Suppl (Stockh). 1989;143:35-9.

20% azelaic acid cream was compared clinically with its vehicle in a 3-month double-blind study of 92 patients with moderate inflammatory acne. In a single-blind study of 289 patients with comedonal acne, the topical azelaic acid preparation was compared with 0.05% tretinoin cream over a period of 6 months. In both controlled studies, 20% azelaic acid cream significantly reduced the number of acne lesions and yielded clinically relevant improvement rates. Azelaic acid cream was significantly and substantially more effective than its vehicle, indicating that the dicarboxylic acid itself is an active drug in acne treatment. In the study of comedonal acne, 20% azelaic acid cream was equally effective as 0.05% tretinoin cream in reducing the number of comedones and with respect to overall response. However, azelaic acid cream was better tolerated, causing fewer local side effects than the topical retinoid.

Cunliffe WJ, Holland KT. Clinical and laboratory studies on treatment with 20% azelaic acid cream for acne. Acta Derm Venereol Suppl (Stockh). 1989;143:31-4.

In a series of investigations using 20% azelaic acid cream as a therapy for acne, it was found that the treatment, compared with its placebo, significantly reduced inflamed lesions after 1 month and non-inflamed lesions after 2 months. No changes in sebum excretion rate occurred, but a significant reduction, 15.9 to 10.5%, of free fatty acids of skin surface lipid was detected after 1 month. The follicular Micrococaceae density was significantly reduced after 1 month, and after 2 months there was a significant reduction in follicular Propionibacterium spp density. The final reductions were 2,500 and 44 fold, respectively.

Nazzaro-Porro M. Azelaic acid. J Am Acad Dermatol. 1987 Dec;17(6):1033-41.

Bladon PT, Burke BM, Cunliffe WJ, Forster RA, Holland KT, King K. Topical azelaic acid and the treatment of acne: a clinical and laboratory comparison with oral tetracycline. Br J Dermatol. 1986 Apr;114(4):493-9.

Topical azelaic acid and oral tetracycline were compared in a 6-month double-blind study for treatment of acne vulgaris in 45 male subjects with clinical acne. Their acne was graded, inflamed or non-inflamed, lesions were counted and the density of their skin microflora was measured. Both treatments were of benefit and produced only a few minor side-effects. Although oral tetracycline was more effective than azelaic acid, the differences were only just significant. The average reduction in numbers of cutaneous micrococaceae and Propionibacterium sp. with azelaic acid treatment was 224 and 30-fold, respectively. In a separate group of 11 male subjects with physiological acne the effect of azelaic acid on sebum excretion rate was assessed, and little change was detected.

Marsden JR, et al. The effect of azelaic acid on acne. Br J Dermatol. 1983 Dec;109(6):723-4.

Nazzaro-Porro M, et al. Beneficial effect of 15% azelaic acid cream on acne vulgaris. Br J Dermatol. 1983 Jul;109(1):45-8.

1.1.2 General reviews on acne-therapy including Azelaic acid

Callender V D. Acne in ethnic skin: Special considerations for therapy. Dermatologic Therapy, 2004, Vol/Iss/Pg. 17/2 (184-195)

Acne vulgaris occurs in people of all ethnicities and races. Although the pathophysiology and treatment options are similar in all skin phototypes, darker-skinned patients have higher incidence rates of two sequelae of acne: postinflammatory hyperpigmentation and keloidal scarring. Postinflammatory hyperpigmentation may also be triggered by skin irritation. In choosing therapies for patients of color, therefore, clinicians must find a balance between aggressive early intervention to target inflammatory acne lesions, and gentle treatments to increase tolerability and avoid skin irritation. For most patients, a combination of topical retinoids, and topical or oral antibiotics with hydroquinone (as needed) to control hyperpigmentation will be successful. For patients with sensitive skin, topical agents in lower concentrations and cream vehicles are preferred. If tolerated, the retinoid strength can be titrated upward after four to six weeks. Ethnic patients also need to be counseled on use of noncomedogenic and nonirritating skin and hair-care products. Individualized care and close monitoring is required.

Haider Aamir, Shaw James C. Treatment of acne vulgaris. JAMA Journal of the American Medical Association 2004 Aug 11, VOL: 292 (6), P: 726-735

CONTEXT: Management of acne vulgaris by nondermatologists is increasing. Current understanding of the different presentations of acne allows for individualized treatments and improved outcomes. OBJECTIVE: To review the best evidence available for individualized treatment of acne. DATA SOURCES: Search of MEDLINE, EMBASE, and the Cochrane database to search for all English-language articles on

acne treatment from 1966 to 2004. **STUDY SELECTION:** Well-designed randomized controlled trials, meta-analyses, and other systematic reviews are the focus of this article. **DATA EXTRACTION:** Acne literature is characterized by a lack of standardization with respect to outcome measures and methods used to grade disease severity. **DATA SYNTHESIS:** Main outcome measures of 29 randomized double-blind trials that were evaluated included reductions in inflammatory, noninflammatory, and total acne lesion counts. Topical retinoids reduce the number of comedones and inflammatory lesions in the range of 40% to 70%. These agents are the mainstay of therapy in patients with comedones only. Other agents, including topical antimicrobials, oral antibiotics, hormonal therapy (in women), and isotretinoin all yield high response rates. Patients with mild to moderate severity inflammatory acne with papules and pustules should be treated with topical antibiotics combined with retinoids. Oral antibiotics are first-line therapy in patients with moderate to severe inflammatory acne while oral isotretinoin is indicated for severe nodular acne, treatment failures, scarring, frequent relapses, or in cases of severe psychological distress. Long-term topical or oral antibiotic therapy should be avoided when feasible to minimize occurrence of bacterial resistance. Isotretinoin is a powerful teratogen mandating strict precautions for use among women of childbearing age. **CONCLUSIONS:** Acne responses to treatment vary considerably. Frequently more than 1 treatment modality is used concomitantly. Best results are seen when treatments are individualized on the basis of clinical presentation.

Cetiner S, Ilknur T, Oezkan S, (Ozkan S). Phototoxic effects of topical azelaic acid, benzoyl peroxide and adapalene were not detected when applied immediately before UVB to normal skin. European Journal of Dermatology, 2004, Vol/Iss/Pg. 14/4 (235-237)

The enhancing effects on UVB erythema of topical agents applied on sun exposed areas are important due to their increased sunburn risk. Since the lesions in acne vulgaris are seen primarily on the face, the effects of topical agents used in acne treatment on the erythemogenicity of UVB is important. The aim of the present study was to examine whether azelaic acid cream, benzoyl peroxide gel, adapalene gel have the enhancing effects on UVB erythema which are widely used in the topical treatment of acne vulgaris. The minimal erythema dose (MED) was determined with phototest in 30 volunteers and the test was repeated with thin (0.1 cc/25 cm²) and thick (0.3 cc/25 cm²) azelaic acid cream, benzoyl peroxide gel, adapalene gel. The effects of each agent on MED was determined after 24 hours. MEDs of UVB were unaffected by azelaic acid cream, benzoyl peroxide gel and adapalene gel when applied immediately before irradiation. According to our results azelaic acid, benzoyl peroxide and adapalene do not seem to have enhancing effects on UVB erythema and thus increased sunburn risk.

Chen K, See J A. Late onset and postadolescent acne in women. Medicine Today, 01 JUL 2003, Vol/Iss/Pg. 4/7 (49-53, 55)

Late onset acne is acne that develops at or after the age of 20 years, whereas postadolescent acne is acne continuing past the teenage years. (bullet) Females may have normal or raised serum androgen levels. (bullet) Polycystic ovary syndrome is often an underlying cause in women with late onset or persistent acne. (bullet) Assessment should include a menstrual history and examination for clinical signs of hyperandrogenism, such as hirsutism. (bullet) Hormonal therapy is a very effective adjunct in the management of these patients, including those with normal serum androgen profiles.

Gollnick H P M, Krauthaim A. Topical treatment in acne: Current status and future aspects. Dermatology, 2003, Vol/Iss/Pg. 206/1 (29-36)

During the last 20 years, the number of topical and systemic drugs for the treatment of acne vulgaris has been enriched. Topical drugs on the one hand have been newly discovered or further developments of already available agents such as in the group of retinoids or galenic formulation have improved efficacy or local tolerance. Topical retinoids are a mainstay in acne treatment since 1962. All-trans retinoic acid was the first and is still in use. Its irritative potential has led to the new galenics, i.e. incorporation in microsponges and in propolyomers, which increased the tolerability significantly. The isomer of tretinoin, isotretinoin, has the same clinical efficacy, but also a lower irritancy. A real breakthrough was adapalene, a retinoid-like agent, with a different retinoid receptor-binding profile, but in addition to the same clinical efficacy on inflammatory and non-inflammatory acne lesions compared to tretinoin, a better tolerability and, therefore, compliance. Unfortunately, over the past years topical retinoids have been less used in inflammatory acne than they should be, taking the mechanisms of action into account. Topical antimicrobials, in particular topical antibiotics, should be used less often than in the past and only for short

periods to avoid the development of resistances. It seems better to combine those agents with topical retinoids, with BPO or with azelaic acid to enhance the efficacy and slow down the development of resistance. BPO is still the gold standard for papular-pustular acne of mild-to-moderate type in concentrations of 2-5%. Azelaic acid is an alternative with efficacy on the comedo and is antibacterial without development of resistances. Finally, the physical removal by electrocautery or CO₂ laser of multiple densely packed closed comedones, macrocomedones and microcysts is necessary to enhance the efficacy of topical comedolytic agents and to speed up the therapeutic results. Photodynamic therapy has not yet been proven efficacious in controlled studies. Blue and red light can probably be used in association with local agents but enhancement of the irritative potential of topical and systemic agents has to be considered. Copyright) 2003 S. Karger AG, Basel.

Berbis P. Treatment of severe acne (Traitment des acnes severes). ANNALES-DE-DERMATOLOGIE-ET-DE-VENERELOGIE, 2003, V130, N1, 2, JAN, pp 136-141

Liao D C. Management of acne. Journal of Family Practice, 01 JAN 2003, Vol/Iss/Pg. 52 /1 (43-51)

Precise classification methods are used to define acne according to type (comedonal, papulo-pustular, or nodular) and severity. The relative effectiveness of several topical and systemic agents has been established in clinical trials, making possible an algorithm of specific treatment decisions based on acne classification.

Barth J H, Clark S. Acne and hirsuties in teenagers. Bailliere's Best Practice and Research in Clinical Obstetrics and Gynaecology, 2003, Vol/Iss/Pg. 17/1 (131-148)

Acne and body hair are both cutaneous responses to androgenic stimulation. They are normal events in adolescent girls. There is considerable variation in the evolution of the two conditions. The sebaceous gland is exquisitely sensitive to androgens, and acne appears with the onset of puberty, peaks in prevalence in the teenage years and gradually improves thereafter. Hair growth on the face, trunk and limbs develops more slowly and generally peaks in the 20s. Indications for endocrine investigation include very severe acne, onset of acne and hirsuties in the very early stage of puberty (Tanner stage 3) and systemic virilism. Treatment for acne and hirsuties can be either topical or systemic. The choice of therapy is based on the severity of the disease rather than the results of endocrine investigation. Further, since PCO is related to impaired glucose tolerance, advice relating to lifestyle changes should be offered to prevent the development of diabetes.

Leyden J J. A review of the use of combination therapies for the treatment of acne vulgaris. Journal of the American Academy of Dermatology 49, 3: 200-210 (2003)

Acne is a disease of the pilosebaceous unit, involving abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation, and inflammation. The major classes of therapeutic agents are topical and systemic retinoids, antimicrobial agents, and systemic hormonal drugs. Combination therapy with a topical retinoid and an antibiotic can normalize follicular epithelial desquamation and reduce bacterial proliferation. The new retinoids (eg, adapalene) have an additional antiinflammatory action along with their effect on the preclinical microcomedo and, coadministered with a topical or an oral antibiotic, are a rational initial therapy for all but the most severe forms of acne. Retinoids can also be used alone for long-term maintenance to prevent the reemergence of comedones and inflammatory acne lesions and to spare the use of antibiotics, thus helping to reduce the risk of bacterial resistance.

Krautheim Andrea, Gollnick Harald. Transdermal penetration of topical drugs used in the treatment of acne. Clinical pharmacokinetics 2003, VOL: 42 (14), P: 1287-304

Acne vulgaris is a very common skin disease. Most patients present with mild to moderate acne comedonica or papulopustulosa grade I-II. The first-line treatment for these cases is generally via the topical route, whereas systemic medication is indicated when higher severity grades with small nodes or scarring occur. There are several topical agents available that affect at least one of the main pathogenetic factors responsible for the development of acne: hyperseborrhoea, hyperkeratosis, microbial colonisation and inflammatory and immunological reactions. Topical retinoids have a comedolytic and anticomedogenic activity, and some of them have anti-inflammatory potency. Azelaic acid and benzoyl peroxide have a moderate to strong antibacterial effect without inducing bacterial resistance, which is becoming a significant problem with the increasing use of topical antibacterials. Topical antiandrogens may soon be available for the treatment of the pathogenetic factor hyperseborrhoea. The transdermal penetration and the resulting systemic bioavailability of the various topical agents has not been widely considered. Apart from the retinoids, which can be associated with the risk of embryotoxicity /teratogenicity, and clindamycin, which might cause pseudomembranous colitis, information on the systemic pharmacokinetics of other topical agents is not readily available. There is still no consensus on the safe use of topical retinoids in pregnancy, and the occurrence of pseudomembranous colitis after the topical use of clindamycin does not appear to be of clinical relevance. In general, topical anti-acne agents are well tolerated and, as would be expected from their limited transdermal uptake, other significant safety concerns have not so far arisen.

Koch H J. Current aspects of pathogenesis and therapy of acne (AKTUELLE ASPEKTE ZUR PATHOGENESE UND THERAPIE DER AKNE). Kosmetische Medizin, 2003, Vol/Iss/Pg. 24/5-6 (175-183)

Acne vulgaris is a dermatosis almost exclusively appearing in adolescents. Primary efflorescence is an acne typical microcomedo. A main cause for the emergence of the illness is a seborrhoea favoured by androgens, accompanied by a disturbance in keratosis of the sebaceous gland duct. P. acnes promotes further inflammatory processes in the progress of acne. Emotional stress can lead to acute exacerbation and neurotic personalities may develop a phenomenon called "psychological acne". The disease is commonly diagnosed clinically, additional examinations (microbiological or immunological tests) may be necessary in atypical forms of the disease. Treatment of acne vulgaris should in general be stage dependent and reluctant. Retinoids can be applied either topically or systemically. Contraceptives (antiandrogens) are an option in therapy of acne vulgaris in women. UV light and laser application are in experimental state, routine implementation is not recommended at present. Numerous innovations in dermatotherapy, like usage of microsponges, introduction of pharmaceuticals combining certain ingredients as well as application of anti-inflammatory substances (lipoxigenase inhibitor type) are therapy options of the future.

Chen K, White TJ, Juzba M, Chang E. Oral isotretinoin: An analysis of its utilization in a managed care organization. Journal-of-Managed-Care-Pharmacy (USA); vol: 8, Pg: 272-277, Is: 4, 2002

OBJECTIVE: To assess utilization of oral isotretinoin within a managed care organization. **METHODS:** A retrospective analysis of pharmacy and medical claims from a southern California HMO was performed to (1) determine the prescribing patterns of oral isotretinoin from 1997 to 2000, stratified by age and gender, (2) categorize and quantify the use of antiacne prescriptions in the 6-month period immediately prior to the first oral isotretinoin prescription claim observed during this study; and (3) identify the amount of oral isotretinoin dispensed in a 210-day period following the dispensing date of the first oral isotretinoin prescription. **RESULTS:** The number of prescriptions was distributed almost equally between males and females, and the average number of prescriptions dispensed per patient decreased with age. A total of 39% of patients who received an oral isotretinoin prescription had not received a prescription for any antiacne medication in the preceding 6 months, and an additional 31% had not received a prescription for a topical retinoid. Approximately 27% of patients received more than a 150-day supply within the 210-day period following the first oral isotretinoin claim. **CONCLUSIONS:** These data suggest that in the 6 months preceding the first observed oral isotretinoin prescription, up to 70% of patients had not received a trial of a topical retinoid before receiving oral isotretinoin even though the product labeling advises that oral isotretinoin should be used only in patients unresponsive to "conventional therapy" (which is generally defined as at least a topical retinoid plus an oral antibiotic). Up to 27% of patients appeared to continue a course of treatment for longer than the 15-20 weeks advised in the isotretinoin product labeling. (No. References: 15).

Basta-Juzbasic A, Klenkar S. Current trends in the treatment of acne vulgaris. Acta Dermatovenerologica Croatica, 2001, Vol/Iss/Pg. 9/2 (131-137)

Acne vulgaris is one of the most frequently seen chronic skin diseases and most common dermatologic disorder of adolescents. Acne is a disease affecting the pilosebaceous follicles, in which there are four major etiologic factors: increased sebum production, hypercornification, abnormal bacterial function, and inflammation. After the initial interview and clinical assessment of acne, decisions should be made as to which treatment to prescribe. Patients with mild acne will do well with topical therapy, and those with more severe acne need oral therapy. It is essential to stress to the patient that topical therapies will need to be used for the next several years. Most frequently used preparations are: mild keratolytics, benzoyl peroxide, retinoic acid and other retinoids, topical antibiotics such as erythromycin and clindamycin as well as azelaic acid. Oral treatment is indicated in subjects with moderate and severe acne. The three main groups of oral therapy in acne are: antibiotics, hormones and retinoids. Antibiotics are usually the first line of oral therapy and are administered for several months. A first generation tetracycline is the first choice, however, lately further alternatives in the tetracycline group are minocycline or doxycycline. Erythromycin has been shown to be effective too, and so has clindamycin. Hormonal therapy is indicated in those females who are not responding well to conventional therapy. One of the commonest hormonal regimen is estrogen plus cyproteron acetate given for 6-12 months. In acne conglobata, but lately also in less severe acne with scarring and significant psychological stress, the treatment of choice is isotretinoin 0.5-1.0 mg/kg/day for 16-30 weeks with a cumulative dose of 120 mg/kg.

Thiboutot D. Hormones and acne: Pathophysiology, clinical evaluation, and therapies. Seminars in Cutaneous Medicine and Surgery, 2001, Vol/Iss/Pg. 20/3 (144-153)

Hormonal aspects of acne are of particular interest in treating adult women. A review of the role of hormones in the pathogenesis of acne, guidelines for the workup of a suspected endocrine disorder, and an overview of the use of hormonal therapy in women with endocrine problems and in normal women is presented. Copyright 2001 by W.B. Saunders Company.

Cunliffe B. Diseases of the skin and their treatment: (1) Acne. Pharmaceutical Journal, 24 NOV 2001, Vol/Iss/Pg. 267/7175 (749-752)

Sefton John TI: Method and composition for treating acne SO: Official-Gazette-of-the-United-States-Patent-and-Trademark-Office-Patents, July 17, 2001, vol. 1248, no. 3, p. No Pagination, e-file ISSN: 0098-1133

The present invention provides a method for treating acne vulgaris by serially applying a topical composition of azelaic acid and a topical composition of benzoyl peroxide. The present invention also provides topical compositions of a peroxide of benzoyl peroxide, and azelaic acid and its derivatives, such as azelaic acid, sodium salt or methylester which are useful for treating acne vulgaris and may be used to simultaneously apply benzoyl peroxide and azelaic acid.

Webster G F TI: Acne vulgaris and Rosacea: Evaluation and management. Clinical Cornerstone, 2001, Vol/Iss/Pg. 4/1 (15-20)

Acne vulgaris, commonly termed acne, is an extremely common disease. It can be found in nearly all teenagers to some degree as well as in women in their 30s. Regardless of severity, acne often has a greater psychologic effect than cutaneous effect. Indeed, most patients overestimate the severity of their disease, while most physicians underestimate its impact on their patients. Studies have shown that people with severe acne as teens are less employable as adults and that self-esteem is low. When combined with other adolescent tensions, acne can be a difficult disease to treat. Rosacea, which usually starts in the late 20s, may affect the eyes as well as the skin. This article describes the pathogenesis of acne and rosacea and treatment approaches the primary care physician can use.

Keeping acne under control: Skin cleansing, topical and oral therapy TT: "SAEUBERN, SCHMIEREN, SCHLUCKEN": DAMIT BEKOMMEN SIE AKNE IN DEN GRIFF. MMW-Fortschritte der Medizin, 26 JUL 2001, Vol/Iss /Pg. 143/30 (12-13)

Layton A M TI: Optimal management of acne to prevent scarring and psychological sequelae. American Journal of Clinical Dermatology, 2001, Vol/Iss/Pg. 2/3 (135-141)

Acne vulgaris is one of the most common inflammatory dermatoses and is seen in both the hospital setting and in general practice. Multiple factors are involved in the pathophysiology of acne, including: an alteration in the pattern of keratinization within the pilosebaceous follicles resulting in comedone formation; an increase in sebum production which is influenced by androgens; the proliferation of *Propionibacterium acnes*; and the production of perifollicular inflammation. Genetic and hormonal factors may also contribute to acne. Better understanding of the pathophysiology of the disease has led to the development of novel therapies which are directed at one or more of the implicated etiologic factors. Systemic antibiotics for acne have been the mainstay of treatment for many years. The main cause for concern following the use of systemic antibiotics is the emergence of antibiotic-resistant strains of *P. acnes*. Concomitant use of non-antibiotic therapies such as benzoyl peroxide helps to decrease the occurrence of resistance and can be effective in the treatment of resistant and nonresistant propionibacterial strains. However, no one agent is able to eradicate resistant strains completely and as resistant strains correlate to poor clinical response to therapy, prescribing strategies are required to minimize the occurrence of resistance to *P. acnes*. When assessing acne it is important to take an all embracing approach and to examine carefully for both the clinical and psychologic effects of the disease process. There are numerous forms of acne scarring and it is important to be aware of these as patients who are developing scarring merit early effective therapy. Some patients with acne will develop psychologic problems as a consequence of their condition. Even mild to moderate disease can be associated with significant depression and suicidal ideation and psychologic change does not necessarily correlate with disease severity. Acne scars themselves have been shown to produce significant psychopathology. When initiating treatment it is important to consider the aims of therapy. Treatment should be aimed at achieving clearance of acne, prevention of scarring and, where necessary, relief from any psychologic stress resulting from the acne. Therapy should be commenced early in the disease process in order to prevent scarring and it is important to select appropriate therapies according to the clinical signs and psychologic disability. It is also important to ensure that the patient is able to comply with therapy and clear guidelines regarding treatment, possible adverse effects and realistic expectations should be provided.

Leyden J TI: Are 2 combined antimicrobial mechanisms better than 1 for the treatment of acne vulgaris? Clinical and antimicrobial results of a topical combination product containing 1% clindamycin and 5% benzoyl peroxide - Introduction. CUTIS, 2001, V67, N2, FEB, SS, pp 5-7

Acne vulgaris is the most common chronic skin condition seen by dermatologists. Available topical therapies include comedolytic agents such as tretinoin, adapalene, azelaic acid, tazarotene, and salicylic acid; bactericidal agents such as benzoyl peroxide, antibiotics such as clindamycin, erythromycin, and tetracycline; and anti-inflammatory agents such as sodium sulfacetamide and metronidazole. Therapeutic failure with some antibiotic regimens due to the presence or development of resistant strains is becoming an increasing problem in the treatment of acne. One strategy aimed at limiting the resistant *Propionibacterium acnes* population is the use of treatment regimens that incorporate agents with complementary but different mechanisms of action. A combination gel consisting of 5% benzoyl peroxide and 1% clindamycin has recently become available. This supplement summarizes the dermatopharmacology, clinical efficacy, and tolerability of this combination gel, along with its potential role in the management of acne vulgaris.

Piquero Martin J TI: Acne TT: ACNE. Medicina Cutanea Ibero-Latino-Americana, 2001, Vol/Iss/Pg. 29/1 (8-23)

Juettner C, (Juttner C) TI: Behandlung mit Minocyclin plus Azelainsaeure bei schwerer rezidivierender Acne papulopustulosa. Haut 12, 1: 12-13 (2001)

Current FDA-related drug information: New drugs approved by the FDA. New dosage forms and indications. Agents pending FDA approval. Hospital Pharmacy, 2001, Vol/Iss/Pg. 36/7 (773-785)

Basta Juzbasic A, Klenkar S TI: Current trends in the treatment of acne vulgaris. Acta Dermatovenerologica Croatica, 2001, Vol/Iss/Pg. 9/2 (131-137)

Acne vulgaris is one of the most frequently seen chronic skin diseases and most common dermatologic disorder of adolescents. Acne is a disease affecting the pilosebaceous follicles, in which there are four major etiologic factors: increased sebum production, hypercornification, abnormal bacterial function, and inflammation. After the initial interview and clinical assessment of acne, decisions should be made as to which treatment to prescribe. Patients with mild acne will do well with topical therapy, and those with more severe acne need oral therapy. It is essential to stress to the patient that topical therapies will need to be used for the next several years. Most frequently used preparations are: mild keratolytics, benzoyl peroxide, retinoic acid and other retinoids, topical antibiotics such as erythromycin and clindamycin as well as azelaic acid. Oral treatment is indicated in subjects with moderate and severe acne. The three main groups of oral therapy in acne are: antibiotics, hormones and retinoids. Antibiotics are usually the first line of oral therapy and are administered for several months. A first generation tetracycline is the first choice, however, lately further alternatives in the tetracycline group are minocycline or doxycycline. Erythromycin has been shown to be effective too, and so has clindamycin. Hormonal therapy is indicated in those females who are not responding well to conventional therapy. One of the commonest hormonal regimen is estrogen plus cyproteron acetate given for 6-12 months. In acne conglobata, but lately also in less severe acne with scarring and significant psychological stress, the treatment of choice is isotretinoin 0.5-1.0 mg/kg/day for 16-30 weeks with a cumulative dose of 120 mg/kg.

Bershad S V TI: The modern age of acne therapy: A review of current treatment options. Mount Sinai Journal of Medicine, 2001, Vol/Iss/Pg. 68/4-5 (279-286)

This review of current acne treatments begins with the crucial discovery in 1979 of isotretinoin treatment for nodulocystic acne. This drug's approval in 1982 revolutionized therapy, since it was the first oral acne-specific drug, and it provided prolonged remissions. In addition, it may prevent the emergence of resistant bacteria, a problem linked to the traditional use of antibiotics for acne. Patients who are not candidates for isotretinoin therapy may benefit from one of the other drugs or drug combinations reviewed, including the third-generation topical retinoids adapalene and tazarotene, retinoic acid reformulated in new vehicles, azelaic acid, and topical antibiotics. Proper selection and education of patients are essential, since serious consequences may result from poorly monitored use of antibiotics and retinoids.

Cargnello J TI: Acne: General principles of management. Medicine Today, 2001, Vol/Iss/Pg. 2/8 (55-60)

Acne affects over 90% of adolescents aged 16 to 19 years. Even mild acne can have a devastating impact on self-esteem. (Acne is an eminently treatable disorder that can be well managed by the GP. The aim of treatment is to suppress and clear acne and to prevent scarring. The benefits of treatment may take two to three months to become evident. Topical, over-the-counter preparations are an essential part of therapy and may be all that is required in some cases. (Fatty foods, dairy products and chocolate do not cause acne.

Fisher D, Kaplan D L TI: Common dermatoses: How to treat safely and effectively during pregnancy, Part 1. Consultant, 2001, Vol/Iss/Pg. 41/7 (1037-1044)

For pregnant women with acne, category B topical antibiotics -such as clindamycin gel, lotion, pledgets, or solution; multiple vehicles of erythromycin 1.5% or 2%; and azelaic acid 20% cream -can be applied after washing with a mild facial cleanser. Oral macrolides are a safe alternative to oral tetracyclines, which are contraindicated during pregnancy, for patients with severe acne. The treatment of perioral dermatitis during pregnancy is limited primarily to topical agents, such as metronidazole 0.75% or 1% cream or erythromycin 2% gel. Oral and vaginal preparations of metronidazole are contraindicated during the first trimester because of an increased risk of birth defects; however, the topical formulation appears to be safe when applied to a small area. Topical metronidazole is also effective in treating rosacea. Clindamycin lotion and erythromycin 2% gel are alternatives for pregnant women with rosacea but are sometimes less effective.

Oral erythromycin also may be prescribed. For pregnant women with seborrheic dermatitis, ciclopirox - a synthetic topical antifungal - has a better safety profile than other therapies, such as corticosteroids.

Cunliffe W J, Holland D B, Clark S M, Stables G I TI: Comedogenesis: Some new aetiological, clinical and therapeutic strategies. British Journal of Dermatology, 2000, Vol/Iss/Pg. 142 /6 (1084-1091)

Hypercornification is an early feature of acne and precedes inflammation. It is associated with ductal hyperproliferation and there are many controlling factors such as androgens, retinoids and cytokines. Cycling of normal follicles and of comedones may explain the natural resolution of comedones and, in the longer term, resolution of the disease itself. There is a need to tailor treatment according to comedonal type. Suboptimal therapy can often result from inappropriate assessments of comedones, especially microcomedones, missed comedones, sandpaper comedones, submarine comedones and macrocomedones. Macrocomedones can produce devastating acne flares, particularly if patients are inappropriately prescribed oral isotretinoin. Gentle cautery under topical local anaesthesia is a useful therapy in the treatment of such lesions. The newer retinoids and new formulations of all- trans-retinoic acid show a better benefit/risk ratio. Evidence-based studies are required to allow adequate comparisons.

Usatine R P TI: The science and art of treating acne in adolescence. West-J-Med 2000 Mar, VOL: 172 (3), P: 155-156

Usatine R P, Quan M A TI: Pearls in the management of acne - An advanced approach PRIMARY-CARE, 2000, V27, N2, JUN, pp 289-308

Acne is a common condition of the sebaceous follicle. The primary care physician can have a large impact on patients with acne by properly classifying the type of acne (obstructive versus inflammatory) and successfully treating the acne based on its severity. Reduction of acne lesions by appropriate topical and oral medications provides great psychological and physical benefits to these patients. By understanding how acne develops and its many manifestations and treatment options, the primary care physician can become an expert in acne diagnosis and treatment.

Federman D G, Kirsner R S TI: Acne vulgaris: Pathogenesis and therapeutic approach. AM-J-MANAGED-CARE, 2000, Vol/Iss/Pg. 6/1 (78-87)

AUDIENCE This activity is designed for primary care providers, internists, and general audiences. GOAL To provide the reader with a basic understanding of the pathogenesis of acne vulgaris and the rationale behind several treatment options. Clinicians should be aware of treatment strategies for various subtypes of acne vulgaris. OBJECTIVES 1. To describe the emotional and financial impact of acne. 2. To describe the differential diagnosis of acne vulgaris. 3. To discuss acne's pathogenesis. 4. To provide information on topical therapy for the treatment of acne vulgaris. 5. To discuss oral therapy for the treatment of acne vulgaris.

Waielewski S TI: Den Pickeln wird der Kampf angesagt Akne, Teil II Topische Behandlung PTA Heute 14, 7: 23-27 (2000) insert in Dtsch Apoth Ztg 140, 28

Garner S E, Eady E A, Popescu C, Newton J, Li Wan Po A TI: Minocycline for acne vulgaris: efficacy and safety , The Cochrane database of systematic {Cochrane-Database-Syst-Rev} 2000 (2)

BACKGROUND: Minocycline is a tetracycline antibiotic that is commonly used in the treatment of moderate to severe acne vulgaris. Although it is more convenient for patients to take than first-generation tetracyclines, as it only needs to be taken once or twice a day and can be taken with food, it is more expensive. Concerns have also been expressed over its safety following the deaths of two patients taking the drug. There is a lack of consensus among dermatologists over the relative risks and benefits of minocycline. As most acne prescribing is undertaken by general practitioners, it is important that guidelines issued to them are based on the best available evidence rather than personal judgements. OBJECTIVES: To collate and evaluate the evidence on the clinical efficacy of minocycline in the treatment of inflammatory acne vulgaris. Specific objectives were to compare the efficacy of minocycline with other drug treatments

for acne and to collate information on the incidence of adverse drug reactions. **SEARCH STRATEGY:** Randomised controlled trials (RCTs) of minocycline for acne vulgaris were identified by searching the following electronic databases; MEDLINE, EMBASE, Biosis, Biological Abstracts, International Pharmaceutical Abstracts, Cochrane Skin Group's Trial Register, Theses Online, BIDS ISI Science Citation Index and Bids Index to Scientific and Technical Proceedings. Other strategies used were scanning the references of articles retrieved, hand-searching of major dermatology journals and personal communication with trialists and drug companies. **SELECTION CRITERIA:** To be eligible for the review, studies had to be RCTs comparing the efficacy of minocycline at any dose to active or placebo control, in subjects with inflammatory acne vulgaris. Diagnoses of papulo-pustular, polymorphic and nodular acne were also accepted. Trials were not excluded on the basis of language. **DATA COLLECTION AND ANALYSIS:** 27 randomised controlled trials met the inclusion criteria and were included in this review. The comparators used were placebo (2 studies), oxytetracycline (1), tetracycline (6), doxycycline (7), lymecycline (2), topical clindamycin (3), topical erythromycin/zinc (1), cyproterone acetate/ ethinyloestradiol (1), oral isotretinoin (2), topical fusidic acid (1) and there was one dose response study. One study is ongoing and it remains to be clarified whether one further study is a RCT. Major outcome measures used in the trials included lesion counts, acne grades/severity scores, doctors' and patients' global assessments, adverse drug reactions and drop out rates. The quality of each study was assessed independently by two assessors and an effect size calculated where possible. **MAIN RESULTS:** The trials were generally small and of poor quality and in many cases the published reports were inadequate for our purpose. Pooling of the studies was not attempted due to the lack of common outcome measures and endpoints and the unavailability of some primary data. Although minocycline was shown to be an effective treatment for acne vulgaris, in only two studies was it found to be superior to other tetracyclines. Both of these were conducted under open conditions and had serious methodological problems. A third study showed it to be more effective than 2% fusidic acid, applied topically, against inflammatory lesions in mild to moderate acne. Differences in the way adverse drug reactions were identified could have accounted for the wide variation between studies in numbers of events reported. This meant that no overall evaluation could be made of incidence rates of adverse events associated with minocycline therapy. No RCT evidence was found to support the benefits of minocycline in acne resistant to other therapies and the dose response has only been evaluated up to eight weeks of therapy.

Jahn S, (:ref.) TI: Akne-Therapie von Innen und Aussen auch fuer Problempatienten, Dermatologie 30, 3: 1-3 (2000)

Johnson B A, Nunley J R TI: Use of systemic agents in the treatment of acne vulgaris. American Family Physician, 15 OCT 2000, Vol/Iss/Pg. 62 /8

Kamran T, Bajwa U M TI: A review of acne treatment. Journal of Pakistan Association of Dermatologists 11: 25-29 (2000) July

Katsambas A D, Nicolaidou E TI: Acne, perioral dermatitis, flushing, and rosacea: Unapproved treatments or indications. Clinics in Dermatology {CLIN-DERMATOL}, 04 MAR 2000, Vol/Iss/Pg. 18/2 (171-176)

Kreusch J, Bextermoller R TI: Efficacy and tolerability of a topical erythromycin/tretinoin combination preparation in acne treatment post-marketing surveillance study involving over 6500 patients. CURR-MED-RES-OPIN, 2000, Vol/Iss/Pg. 16/1 (1-7)

The good efficacy and tolerability of an alcoholic erythromycin /tretinoin solution was confirmed in a multicentre data investigation of over 6500 patients. The mean score for comedones declined clearly from 1.9 to 0.9 during treatment (average duration 70 days). The score for papules and pustules was reduced from 1.6 to 0.5. Overall medical assessment indicated 'very good' to 'good' efficacy in 86.1% of documented cases. Adverse drug reactions during treatment were mostly only very mild and were nearly always the known symptoms of redness, scaling, dryness and itching. Overall assessment of tolerability was 'very good' or 'good' in 88.1% of cases.

Ferreira E O TI: Infantile and juvenile acne TT: ACNE INFANTILE JUVENIL SO: NASCER-CRESCER, 2000, 9: 28-32

Although we think of acne as a disease which begins in adolescence, it frequently occurs during the first years of life. Its presentation in infancy is disturbing but not necessarily serious. Several types are recognised; some of them will be discussed in this article. Acne is often the herald of adolescence. In fact, conservative estimates indicate that approximately 85% of all adolescents experience some degree of acne. While acne is not a life-threatening disease, it can have far-reaching and severe psychosocial effects in adolescents and young adults, negatively influencing their self-esteem during a time of life that is fraught with difficult sexual/social issues and intense interpersonal relationships. Although the same therapies are available and used for acne in childhood and adolescence, the way in which these drugs are used and the restrictions of certain drugs are unique and tailored to the particular age group affected, also consideration of the psychological aspects are important in the successful treatment of acne in infants and children.

Maddin W S, Landells I D R, Poulin Y, Searles G E, Smith K C, Tan J K L, Toole J, Zip C M, Degreef H TI: Treatment of acne vulgaris and prevention of acne scarring: Canadian consensus guidelines Journal of Cutaneous Medicine and Surgery, 2000, Vol/Iss/Pg. 4/SUPPL. 1 (S4-2-S4-13)

Krowchuk D P TI: Treating acne: A practical guide Medical Clinics of North America {MED-CLIN-NORTH-AM}, 2000, 84: 811-828

Krowchuk D P TI: Managing acne in adolescents SO: Pediatric Clinics of North America 2000, 47: 841-857

Acne is the most common skin disorder affecting adolescents. Although no cure exists for acne, most patients benefit from currently available medications, and most can be managed effectively by their primary care providers. By offering this care, pediatricians can reduce the emotional burden of acne and help to prevent the permanent scarring so commonly seen in the past.

Russell J J TI: Topical therapy for acne SO: AM-FAM-PHYS, 2000, 61: 357-365

Acne is a common problem in adolescents and young adults. The disorder is caused by abnormal desquamation of follicular epithelium that results in obstruction of the pilosebaceous canal. This obstruction leads to the formation of comedones, which can become inflamed because of overgrowth of *Propionibacterium acnes*. Topical retinoids such as tretinoin or adapalene are effective in many patients with comedonal acne. Patients with inflammatory lesions benefit from treatment with benzoyl peroxide, azelaic acid or topical antibiotics. Frequently, the use of comedonal and antibacterial agents is required.

Schmidt R TI: Akne richtig behandeln. Deutsche Apotheker Zeitung 140, 29: 79-80 (2000)

Sidbury R, Paller A S TI: The diagnosis and management of acne. PEDIATR-ANN, 2000, Vol/Iss/Pg. 29/1 (17-24)

Thiboutot D TI: New treatments and therapeutic strategies for acne ARCHIVES-OF-FAMILY-MEDICINE, 2000, 9: 179-187

Successful management of acne requires careful patient evaluation followed by consideration of several patient and medication factors when selecting a particular therapeutic regimen. Within the last few years, several new agents for the treatment of acne have become available that afford greater flexibility in the treatment of this prevalent dermatologic disorder. These include adapalene, tazarotene, 2 new topical tretinoin formulations, azelaic acid, a new sodium sulfacetamide formulation, and an oral contraceptive recently approved by the Food and Drug Administration for the treatment of acne. After a brief overview of the pathophysiology of acne and existing therapies, this review evaluates the new antiacne agents and

how they can be integrated into a successful treatment strategy that takes into account acne severity and predominant lesion type as well as age, skin type, lifestyle, motivation, and the presence of coexisting conditions.

Cassano N, Alessandrini G, Mastrolonardo M, Vena G A TI: Peeling agents: Toxicological and allergological aspects J-EUR-ACAD-DERMATOL-VENEREOL, 1999, 13: 14-23

Background: The use of peeling agents is very common in clinical practice. However, despite the overall good safety profile, it is not without any inherent risk; therefore, clinicians should be adequately informed about potential risk in order to avoid or prevent them. Objective: This paper reviews toxicological and allergological aspects of peeling agents in general, also beyond their actual use in peeling procedures. Toxic and allergic reactions from peeling agents are rather uncommon and have been rarely reported in association with the medical use of peels. Methods: Systemic toxic effects may essentially derive from phenol and potentially from two phenol derivatives, resorcinol and salicylic acid. A complete understanding of the toxicological profile of peeling agents, along with a correct execution of the technique and a carefully selection of patients, can help avoid serious side effects. Results: Allergic contact reactions occur most frequently with resorcinol, while most peeling agents are only rare sensitizers or appear to be free of true sensitizing power. Other types of hypersensitivity response seem to be very rare.

Bergfeld W F TI: A lifetime of healthy skin: implications for women Int J Ferti 1999 44, 2: 83-95

During her lifetime, a woman faces the possibility of seeking dermatological assistance for a myriad of conditions, including acne, rosacea, striae, photodamage, and skin cancers. It is important for clinicians and patients to be aware of the symptoms of these conditions as well as the most beneficial approaches for prevention, diagnosis, treatment, and management. The life expectancy of women has increased and predictions for the year 2050 estimate the average age at 81 years. This will place women at greater risk for dermatological problems, especially photodamage and skin cancer. In addition, various ethnic groups may manifest these conditions differently. Although acne is most prevalent among teenaged males, most can expect clearing by age 25. Females may continue to experience acne into the adult years, sometimes beyond the age of 40. Although it is not a life-threatening disease, acne may have psychosocial and quality-of-life consequences. Treatments for acne can be topical or systemic, and include retinoids, antibiotics, benzoyl peroxide, azelaic acid, and hormonal therapy. Rosacea is more common in women (especially during menopause) than in men. It is a chronic condition that can cause complications, including telangiectasia, conjunctivitis, and blepharitis. Although there is no cure, rosacea can be managed and controlled with medication. Topical antibiotics, such as metronidazole, and systemic antibiotics, such as tetracycline, clarithromycin, and doxycycline, are used to manage rosacea. Striae, or stretch marks, occur most frequently in pregnant women, adolescents experiencing growth spurts, weight lifters, and the obese. Although not a health threat, they can be psychologically distressing. There are not many treatment options for striae, but topical tretinoin and the pulsed dye laser offer promising results. Intrinsic, or normal, aging of the skin results from the process of chronological aging. Photodamage is skin damage caused by chronic exposure to ultraviolet (UV) light. It is the leading cause of extrinsic aging, or alterations of the skin due to environmental exposure. Estimates indicate that almost half of a person's UV exposure occurs by age 18. Photoaging causes numerous histologic, physiologic, and clinical changes; it also increases the risk for skin cancer. Photodamage can be prevented through the use of sun screens, protective clothing, and avoidance of the sun during peak intensity time. The only product approved by the FDA for the treatment of photodamage (fine wrinkles, mottled hyperpigmentation, and skin roughness), topical tretinoin emollient cream, may help prevent additional photoaging when it is used to treat existing photoaging. Other management options for photodamaged skin include alpha-hydroxy acids, antioxidants, antiandrogens, moisturizers, and exfoliants. In patients with excessive manifestations of photodamage, surgical management may be needed, including dermabrasion, chemical peels, soft tissue augmentation, laser resurfacing, botulinum toxin, and Gortex(R) threads. Clinicians must educate their patients about the most appropriate skin care regimen as well as approaches for preventing and treating common afflictions. In this way, women will have the best opportunity for having and maintaining healthy skin.

Draelos Z D TI: Topical agents used in association with cosmetic surgery. Seminars in Cutaneous Medicine and Surgery 1999, 18: 112-118

Effective cosmetic surgery depends on proper preparation of the skin prior to the procedure, excellent wound care, and an appropriate postoperative skin maintenance program. Accomplishing this goal requires a thorough understanding of topical agents. Substances applied to the skin can alter barrier function,

permeability, transepidermal water loss, immune response, wound repair, vasostability, collagen deposition, epidermal turnover, and melanin formation, to name a few. Each of these skin characteristics can affect the quality of the end surgical result. This article discusses topical agents used in association with cosmetic surgery.

Kwiecien A, Zalewska A TI: (Acne vulgaris: local and systemic treatment) Trcadzik popsolity--leczenie miejscowe i ogolne. Polski merkuriusz lekarski {Pol-Merkuriusz-Lek} 1999;; 6: 291-3.

Acne vulgaris is a skin disease affecting mainly young people. To its pathogenetical factors belong: excessive serum production, cornification of hair follicles and presence of different bacteria (Propionibacterium acnes, Staphylococcus epidermidis, Pityrosporum ovale) on the skin and within hair follicles leading to skin inflammation. Therapeutical approach to the patient depends on the clinical presentation of the disease. And so, in its local treatment are benzyl peroxide, azelaic acid, topical antibiotics, hormonal therapy and retinoids whereas in systemic one are found oral antibiotics, hormonal therapy and retinoids.

Gollnick H, Schramm M. Topical therapy in acne. J Eur Acad Dermatol Venereol. 1998 Sep;11 Suppl 1:S8-12.

The majority of acne patients will receive a topical treatment either as monotherapy or in combination with a systemic drug therapy depending on the severity of the disease. The currently available topical agents affect at least one of the four main pathogenetic factors responsible for the development of acne, i.e. hyperkeratosis, microbial colonization, immune response and inflammation. Retinoids, azelaic acid, benzoyl peroxide and topical antibiotics represent the spectrum of the established and proven topical agents. Presumably, antiandrogenic agents will soon be available for topical use to treat the important factor of seborrhea. In general, by combining topical agents, their potency can be enhanced and toxicity diminished. Unfortunately, bacterial resistances are beginning to emerge as a significant problem.

Gollnick H, Schramm M. Topical drug treatment in acne. Dermatology. 1998;196(1):119-25.

The main part of acne treatment uses the topical route. More than 50% of acne patients belong to the group presenting with acne comedonica and papulopustulosa. Whenever small nodes or scarring occur, systemic comedication is indicated, however. Topical treatment affects at least three of the four main pathogenetic factors responsible for the development of acne, i.e. hyperseborrhea, hyperkeratosis, microbial colonization and inflammation. The agents currently available influence at least one of these factors but often have additional properties. Those which act in a comedolytic and anticomedogenic manner are the retinoids tretinoin, isotretinoin, adapalene and tazarotene and azelaic acid as well, some of the retinoids having additional anti-inflammatory potency. Azelaic acid has strong antibacterial potency without inducing bacterial resistance similar to benzoyl peroxide. Unfortunately, bacterial resistances are beginning to emerge as a significant problem. Propionibacterium acnes resistance to the commonly used erythromycin can also be transferred to clindamycin, whereas no resistance has been reported to nadifloxacin so far. Today, more and more evidence comes up that topical antiandrogenic agents will soon be available to treat the important factor seborrhea, because patients with marked hyperseborrhea frequently relapse. Finally, liposome encapsulation of agents including phospholipids can enhance penetration and efficacy but, particularly with regard to retinoids, can lead to higher absorption and adverse drug reactions.

Usatine RP, et al. Acne vulgaris: a treatment update. Hosp Pract (Off Ed). 1998 Feb 15;33(2):111-7, 121-4, 127.

Weiss JS. Current options for the topical treatment of acne vulgaris. Pediatr Dermatol. 1997 Nov-Dec;14(6):480-8. Review.

The etiopathogenesis of acne vulgaris, a common disorder of youth and adolescence, includes four primary processes: hyperkeratinization (plugging) of the pilosebaceous follicles, increased testosterone levels, bacterial colonization with Propionibacterium acnes, and inflammation. No single agent has yet

been developed that addresses all of these factors. Combination regimens, therefore, which usually include an antibiotic and an agent to reduce follicular plugging, have become the mainstay of treatment. Despite a relative dearth of new treatments for almost a decade, recent research has produced a number of new significant oral and topical agents. Azelaic acid, a naturally occurring dicarboxylic acid analogue, has shown promise, and a group of retinoids that include adapalene, tazarotene, and reformulations of tretinoin represent new and forthcoming agents for topical treatment of acne vulgaris. Some studies indicate that several of these agents are associated with less skin irritation than previous formulations while they retain potent comedolytic activity. Adapalene also possesses significant anti-inflammatory activity.

Chang YC, Maibach HI. Advances in dermatopharmacology. Int J Clin Pharmacol Ther. 1997; 35, 5: 188-194

Jansen T, Plewig G. Advances and perspectives in acne therapy. Eur J Med Res. 1997 Aug 28;2(8):321-34. Review.

Acne is one of the most common diseases in dermatology. It is of considerable esthetic significance, which explains the mental stress in affected patients. Although acne almost always heals spontaneously in early adulthood, treatment measures can shorten the course, reduce the severity of the disease, and avoid complications such as scarring. Treatment has changed substantially in recent years. In accordance with pathogenic principles, effective treatment is possible. In most patients, a combination of drugs aimed at correcting abnormal keratinization and reducing the proliferation of *Propionibacterium acnes* is sufficient to control the disease. For more severely affected patients with no response to this approach, therapy to suppress sebum production is indicated. Of all therapeutic modalities available, only oral isotretinoin alters the natural course of the disease. In acne inversa, surgical management should be undertaken as early as possible.

Ely H. Dermatologic therapies you've probably never heard of. Dermatol Clin. 1989 Jan;7(1):19-35.

This article presents numerous alternative therapies for stubborn dermatologic conditions. Agents include hypertonic saline, mexiletine, alpha-acetoxymandelic acid, deladumone, emulsified steroids, activated charcoal, azelaic acid, silymarin, and dexamethasone. Several surgical tips are also included for the practitioner's consideration.

1.2 Rosacea

1.2.1 Clinical studies and reviews on Azelaic acid.

[No authors listed] Extended licence: Azelaic acid also for the treatment of rosacea (Azelaic acid jetzt auch zur Behandlung von Rosacea). Deutsche Apotheker Zeitung 144, 4: 310-311 (54-55) (2004)

Del Rosso J Q. Medical treatment of rosacea with emphasis on topical therapies. Expert Opinion on Pharmacotherapy, 2004, Vol/Iss/Pg. 5/1 (5-13)

Due to the development and release of newer topical formulations, the diagnosis and treatment of rosacea has received renewed attention over the past 3 - 5 years both in the literature and at medical symposia. Rosacea is a very common facial dermatosis. In the US, rosacea is estimated to affect > 14 million people, predominantly adults with (similar to) 60% of cases diagnosed before the age of 50 (1). A frustrating aspect of the disease is its inherent chronicity punctuated with periods of exacerbation and relative remission. A variety of subtypes have been identified which correlate with clinical presentation. Although the pathogenesis of rosacea is poorly understood, multiple topical agents are available. The efficacy of

topical therapy for rosacea relates primarily to reduction in inflammatory lesions (papules, pustules), decreased intensity of erythema, a reduction in the number and intensity of flares and amelioration of symptoms, which may include stinging, pruritus and burning. The list of main topical agents utilised for the treatment of rosacea include metronidazole, sulfacetamide-sulfur, azelaic acid and topical antibiotics (clindamycin, erythromycin). Depending on the severity at initial presentation, topical therapy may be combined with systemic antibiotic therapy (e. g., oral tetracycline derivative) . Newer therapeutic choices primarily involve improved vehicle formulations, which demonstrate favourable skin tolerability and cosmetic elegance.

[No authors listed] Azelaic acid gel in the topical therapy of moderate papulopustular rosacea (AZELAINSAEURE-GEL IN DER TOPISCHEN THERAPIE DER MODERATEN PAPULOPUSTULOESEN ROSAZEA). Haut, 2004, Vol/Iss/Pg. 15/1 (41-42)

Frampton J E, Wagstaff A J. Azelaic acid 15% gel: In the treatment of papulopustular rosacea. American Journal of Clinical Dermatology 5, 1: 57-64 (2004)

Azelaic acid is a naturally occurring, straight-chain dicarboxylic acid which is effective in the treatment of rosacea, presumably on account of its anti-inflammatory properties. In randomized, double-blind, multicenter studies involving patients with moderate papulopustular facial rosacea, twice-daily topical application of azelaic acid 15% gel to the face was significantly more effective than twice-daily administration of either its vehicle (two studies) or metronidazole 0.75% gel (one study) in reducing inflammatory lesion counts and erythema severity. However, neither active treatment had a clinically discernable effect on telangiectasia. In all three studies, azelaic acid 15% gel recipients experienced continuous decreases in lesion counts and erythema throughout the 12- to 15-week treatment periods. However, the effects of metronidazole 0.75% gel plateaued after 8 weeks. In other efficacy assessments in these studies, azelaic acid 15% gel was superior to its vehicle and metronidazole 0.75% gel in both the investigators' global assessment of rosacea and the investigators' end-of-study evaluation of overall improvement, and superior to its vehicle in the patients' end-of-study evaluation of overall improvement. The most frequent treatment-related cutaneous adverse events during administration of azelaic acid 15% gel include burning/stinging/tingling and pruritus (itching); however, these events are predominantly transient in nature and mild-to-moderate in intensity.

Bershad S. Azelaic Acid. American Journal of Clinical Dermatology 5, 1: 65 (2004)

Gupta K. Azelaic Acid. American Journal of Clinical Dermatology 5, 1: 65-66 (2004)

Kowalzick L, Mischke D. 15% Azelaic acid hydrogel in the topical treatment of papulopustular rosacea (15% AZELAINSAEURE IN HYDROGEL ZUR THERAPIE DER PAPULOPUSTULOESEN ROSAZEA). Aktuelle Dermatologie, 2004, Vol/Iss/Pg. 30/5 (158-161)

Recently, the good therapeutic effect of 15% azelaic acid hydrogel in patients with papulopustular rosacea was reported. We report on 4 patients with papulopustular rosacea, treated twice daily for up to 12 weeks with Skinoren 15% gel. In all 4 treated patients the skin improved within 4 weeks. At the end of the observation period the mean clinical IGA score had dropped to 61% of baseline. Especially the inflammatory lesions (papules and pustules) responded well to treatment (44%), followed by the improvement of erythema (63%). The therapeutic effect on telangiectasia was only weak (74% of baseline) . All patients tolerated the treatment well and no local side effects occurred.

Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: Results from two vehicle-controlled,

randomized phase III studies. Journal of the American Academy of Dermatology 48, 6 Pt. 1: 836-845 (2003)

Background: Rosacea is a common, chronic dermatosis for which safe and effective new treatment options are needed. Objective: The objective of these studies was to evaluate the efficacy, tolerability, and safety of a new formulation of 15% azelaic acid (15%) gel (AzA gel), for the topical treatment of moderate, papulopustular rosacea. Methods: Two multicenter, double-blind, randomized, parallel-group, vehicle-controlled studies were conducted using identical study designs, patient-selection criteria, and efficacy end points. Overall, 329 patients were enrolled in study 1 and 335 patients in study 2. Results: Both studies consistently demonstrated the superiority of AzA gel over vehicle in the topical treatment of moderate, papulopustular rosacea. AzA gel yielded statistically significantly higher reductions in mean inflammatory lesion count than vehicle: 58% versus 40%, study 1 ($P = .0001$); 51% versus 39%, study 2 ($P = .0208$). Significantly higher proportions of patients treated with AzA gel experienced improvement in erythema compared with vehicle gel: 44% versus 29%, study 1 ($P = .0017$); 46% versus 28%, study 2 ($P = .0005$). Using the investigator's global assessment, therapeutic success in terms of a clear, minimal, or mild final result was achieved in 61% and 62% of patients treated with AzA gel in studies 1 and 2, respectively, which was significantly superior to the result achieved with vehicle (40% and 48%, respectively) ($P < .0001$, study 1; $P = .0127$, study 2). No serious, treatment-related adverse events were reported. Conclusion: The results of these 2 controlled studies demonstrate that AzA gel, used twice daily, is an efficacious, safe, and well-tolerated topical treatment for moderate, papulopustular rosacea.

[No authors listed] Azelaic acid (Finacea) for rosacea. Medical Letter on Drugs and Therapeutics 2003 Sep 15, VOL: 45 (1165), P: 76

Elewski B E, Fleischer A B, Pariser D M. A Comparison of 15% Azelaic Acid Gel and 0.75% Metronidazole Gel in the Topical Treatment of Papulopustular Rosacea. Archives of Dermatology 139, 11: 1444-1450 (2003)

Objective: To compare the efficacy and safety of a novel formulation of 15% azelaic acid gel (Finacea; Berlex Laboratories, Inc, Montville, NJ) with 0.75% metronidazole gel (MetroGel; Galderma Laboratories LP, Fort Worth, Tex) as topical therapy for moderate, papulopustular facial rosacea. Design: Multicenter, double-blind, randomized, parallel-group study. Setting: Thirteen US centers. Patients: A total of 251 patients with papulopustular rosacea with persistent erythema and telangiectasia. Interventions: Patients were randomized to receive azelaic acid gel or metronidazole gel twice daily for 15 weeks. Main Outcome Measures: Nominal and percent change in inflammatory lesion count, change in erythema and telangiectasia severity ratings, investigator's global assessment of rosacea, and investigator's and patient's overall improvement ratings. Results: Azelaic acid gel was superior to metronidazole gel in reduction of mean nominal lesion count (-12.9 vs -10.7, respectively) ($P = .003$) and mean percent decrease in inflammatory lesions (-72.7% vs -55.8%, respectively) ($P < .001$). With respect to erythema severity, 56% of azelaic acid gel-treated patients were rated improved vs 42% of metronidazole gel-treated patients ($P = .02$). The effectiveness of metronidazole gel on these variables seemed to plateau after week 8, whereas azelaic acid gel demonstrated progressive improvement through week 15. Neither treatment had a clinically appreciable effect on telangiectasia. Both the investigator's global assessment ($P = .02$) and overall assessment of improvement ($P = .005$) showed a significant therapeutic advantage for azelaic acid gel. Azelaic acid gel also scored higher on the patient's overall assessment of efficacy. Both treatments were rated as having high cosmetic acceptability. No serious or systemic treatment-related adverse events were reported in either group. Conclusion: Use of 15% azelaic acid gel twice daily for 15 weeks demonstrated significant superiority over using 0.75% metronidazole gel in improving principal signs of rosacea (inflammatory lesions and erythema).

Bamford J {a}, Gessert C, Renier C. Topical azelaic acid in the treatment of rosacea. 62nd Annual Meeting of the Society for Investigative Dermatology, Washington, DC, USA, May 09-12, 2001. Journal-of-Investigative-Dermatology, August, 2001, vol. 117, no. 2, p. 547, Abstr No 947

Kurdina M I TI: Azelaic acid (skinoren) for rosacea therapy SO: Vestnik-Dermatologii-i-Venerologii, 2000, no. 1, p. 34-36

In the present paper, a review of the literature on pharmacological characteristics and therapeutic effects of azelaic acid is supplemented by the results of the evaluation of its clinical efficiency in 23 female patients with rosacea. Eight (34,8%) women having erythematopapular rosacea received monotherapy with skinoren cream containing 20% of azelaic acid (group 1). Fifteen remaining patients (65,2%) were offered combined treatment which included Trichopol tablets (0,25 g thrice daily for one month) and skinoren (group 2). Patients of both groups responded to the treatment by marked improvement of eruption within 7-10 days (mean) after the initiation of therapy, in the absence of subjective sensations and newly-formed erythematous or papular elements. Pustules were totally resorbed 4 weeks after the beginning of therapy (group 2). All morphological elements except telangiectasia degenerated after 8-12 weeks. Neither therapeutic modality induced adverse reactions.

Bjerke R , Fyrand O, Graupe K. A double-blind comparison of azelaic acid 20% cream and its vehicle in the treatment of papulo-pustular rosacea. Acta –Derm-Venereol 1999; 79/6 : 456-459

Previous investigations have indicated that topical azelaic acid has beneficial effects in rosacea. Therefore, this 3-month randomized, double-blind, multicenter study compared the efficacy and safety of azelaic acid 20% cream to its vehicle in the treatment of papulo-pustular rosacea. One hundred sixteen patients were enrolled in the study, medication was applied twice daily. Azelaic acid cream produced significantly greater mean reductions than vehicle in total inflammatory lesions (azelaic acid: 73.4%; vehicle: 50.6%; ($P = .011$), and erythema severity score (azelaic acid: 47.9%; vehicle: 37.9%; ($P = .031$). Azelaic acid cream treatment also resulted in significantly more favorable overall improvements than vehicle in both physician ($P = .020$) and patient ratings ($P = .042$). Neither azelaic acid cream nor vehicle produced any clinically relevant improvement in telangiectasia. Local adverse events were transient and mainly mild or moderate, and rates were similar for azelaic acid cream (39.5%) and vehicle (38.5%). Burning was the symptom most frequently reported. More than 90% of patients rated the overall local tolerability of their treatment as good or acceptable. In conclusion, azelaic acid 20% cream is effective and well-tolerated in the treatment of papulo-pustular rosacea.

Maddin S. A comparison of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea_ J-AM-ACAD-DERMATOL, 1999; 40: 961-965

Background: Although it is important for physicians to have sufficient clinical data on which to base treatment decisions, little comparative data exist regarding newer treatment modalities for rosacea. Objective: The goal of the study was to compare the efficacy and safety of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. Parameters of patient satisfaction to treatment were also assessed. Methods: Forty patients with the clinical manifestation of symmetric facial rosacea were investigated in this single-center, double-blind, randomized, contralateral split-face comparison clinical trial. Results: After 15 weeks of treatment, both azelaic acid and metronidazole induced significant, albeit equal reductions in the number of inflammatory lesions (pustules and papules). A significantly higher physician rating of global improvement was achieved with azelaic acid. Changes in the rosacea signs and symptoms of dryness, burning, telangiectasia, and itching were equal between treatments. A reduction in erythema tended toward significance with azelaic acid at week 15. A trace amount of stinging on application was noted with azelaic acid; however, such discomfort did not appear to concern patients because their overall impression of azelaic acid was superior to that of metronidazole. Conclusion: Azelaic acid 20% cream provides an effective and safe alternative to metronidazole 0.75% cream with the added benefit of increased patient satisfaction.

Bjerke R , Fyrand O, Graupe K, Zaumseil R-P. A multicentre comparison of 20% azelaic acid cream against placebo in the treatment of papulopustular rosacea. Presentation at the Annual Meeting of the Norwegian Dermatological Society, 1994.

Nazzaro-Porro M, Passi S, Picardo M, Balus L, and Breathnach AS. L'acido azelaico nella rosacea? (Azelaic acid in rosacea ?) Giornale Italiano di Dermatologica e Venerologica 1991; 126: 19-27

Carmichael AJ, Marks R, Graupe KA, and Zaumseil RP. Topical azelaic acid in the treatment of rosacea. J Derm Treat 1993; 4: S19-S22

Azelaic acid is now an established therapeutic agent for acne vulgaris, where its antibacterial and comedolytic activity is responsible in the main for its beneficial effects. In this report we describe the results of a single-centre double-blind controlled contralateral split-face study of the effects of 20% azelaic acid cream in patients with rosacea. The study was designed as a randomized half-face comparison between a 20% azelaic acid cream preparation and its identical-appearing vehicle as placebo. Patients were treated over a 9-week period and reviewed 4 weeks after the end of the treatment period. Both 'sides' showed a reduction in papules, pustules and erythema, although the degree of improvement was superior on the azelaic acid-treated sides. This was also the case for the subjective overall evaluation used. No effect on telangiectasia was recorded. Minor degrees of skin irritation were recorded on both treatment sides in nearly equal numbers, although in the first 3 weeks this was more pronounced on the azelaic acid-treated sides. No serious adverse effects were experienced and no patient had to stop treatment prematurely on this account.

1.2.2 General reviews on rosacea-therapy including Azelaic acid

Gupta A K, Chaudhry M M. Critical review of the manner in which the efficacy of therapies for rosacea are evaluated. INTERNATIONAL-JOURNAL-OF-DERMATOLOGY, 2003, V42, N11, NOV, pp 909-916

Background Rosacea is a relatively common disorder that may affect individuals of all races, particularly those of northern European descent. Its onset generally occurs in individuals between the ages of 20 and 50 years. Rosacea may be classified into four subtypes and one variant. Although individuals with rosacea may not pass through all of the stages, the primary features of the disorder include frequent flushing and blushing, nontransient erythema, the presence of papules and pustules, and telangiectasia. Many agents have been used to treat rosacea stigmata, especially because none of these is uniformly effective. Aim To identify the parameters that are used to evaluate the response to therapy when different agents are used to treat rosacea. For a given parameter, to determine whether the different trials are consistent in the manner in which this variable is measured. Methods The reports on the efficacy and safety of the different drug therapies used to treat rosacea were identified. We searched MEDLINE (1966 to June 2002) for studies where rosacea was treated. The parameters used to evaluate the efficacy of therapy were determined. For each parameter, the ways in which it has been measured were identified. Results Efficacy of treatment is generally judged by evaluating the effect of the intervention on papules and pustules, erythema, and telangiectasia. Manual lesional counts of papules and pustules are usually performed. There is, however, substantial variation in the methodology chosen for comparison of erythema and telangiectasias. Color scales are popular for erythema and telangiectasia, while grading scales are most commonly used for physician and patient evaluations. Conclusions For each of the parameters that are commonly used to measure the efficacy of treatments for rosacea, the different approaches by which it has been measured in the various trials have been highlighted; these dissimilarities can make it problematic to compare between clinical trials. A greater degree of uniformity in the manner in which the various parameters are evaluated would enable a more objective comparison between the studies.

Cohen A F, Tiemstra J D. Diagnosis and treatment of rosacea. Journal of the American Board of Family Practice, 2002, Vol/Iss/Pg. 15/3 (214-217)

Background: Rosacea is a common skin disorder affecting middle-aged and older adults. Many patients mistakenly assume that early rosacea is normally aging skin and are not aware that effective treatments exist to prevent progression to permanent disfiguring skin changes. Methods: The medical literature was reviewed on the pathophysiology, diagnosis, and treatment of rosacea. MEDLINE was searched using the key search terms "rosacea", "rhinophyma", "metronidazole", "Helicobacter pylori", and "facial redness." Results and Conclusions: Rosacea is easily diagnosed by physician observation, and physicians should initiate discussion of rosacea treatment with patients. Effective treatment of rosacea includes avoidance of triggers, topical and oral antibiotic therapy, both topical and oral retinoid therapy, topical vitamin C therapy, and cosmetic surgery.

Del Rosso J Q. A status report on the medical management of rosacea: Focus on topical therapies. CUTIS, 2002, V70, N5, NOV, pp 271-275

1.3 Pigmentation disorders

Halder R M, Richards G M. Management of dyschromias in ethnic skin. Dermatologic Therapy, 2004, Vol/Iss/Pg. 17/2 (151-157)

Pigmentary disorders are one of the most common skin disorders among people of color. Dyspigmentation in the form of either hyperpigmentation or hypopigmentation is often psychologically devastating to patients with darker skin. There is marked contrast between normally pigmented hyperpigmented, hypopigmented or depigmented skin in people of color. Despite being common, pigmentary disorders remain difficult to treat.

Lacz N L, Vafaie J, Kihiczak N I, Schwartz R A. Postinflammatory hyperpigmentation: A common but troubling condition. International Journal of Dermatology, 2004, Vol/Iss /Pg. 43/5 (362-365)

Victor F C, Gelber J, Rao B. Melasma: A review. Journal of Cutaneous Medicine and Surgery, 2004, Vol/Iss/Pg. 8/2 (97-102)

Objective: To better understand melasma, a review of its etiologic factors, classification, pathogenesis, and treatment was undertaken. Methods: Articles discussing the above aspects of melasma were used to demonstrate what is currently known about the disease and how to treat it. Results: Melasma is associated with many etiologic factors, most importantly, sun exposure. It occurs in three distributions and has four reported patterns of pigmentation. Among the many differences between melasma and normal skin, melasma skin contains increased melanin, melanocytes, and melanosomes, as well as increased synthesis of tyrosinase. Its pathogenesis remains largely unknown. Treatment consists of phenolic and nonphenolic depigmenting agents, chemical peels, lasers, and dermabrasion. Conclusion: Melasma is a common skin disorder. Although melasma has been studied, its pathogenesis remains largely unknown and its treatment is still met with difficulty. Randomized controlled trials involving larger numbers of patients and comparing treatments, as well as studying combination therapies, would be beneficial.

Pezeshki S, Bell F E, Grummer S, McMichael A J. Therapeutic options for melasma. Cosmetic Dermatology, 01 MAR 2003, Vol/Iss/Pg. 16/3 (33-36+39-42+45)

Melasma is a relatively common dark brown hyperpigmentation, occurring most often on the female face (forehead, cheeks, nose, upper lip, chin) and adversely affecting quality of life. Numerous treatments are available for this disease, but no single one is totally effective. This review underscores the most and least effective treatments and those being developed. Hydroquinone used alone and with other agents, as well as topical retinoids, (alpha)-hydroxy acids, topical corticosteroids, and other topical regimens, are reviewed. Response of melasma to chemical peels, lasers, and sunscreens is described, and relevant clinical trial and experimental data are presented. This review is a reasonable guide to available treatments and expectations regarding outcomes.

Scheman A J, Conde A. Contact dermatitis from *Cnidioscolus angustidens*. Contact Dermatitis, 2001, Vol/Iss/Pg. 45/1 (39)

Katsambas A D, Stratigos A J. Depigmenting and bleaching agents: Coping with hyperpigmentation. CLINICS-IN-DERMATOLOGY, 2001, V19, N4, JUL-AUG, pp 483-488

Jimbow K, Minamitsuji Y TI: Topical therapies for melasma and disorders of hyperpigmentation Dermatologic Therapy, 2001, Vol/Iss/Pg. 14/1 (35-45)

Facial hyperpigmentation is usually a reflection of an increased amount of melanin either within the epidermis, the dermis, or both (mixed pattern). The increase in melanin content is due to an increased number of functioning melanocytes (melanocytosis), an increased amount of melanin production without a numerical alteration of melanocytes (melanosis), or both. Topical hypo/depigmenting agents are most effective in those disorders where the increased melanin pigment (secondary to melanocytosis or melanosis) is within the epidermis. In patients with melasma, one of the more common causes of facial hyperpigmentation, two major groups of hypo/depigmenting agents have been used: phenolic derivatives and nonphenolic compounds. Hydroquinone, a phenolic derivative, has been used most extensively. It is applied to areas of involvement, either alone or in combination with one or two of the following: tretinoin, salicylic acid, glycolic acid, or corticosteroid. Phenolic thioethers are a new class of phenolic derivatives, and they exhibit both cytotoxic and cytostatic effects selectively on melanocytes. Nonphenolic depigmenting agents include azelaic acid and kojic acid. If the facial hyperpigmentation is not improved by first-line topical therapies, chemical peels may be used in combination. The precise cause of melasma is not known, and multiple factors have been implicated. However, a genetic predisposition and exposure to ultraviolet (UV) light are very important factors. Avoidance of direct exposure to sunlight and application of broad-spectrum sunscreens are required during and after the period of active treatment. In addition to melasma, other causes of facial hyperpigmentation include Riehl's melanosis, photocontact dermatitis, the sequelae of inflammatory diseases such as acne vulgaris and cutaneous lupus, and nevus of Ota.

Gibbs P, Gonzalez R, Lee L A, Walsh P TI: Medical management of cutaneous malignancies. Clinics in Dermatology 19, 3: 298-304 (2001)

Fusco F J TI: The aging face and skin: Common signs and treatment. Clinics in Plastic Surgery, 2001, Vol/Iss/Pg. 28/1 (1-12)

In this article, the most common cutaneous manifestations of photodamage and chronological aging, with the exception of invasive malignancies, are reviewed. Current nonsurgical approaches to the amelioration of the manifestations are discussed, including application of various topical preparations, noninvasive physical and chemical procedures for removal of proliferative lesions, and the options for soft-tissue augmentation.

Alchorne M M A, Cestari S C P TI: Dermatologic treatment of hyperchromic lesions of skin TT: TRATAMENTO DERMATOLOGICO DAS HIPERCROMIAS. Revista Brasileira de Medicina, 2001, Vol/Iss/Pg. 58/3 (162-163)

The alterations of the skin colour are divided in hypopigmentation or hypochromic lesions and hyperpigmentation or hyperchromic lesions. The authors made general considerations on clinical aspects and treatment of the most frequent hyperchromic lesions of the skin.

Dover J S, Hruza G TI: Lasers in skin resurfacing. Australasian Journal of Dermatology, 2000, Vol/Iss/Pg. 41/2 (72-85)

Laser skin resurfacing has revolutionized the approach to facial skin rejuvenation over the last decade. It has also added an approach to managing both atrophic and hypertrophic scars. This paper will review the basic principles of laser skin resurfacing, the different lasers used, the approach to treatment and potential complications of the procedure, followed by a discussion of future prospects in the field.

Draelos Z D TI: Novel topical therapies in cosmetic dermatology. CURRENT-PROBLEMS-IN-DERMATOLOGY-US, 2000, V12, N5, SEP-OCT, pp 235-239

Fernandes D TI: Hydroquinone - A harmful agent (3). South African Medical Journal, 2000, Vol/Iss/Pg. 90/9 I

Pandya A G, Guevara I L TI: Disorders of hyperpigmentation. DERMATOL-CLIN, 2000, V18, N1, JAN, pp 91-98

Hyperpigmentation is a common disorder of the skin, particularly in brown-skinned patients. Melasma is a common cause of facial hyperpigmentation and can be resistant to treatment. A combination of topical creams and gels, chemical peels, and sunscreens may be necessary for significant improvement. Erythema dyschromicum perstans is a dermal pigmentation seen on the trunk and proximal extremities, most commonly presenting in dark-skinned Hispanics. Drug-induced and postinflammatory hyperpigmentation may last for many months after the offending drug or dermatitis has been eliminated. These disorders, including their management, is reviewed in this article.

Griffiths C E M TI: Melasma SO: Journal of Dermatological Treatment, 2000, Vol/Iss/Pg. 11/3

Grimes P E TI: Skin and hair cosmetic issues in women of color , Dermatologic Clinics 18, 4: 659-665 (2000)

Women of color comprise many phenotypically heterogeneous groups. Despite the general heterogeneity, however, there are unique skin and hair care issues and needs. These issues often present therapeutically challenging problems for the dermatologist and the skin and hair care industry.

Herlyn M, Schneeberger A, Maurer D, Stingl G, Kuwert C, Slominski A, Lukiewicz S, Armstrong C, Ansel J TI: Controversies in experimental dermatology. What is the most promising strategy for the treatment of metastasizing melanoma? Experimental Dermatology, 2000, Vol/Iss/Pg. 9/6 (445-451)

Jansen T TI: Chemical peeling TT: CHEMICAL PEELING, MMW-FORTSCHR-MED, 20 JAN 2000, Vol/Iss/Pg. 142/3 (39-41)

The dividing line between dermatology and cosmetology is sometimes fluid. At dermatological congresses, cosmetological questions often take up a considerable amount of time. A connection between dermatology and cosmetology are the therapeutic procedures, now known as chemical peeling, aimed in particular at treating photodamaged skin, and hyperpigmentation.

Hermanns J F, Petit L, Martalo O, Pierard-Franchimont C, Cauwenbergh G, Pierard G E {a} TI: Unraveling the patterns of subclinical pheomelanin-enriched facial hyperpigmentation: Effect of depigmenting agents, Dermatology (Basel), 2000, vol. 201, no. 2, p. 118-122

Background: During photoaging, the density of melanin chromatophores is heterogeneous in the epidermis. Aims: To define the patterns of pheomelanin-enriched melanotic hypermelanosis of the face in phototype II subjects and to assess the effect of depigmenting agents. Azelaic acid and glycolic acid were tested as well as a soy extract, reported to reduce pigmentation through interaction with the protease-activated receptor 2 (PAR-2) of keratinocytes. Method: Evaluations were made by image analysis of high magnification pictures obtained by a video camera equipped with an internal ultraviolet-emitting unit (Visioscan(R)). Results: Three patterns of subclinical facial hypermelanosis were recognized including the spotty perifollicular type, the accretive globular type and the elongated type of the sunny side of wrinkles. Azelaic acid and the soy extract led to significant skin lightening after a 3-week treatment. By contrast,

glycolic acid showed an inconsistent effect. Conclusion: Sensitive fluorescence video recording combined with image analysis represents an advance in the noninvasive assessment of the mottled subclinical skin pigmentation. The depigmenting effect observed with the soy extract indicates that the inhibition of PAR-2 may be a novel way to approach certain pigmentary disorders of the skin.

Nouri K, Bowes L, Chartier T, Romagosa R, Spencer J TI: Combination treatment of melasma with pulsed CO2 laser followed by Q-switched alexandrite laser: A pilot study DERMATOLOGIC-SURGERY, 1999, 25: 494-497

BACKGROUND. Melasma is very difficult to treat and often refractory to treatment with topical creams and pigmented-lesion lasers. **OBJECTIVE.** Pulsed CO2 laser alone is compared with the combination of pulsed CO2 laser followed by Q-switched alexandrite laser in the treatment of dermal-type melasma. This combination is proposed to be effective by first destroying the abnormal melanocytes with the pulsed CO2 laser and then selectively eliminating the dermal melanin with the alexandrite laser. **METHODS.** Four patients were randomly chosen for each treatment arm. There were multiple follow-up visits for examination by an objective blinded investigator. **RESULTS.** All patients in the combination laser group showed complete resolution, and two patients in the CO2 laser only group had peripheral hyperpigmentation in the long-term follow-up evaluation. **CONCLUSION.** These laser therapies are safe, as there was no scarring and no infection. The combination laser therapy was highly effective in removing the hyperpigmentation and all patients in this group showed complete resolution without any peripheral hyperpigmentation.

Breathnach A S, Azelaic acid : Potential as a general antitumoural agent. Medical Hypotheses {MED-HYPOTHESES}, 1999, 52: 221-226

Azelaic acid is a naturally occurring straight-chained 9-carbon atom dicarboxylic acid which is non-toxic, non-teratogenic, and non-mutagenic. Its antiproliferative and cytotoxic effect on a variety of tumoural cell lines in culture, due to inhibition of mitochondrial oxidoreductases of the respiratory chain and of enzymes concerned with DNA synthesis is well established; normal cells are unaffected at similar dosages and times of exposure. Human melanoma cells xenotransplanted onto athymic nude mice are significantly affected by administration of azelaic acid. Clinically, in humans, it has already been shown to cause regression of melanoma in situ and primary invasive malignant melanoma. These results rank azelaic acid as a potential general antitumoural agent. It can be administered topically, focally, orally, intravenously, intra-arterially, and intralymphatically, all without local or general ill-effects, and is metabolized without harmful side-products. Simultaneous administration by different routes can ensure delivery of high concentrations at lesional sites and for sustained periods. Courses can be repeated. In addition to melanoma, cutaneous and bronchial squamous cell carcinoma, bladder and breast cancers, and leukaemia would seem to be ideal candidates for further clinical investigation and trial of the anti-cancer potential of azelaic acid, as prime, adjuvant, and palliative therapy, and for disseminated disease.

Nazzaro Porro M, Zina G, Breathnach A S, Bernengo M, Passi S, Picardo M, Balus L, De Luca C TI: Topical azelaic acid therapy for palpebral lesions of melanoma in situ (lentigo maligna) and for melanoma in situ progressed to invasive melanoma. A report on four cases . Giornale Ital Dermatol Venereol 133, 2: 79-85 (1998)

Azelaic acid has been shown to have a biological antiproliferative and cytotoxic effect on the abnormally hyperactive and malignant melanocyte both in vivo and in vitro. Here, beneficial effects of topical azelaic therapy on four facial lesions where surgery was not considered to be a primary or available option are described. Two were cases of melanoma in situ involving the lower eyelid. In one, complete regression of the lesion was achieved and maintained for six years. In the other, the overall lesional area was greatly reduced, allowing discrete excision of small relapses with no recurrences for up to nine years: this case demonstrates an adjuvant effect of azelaic acid therapy on surgery, in reducing the overall area to be excised. The other two cases were of melanoma in situ progressed to invasive malignant melanoma in which complete clinical regression of the lesions was achieved, in one case for up to five years. Treatment in these cases was essentially palliative, with probable prolongation of life in one, and certainly, improvement in quality of remaining life in both. Newer formulations for topical application, possibly combined with oral or even systemic administration, could lead to increased delivery of azelaic acid to lesional sites and reduction in treatment time with similar cases in future.

Kakita LS, Lowe NJ. Azelaic acid and glycolic acid combination therapy for facial hyperpigmentation in darker-skinned patients: a clinical comparison with hydroquinone. Clin Ther. 1998 Sep-Oct;20(5):960-70.

This multicenter, randomized, double-masked, parallel-group, 24-week clinical study compared the efficacy of the combination of azelaic acid 20% cream and glycolic acid 15% or 20% lotion with hydroquinone 4% in the treatment of facial hyperpigmentation in darker-skinned patients. At week 24, overall improvement and reduction in lesion area, pigmentary intensity, and disease severity were comparable in the two treatment groups. At some visits, patients treated with an azelaic/glycolic acid combination had slightly greater levels of peeling, burning, stinging, or dryness than did patients treated with hydroquinone, although scores for cutaneous signs and symptoms were always low. The present study demonstrated that the combination of azelaic acid 20% cream and glycolic acid 15% or 20% lotion was as effective as hydroquinone 4% cream in the treatment of hyperpigmentation in darker-skinned patients, with only a slightly higher rate of mild local irritation. These findings suggest that the addition of glycolic acid to azelaic acid treatment for hyperpigmentation is an appropriate alternative in selected darker-skinned patients.

Lowe NJ, Rizk D, Grimes P, Billips M, Pincus S. Azelaic acid 20% cream in the treatment of facial hyperpigmentation in darker-skinned patients. Clin Ther. 1998 Sep-Oct;20(5):945-59.

This multicenter, randomized, double-masked, parallel-group study assessed the efficacy, safety, and tolerability of azelaic acid 20% cream compared with those of its vehicle for the treatment of facial hyperpigmentation in darker-skinned patients (phototypes IV to VI). Following a 24-week treatment period, azelaic acid produced significantly greater decreases in pigmentary intensity than did vehicle as measured by both an investigator's subjective scale ($P = 0.021$) and a chromometer analysis ($P = 0.039$). There was a significantly greater global improvement with azelaic acid than with vehicle at week 24 ($P = 0.008$). Azelaic acid produced a slightly but significantly greater amount of burning (weeks 4 and 12, $P < 0.046$) and stinging (week 4, $P = 0.002$) than did vehicle. At the end of the study, more patients treated with azelaic acid than with vehicle reported having much smoother skin and being very satisfied or satisfied with their treatment. Also, more patients treated with azelaic acid than with vehicle rated their medication as being more effective or the same as past treatments. Thus azelaic acid is an effective and well-tolerated treatment for hyperpigmentation in darker-skinned patients.

McMichael A J TI: Diagnosis and treatment of cutaneous disorders in African-American patients. Current Problems in Dermatology 1998, 10: 93-126

The evaluation and treatment of skin disease in patients of color has long presented a challenge to many dermatologists. From deep pigmentation masking erythema to a predilection for pilar structures, skin disease in African-Americans has many distinguishing factors that may not be observed in other populations. Most dermatologists have little formal training in examining skin of various levels of pigmentation, so it is necessary to identify common presentations of disease in this population. Pigment lability is a common concern among patients of deeply pigmented skin, and it is necessary to understand what is known about therapeutic options for dyschromia. Follicular prominence, granulomatous, and fibromatous changes are common presentations of disease in this population where differential diagnosis must be broadened to ensure correct diagnosis and effective treatment. For all these disorders there are options for treatment that should be enumerated to patients along with potential side effects of treatment. The goal of improving understanding of cutaneous disease in patients of color is to dispel myths that cultural impact is the primary variable causing reaction patterns in African-Americans and to report on the findings of skin disease in this group, which represents an intermixed population. As dermatologists broaden their view of potential disease presentation, patient satisfaction, treatment choices, and, potentially, access to care will be improved. This monograph provides an overview of the ultrastructure of the pigmentation system at the cellular level and what is understood about the role the pigmentation system may play in living patients in response to sun exposure, irritants, allergens, and trauma. Normal variants of skin seen in patients of color are described and what is known about the epidemiology of these normal states is reported. Diagnosis, treatment, and the psychosocial impact of vitiligo is reported as a representative disease of dyschromia. Pseudofolliculitis barbae is discussed as a prototypic disorder of the pilar apparatus and the approach to treatment is discussed. Special attention is given to children with the disorders discussed, and the need to amend therapy to fit a younger patient is explored. Finally, skin cancer in African-American patients is discussed. Reports of predisposing variables to the various forms of skin cancers including basal cell, squamous cell, Bowen's disease and melanoma are discussed. Pigmentation may play a role in protection but is clearly not the only factor protecting against the

development of cutaneous malignancy. What is known about incidence, mortality, and response to treatment for cutaneous basal cell, squamous cell, Bowen's disease, and melanoma are discussed.

Lemon B, Burns R TI: Malignant melanoma: A literature review and case presentation J-FOOT-ANKLE-SURG, 1998, 37: 48-54

The authors present a case report of acral lentiginous malignant melanoma in a 77-year-old male. Melanoma is a rare but increasingly present malignant lesion of the lower extremity. It is the most common malignant neoplasm in blacks and is often misdiagnosed. Early, accurate diagnosis and biopsy of suspicious lesions is the cornerstone of treatment in order to decrease possible future morbidity and mortality. The authors discuss the clinical features, differential diagnosis, predisposing factors,

Piamphongsant T TI: Treatment of melasma: a review with personal experience. Int J Dermatol, 1998, 37: 897-903

Gaspar ZS, Dawber RP. Treatment of lentigo maligna. Australas J Dermatol. 1997 Feb;38(1):1-6; quiz 7-8.

Lentigo maligna (LM) is the in situ phase of lentigo maligna melanoma (LMM) and, if left untreated, 30-50% of cases will progress to LMM, which is now thought to behave as aggressively as any other melanoma. Literature on the treatment of LM including conventional surgery, micrographic Mohs surgery, cryosurgery, radiotherapy, electrodesiccation and curettage. 5-fluorouracil (5-FU), azelaic acid, retinoic acid and lasers are reviewed. It is concluded that micrographic Mohs surgery has the lowest recurrence rates and that conventional surgery, cryosurgery and radiotherapy all have recurrence rates in the order of 7-10%. Therefore, on the basis of the current literature available, all three of these methods could be recommended as primary treatment of LM. It is extremely important when choosing one of the above treatments that the physician is adequately trained in the appropriate technique and understands the limitation of the method used and the need for close follow up of the patient.

Laude TA. Skin disorders in black children. Curr Opin Pediatr. 1996 Aug;8(4):381-5.

Recently, progress and developments have been made in six skin conditions relevant to black children. Infantile acropustulosis may either be idiopathic or may be a sequela of scabies in young infants. The approach to small- or medium-sized congenital melanocytic nevi in black children must be different because the risk for malignant transformation into melanoma is exceedingly small. Keloids and hypertrophic scars in children are effectively treated with silicone gel sheeting. Tinea capitis caused by *Trichophyton tonsurans* remains to be a very common infection among black children. The newer systemic antifungal agents have no significant advantage over griseofulvin. Hair problems resulting from grooming practices or hair styling are preventable. For postinflammatory hyperpigmentation, azelaic acid holds promise.

Nazzaro-Porro M, et al. A case of recurrent (following surgery x2) invasive malignant melanoma with satellitosis (stage IIIA) successfully resolving after azelaic acid treatment administered by several routes. Clin Exp Dermatol. 1996 Jul;21(4):321-3.

Breathnach AS. Melanin hyperpigmentation of skin: melasma, topical treatment with azelaic acid, and other therapies. Cutis. 1996 Jan;57(1 Suppl):36-45.

Clinical studies of patients with melasma have shown that topical 20 percent azelaic acid is superior to 2 percent hydroquinone and as effective as 4 percent hydroquinone, without the latter's undesirable side effects. Tretinoin appears to enhance this effect of azelaic acid. Azelaic acid with tretinoin caused more skin lightening after three months than azelaic acid alone, and a higher proportion of excellent responders at the end of treatment. The effect of azelaic acid can be attributed to its ability to inhibit the energy production and/or DNA synthesis of hyperactive melanocytes, and partially to its antityrosinase activity. This may also account for the beneficial effect on postinflammatory hyperpigmentation. Destruction of malignant melanocytes by a combination of the same activities, enhanced by the greater permeability of tumoral cells to azelaic acid

Grimes PE. Melasma. Etiologic and therapeutic considerations. Arch Dermatol. 1995 Dec;131(12):1453-7.

BACKGROUND: Melasma is a common acquired symmetric hypermelanosis characterized by irregular light- to gray-brown macules and patches involving sun-exposed areas of skin. Etiologic factors in the pathogenesis of melasma include genetic influences, exposure to UV radiation, pregnancy, hormonal therapies, cosmetics, phototoxic drugs, and antiseizure medications. **OBSERVATIONS:** Melasma is often a therapeutically challenging disease, and current treatments include hypopigmenting agents, chemical peels, and lasers. Hypopigmenting agents include phenolic and nonphenolic derivatives. Phenolic agents include hydroquinone and hydroquinone combination preparations. Despite controversies regarding the issue of hydroquinone-induced ochronosis, hydroquinone remains the most effective topically applied bleaching agent approved by the Food and Drug Administration for the treatment of melasma. Nonphenolic bleaching agents include tretinoin and azelaic acid. Superficial, medium, and deep chemical peels are more often used in lighter-complexioned patients. Such peels should be used with caution in blacks. Although lasers have demonstrated significant efficacy in the treatment of a variety of hyperpigmentary disorders, their precise efficacy and place in the therapy of melasma have yet to be established. **CONCLUSIONS:** In the hierarchy of therapies for melasma, the treating physician must consider the devastating psychosocial impact of pigmentary imperfections within the realm of the benefits and risks associated with each treatment.

Sivayathorn A, Verallo-Rowell VM, Graupe K. 20% Azelaic acid cream in the topical treatment of melasma: a double-blind comparison with 2% hydroquinone. Eur J Dermatol 1995

Zaumseil R-P, Graupe K. Topical azelaic acid in the treatment of melasma: pharmacological and clinical considerations. In : Melasma-New approaches to therapy. pp. 19-41, Martin Dunitz Ltd, 1995.

Kang H, Lee J Y, Kim C W TI: A case of acute reticulate hyperpigmentation on the face and neck SO: Annals of Dermatology 1995, 7: 244-247

Multiple, reticulated, dark brown colored, macules and patches suddenly developed on the face and neck of a 48-year-old Korean woman two days after a traffic accident. On physical examination and laboratory tests including serum melanocyte-stimulating hormone, estrogen and progesterone level, no abnormalities were found except cervical pain. Histological examination of hematoxylin-eosin stained sections revealed increased melanin pigmentation in the basal layer, but the number of melanocytes was not changed in DOPA stained section. Topical application of 2% hydroquinone and 20% azelaic acid ointments had been applied successively for two months each without any apparent improvement. Herein we present a case of reticulate hyperpigmentation on the face and neck, which is very acute and whose causative factors are not certain.

Gatti S, et al. Treatment of reticulate acropigmentation of Kitamura with azelaic acid. J Am Acad Dermatol. 1993 Oct;29(4):666-7.

Verallo-Rowell WM, Sioson-delos Reyes G. South Asian experience with azelaic acid in melasma. Med Prog J 1993; 20(Suppl): 26-30.

Rodriguez Prieto MA, et al. Treatment of lentigo maligna with azelaic acid. Int J Dermatol. 1993 May;32(5):363-4.

Kameyama K, et al. Treatment of reticulate acropigmentation of Kitamura with azelaic acid. An immunohistochemical and electron microscopic study. J Am Acad Dermatol. 1992 May;26 (5 Pt 2):817-20.

No successful therapy has been reported for reticulate acropigmentation of Kitamura, which is an autosomal dominant dermatosis. We treated a patient with 20% azelaic acid ointment. Within several weeks the pigmentation was remarkably decreased and no side effects were observed. Histologic examination revealed an increased number of dopa-positive melanocytes. These cells reacted strongly to staining with antityrosinase antibody or antityrosinase-related protein antibody. Electron microscopic findings showed many melanosomes within melanocytes, keratinocytes, and melanophages. These findings suggest that the hyperpigmentation of reticulate acropigmentation of Kitamura is the result of an excess amount of melanin production caused by activation of melanocytes in the basal layer.

Duteil L, Ortonne JP Colorimetric assessment of the effects of azelaic acid on light-induced skin pigmentation. Photodermatol Photoimmunol Photomed. 1992 Apr; 9(2):67-71.

A 20% azelaic acid (AZA) cream is currently used as a therapeutic agent in the treatment of acne vulgaris. Therefore, this product is intended to be applied on frequently or continuously sun-exposed skin. In certain disorders of hyperpigmentation, AZA has been reported to have a depigmenting effect as well, while showing no significant activity on normal skin. It has been suggested that AZA selectively inhibits hyperactive or malignant melanocytes. Knowing that light-stimulated melanocytes are in a state of hyperactivity, it seemed worthwhile to investigate AZA activity on light-induced skin pigmentation. This study aimed to assess the activity of 20% AZA cream on light-induced skin pigmentation in 10 subjects. There were 5 test zones, all located on the middle of the back: 2 were treated with AZA cream, 2 others with the vehicle and 1 was left untreated. Each product was applied twice daily, 5 days a week, for 4 weeks on one zone, and for 5 weeks on the other. In the middle of the fourth week, the tested zones were exposed to ultraviolet B (UVB) + UVA + visible light, with a total of 3 times the minimal erythema dose distributed progressively over 3 consecutive days. Seven and 10 days after the last irradiation, the induced photopigmentation was assessed by colorimetric and visual means. Compared with its vehicle, the AZA cream had neither a depigmenting effect nor a preventive effect on the light-acquired skin pigmentation. Moreover, interrupting or continuing the AZA treatment after skin irradiation had no influence on the resulting pigmentation.

Balina LM, Graupe K. The treatment of melasma. 20% azelaic acid versus 4% hydroquinone cream. Int J Dermatol. 1991 Dec;30(12):893-5.

The efficacy of 20% azelaic acid cream and 4% hydroquinone cream, both used in conjunction with a broad-spectrum sunscreen, against melasma was investigated in a 24-week, double-blind study with 329 women. Over the treatment period the azelaic acid cream yielded 65% good or excellent results; no significant treatment differences were observed with regard to overall rating, reduction in lesion size, and pigmentary intensity. Severe side effects such as allergic sensitization or exogenous ochronosis were not observed with azelaic acid.

Landthaler M, Stolz W, Braun-Falco O [Lentigo of the glans penis]. Hautarzt. 1989 Apr;40(4):222-5. German.

The report deals with two male patients with penile lentigo. Histologically acanthosis, basal hyperpigmentation, and melanocytes without atypia were found. Ultrastructural analysis revealed the presence of single melanosomes within the keratinocytes as the most prominent feature of penile lentigo. In one patient, topical treatment with azelaic acid resulted in some improvement within 4 months.

Breathnach AS, et al. Azelaic acid therapy in disorders of pigmentation. Clin Dermatol. 1989 Apr-Jun;7(2):106-19. Review.

Nazzaro-Porro M, et al. Ten years' experience of treating lentigo maligna with topical azelaic acid. Acta Derm Venereol Suppl (Stockh). 1989;143:49-57.

Topically applied azelaic acid led to complete clinical and histological resolution of lentigo maligna in more than 50 patients. The therapeutic results are highly durable, in fact 27 out of the 50 are still disease-free, 5-

10 years after treatment. There was a recurrence in 11 cases, but all resolved on renewing treatment. The effect of azelaic acid is illustrated in a patient with lentigo maligna monitored clinically, histologically and ultrastructurally over the past 5 years.

Rigoni C, Toffolo P, Serri R, Caputo R Use of a cream based on 20% azelaic acid in the treatment of melasma. G Ital Dermatol Venereol. 1989 Jan-Feb;124(1-2):I-VI. (Italian)

A 20% azelaic acid base cream (Skinoren-Schering) known in the treatment of acne has been used in melasma. The statistically processed results refer to 39 patients treated for 6 months with 2 applications/die. The reduction in melasma intensity was obtained in all patients bar two whose basal pigmentation situation was already compromised. Overall assessment on a graduated scale in cm evidences, after 6 months of treatment, a mean reduction in pigmentation of 51.3% understood as intensity and surface. The overall judgment of physician and patient on the preparation coincide with some 79% excellent and good on the part of the physician and 85% on the part of the patient. Noteworthy is the absolute absence of sensitisation or leukoderma or any of the other typical side-effects of the other depigmentants available thus far.

Verallo-Rowell VM, Verallo V, Graupe K, Lopez-Villafuerte L, Garcia-Lopez M. Double-blind comparison of azelaic acid and hydroquinone in the treatment of melasma. Acta Derm Venereol Suppl (Stockh). 1989;143:58-61.

Melasma is a macular hypermelanosis of the sun-exposed areas of the face and neck. The clinical efficacy of azelaic acid (20%) and hydroquinone creams (2%) in the treatment of this benign pigmentary disorder was compared in a randomized, double-blind study with 155 patients of Indo-Malay-Hispanic origin. The creams were applied twice daily. A broad spectrum sunscreen was used concomitantly. Over a period of 24 weeks, 73% of the azelaic acid patients, compared with 19% of the hydroquinone patients, had good to excellent overall results, as measured by the reduction of melasma pigmentary intensity and lesion size. Transient mild to moderate irritant reactions were initially seen with both test drugs.

Sowden J, et al. Malignant melanoma arising in the scar of lupus vulgaris and response to treatment with topical azelaic acid. Clin Exp Dermatol. 1988 Sep;13(5):353-6.

Piquero Martin J, et al. Double-blind clinical study of the treatment of melasma with azelaic acid versus hydroquinone. Med Cutan Ibero Lat Am. 1988;16(6):511-4. (Spanish)

A comparative double-blind study was carried out on sixty patients received oral contraceptives. Patients were treated with 20% azelaic acid or 4% hydroquinone. They were observed for 24 weeks and the results compared and checked for side effects. The results showed that the azelaic acid was not better than the hydroquinone in the treatment of melasma but it could be used as alternative drug.

Grosshans E, et al. Therapeutic depigmentation agents. Schweiz Rundsch Med Prax. 1987 Sep 22;76(39):1077-81.

[No authors listed] Azelaic acid in lentigo maligna. Br J Dermatol. 1987 Apr;116(4):605-7.

Robins EJ, et al. Effectiveness of azelaic acid as a depigmenting and chemotherapeutic agent. J Invest Dermatol. 1986 Aug;87(2):293-4.

McLean DI, Peter KK. Apparent progression of lentigo maligna to invasive melanoma during treatment with topical azelaic acid. Br J Dermatol. 1986 Jun;114(6):685-9.

Nine patients with lentigo maligna were treated with topical azelaic acid. Clinical improvement was observed in four, with complete clearing in one. Two patients developed invasive lentigo maligna

melanoma while on treatment. Caution should be exercised in the use of topical azelaic acid in the treatment of lentigo maligna.

Ortonne JP. Depigmenting chemical agents. Ann Dermatol Venereol. 1986;113(8):733-6. (French)

Willshaw HE, et al. Azelaic acid in the treatment of ocular and adnexal malignant melanoma. Br J Ophthalmol. 1983 Jan;67(1):54-7.

[No authors listed] [Advances in pigment studies]. Hautarzt. 1983;34 Suppl 6:211-23. (German)

Nazzaro-Porro M, et al. Effect of azelaic acid on human malignant melanoma. Lancet. 1980 May 24;1(8178):1109-11.

Nazzaro-Porro M, et al. Effect of dicarboxylic acids on lentigo maligna. J Invest Dermatol. 1979 Jun;72(6):296-305.

Nazzaro-Porro M, Passi S. Effetto degli acidi dicarbossilici in alcune dermatosi pigmentarie. G Ital Dermatol Venereol 1978a; 113: 401-404.

2. Pharmacology and pharmacokinetics

2.1 Pharmacology and mechanism of action

Malaisse W J {a}, Greco A V, Mingrone G TI: Effects of aliphatic dioic acids and glycerol-1,2,3-tris (dodecanedioate) on D-glucose-stimulated insulin release in rat pancreatic islets. British-Journal-of-Nutrition, November, 2000, vol. 84, no. 5, p. 733-736

Aliphatic dioic acids have been proposed as alternative nutrients in selected clinical situations. In this study, their possible insulinotropic action was investigated in isolated rat pancreatic islets prepared from fed rats. Azelaic acid, sebacic acid and tridecanedioic acids, when tested at a 10.0 mM concentration, were found to augment insulin release evoked by D-glucose (7.0 mM) in the pancreatic islets. Likewise, glycerol-1,2, 3-tris(dodecanoedioate), when used at concentrations close to 1.0 mM, increased the secretory response to the hexose. It is speculated that these findings may extend to insulin-producing cells, the knowledge that aliphatic dioic acids or their esters may act as energy substrates, e.g. in parenteral nutrition.

Mingrone G {a}, Malaisse W J TI: Effects of azelaic, sebacic and dodecanoic acids on insulin release. 35th Annual Meeting of the European Association for the Study of Diabetes, Brussels, Belgium, September 28-October 2, 1999 Sponsored by: European Association for the Study of Diabetes. Diabetologia 42, SUPPL 1: A161 (1999), Abstr No 600

2.1.1 Acne and rosacea

Kroll C, Langner A, Borchert H H TI: Nitroxide metabolism in the human keratinocyte cell line HaCaT. FREE-RADICAL-BIOLOGY-AND-MEDICINE, 1999, V26, N7-8, APR, pp 850-857. ISSN: 0891-5849

Metabolism of different nitroxides with piperidine structure used as spin labels in electron spin resonance (ESR) studies in vitro and in vivo was investigated in human keratinocytes of the cell line HaCaT by GC and GC-MS technique combined with S-band ESR. Besides the well known reduction of the nitroxyl radicals to the ESR silent hydroxylamines as primary products our results indicate the formation of the corresponding secondary amines. These reductions are inhibited by the thiol blocking agent N-ethylmaleimide and by the strong inhibitors of the thioredoxin reductase (TR) 2-chloro-2, 3-nitrobenzene and 2, 6-dichloroindophenol. The competitive inhibitor TR inhibitor azelaic acid and the cytochrome P-450 inhibitor metyrapone lack any effects. The rates of reduction to the hydroxylamines and secondary amines were dependent on the lipid solubility of the nitroxides. Therefore, it can be assumed that the nitroxides must enter the cells for their bioreduction. The mostly discussed intracellular nitroxide reducing substances ascorbic acid and glutathione were unable to form the secondary amines. In conclusion, our results suggest that the secondary amine represents one of the major metabolites of nitroxides besides the hydroxylamine inside keratinocytes formed via the flavoenzyme thioredoxin reductase most probably. Further metabolic conversions were detected with 4-oxo-2,2,6, 6-tetramethylpiperidine-1-oxyl and the benzoate of 4-hydroxy-2,2, 6,6-tetramethylpiperidine-1-oxyl as substrates.

Choi Seung Man {a}, Kim Chang Deok, Lee Min Ho, Choi Young Ho, Rang Moon Jeong, Ahn Ho Jung, Yun Yeo Pyo TI: Screening of 5alpha-reductase inhibition and comedolytic effects from natural products. Yakhak-Hoeji, June, 1999, vol. 43, no. 3, p. 342-350 ISSN: 0513-4234

The antibacterial activity against *Propionibacterium acnes* (*P. acnes*), 5alpha-reductase inhibition and comedolytic effects are the important pharmacological target sites of antiacne drugs. We previously reported on the antibacterial activities against *P. acnes* by natural products. In the present study the screening of 5alpha-reductase inhibition and comedolytic effects from natural products were performed. Seven natural products such as *Angelica koreana*, *Sophora flavescens*, *Prunus persica*, *Bombyx mori*, *Areca catechu*, *Galla rhois* and *Gleditschia koraiensis* perfectly inhibited the activity of 5alpha-reductase at the concentration of 0.01% (w/v). Sixteen natural products which were shown to have the potent antibacterial activities against *P. acnes* or 5alpha-reductase inhibition activities were assayed for the comedolytic test. In the results of comedolytic effects on experimentally-induced comedones (EIC), *Sophora flavescens* showed the strongest comedolytic effect on EIC, and *Polygonum cuspidatum* and *Angelica koreana* showed stronger comedolytic effects on EIC than azelaic acid used for a positive control at the concentration of 3% (w/v). These results suggest that several natural products including *Sophora flavescens* can be developed as noble antiacne agents.

van Hoogdalem E J TI: Transdermal absorption of topical anti-acne agents in man: review of clinical pharmacokinetic data J Eur Acad Dermatol Venereol 1998, 11, Suppl 1: 13-19

Background Apart from oral drug treatment, drug therapy in acne vulgaris comprises topical treatment with agents with a primarily keratolytic action (e.g. tretinoin and benzoylperoxide), and with antibiotics (clindamycin, erythromycin, and erythromycin-zinc complex). The acne grade in the particular patient usually determines the selection of the preferred route of administration, viz. topical or oral, or a combination of both, and topical treatment is usually preferred in mild to moderate acne. The fact that a topically applied compound may also become systemically available to a quantifiable extent, is not generally considered. Aim The present paper reviews the clinical data on transdermal uptake of anti-acne agents in man, also with respect to their relevance for daily clinical practice. Outcome The majority of published data on transdermal penetration of topical anti-acne agents focuses on the retinoid tretinoin, and on the antimicrobial agent clindamycin. This interest emerges from the fact that these agents have been associated with embryotoxicity /teratogenicity, and pseudomembranous colitis, respectively. For both compounds the extent of systemic availability after topical application is low, viz. 5-7% and 8%, respectively, at its highest. The height and variability in endogenous retinoid levels is very likely to outweigh any contribution of exogenously applied tretinoin, but a full consensus on the safe use of topical tretinoin in pregnancy is still lacking. With respect to clindamycin, the suggested association between its topical use and the occurrence of pseudomembranous colitis appears not to be of clinical relevance. In order to reduce systemic exposure to clindamycin as much as possible, topical application of clindamycin

phosphate is to be preferred over clindamycin hydrochloride salt. Regarding other topical anti-acne agents, it has been suggested that topical zinc-erythromycin is to be preferred over erythromycin, both from clinical efficacy and safety viewpoints. With respect to the currently used compounds like benzoylperoxide, azelaic acid, and adapalene, available clinical pharmacokinetic data are scarce, and significant safety concerns did not emerge as yet. Conclusion The limited transdermal uptake of topical anti-acne agents underpins their safe use in daily clinical practice. With respect to topical retinoids, formal consensus is lacking regarding their use in pregnancy.

The emergence of mupirocin resistance: a challenge to infection control and antibiotic prescribing practice. J-Antimicrob-Chemother (41, No. 1, 11-18, 1998)

The emergence of mupirocin (MU) resistance in staphylococci is reviewed. The mechanism of action of MU, the mechanism, clinical significance and genetic basis of MU resistance, the relationship between MU and other resistances including triclosan, tetracycline, trimethoprim and cadmium, the incidence, origin and prevention of MU resistance, potentially useful agents including azelaic acid, nitrofurazone, silver sulfadiazine, ramoplanin, tea-tree oil, gentian violet, thiomarinol and magainin MSI-78, and the treatment of MU-resistant staphylococci with ciprofloxacin, rifampicin, bacitracin, fusidate and colistin, are discussed. The mechanism of action of MU is outlined. The level of MU resistance is related to alterations in isoleucyl-tRNA synthetase (IleS). Low-level resistance is probably due to mutations of chromosomally encoded IleS, and high-level resistance to the acquisition of an additional novel IleS. Highly resistant (MuH) strains of staphylococci cannot be eradicated with MU. The genetic basis of MU resistance is described. Co-transfer of triclosan, tetracycline, trimethoprim and cadmium resistance with the resistance element mupA has been described. The incidence of MU resistance is discussed. High-level MU resistance has been documented in isolates of Staph. aureus and Staph. epidermidis stored before MU was used clinically. MuH coagulase-negative staphylococci have also been found in settings with no exposure to MU. Coagulase-negative staphylococci may thus be a natural reservoir for MuH. Low-level MU resistance (MuL) does not seem to be a prerequisite for mupA transfer. The elimination of MuH staphylococci is considered. Azelaic acid, nitrofurazone, silver sulfadiazine and ramoplanin have in-vitro activity against MuH and Mu L Staph. aureus. Other potentially useful agents include bacitracin, tea-tree oil, gentian violet, thiomarinol (MU-like substance + holothin) and magainin MSI-78. Combined systemic ciprofloxacin + rifampicin and topical bacitracin and fusidate were used in an outbreak of MRSA with MuH. Topical colistin, bacitracin and fusidate have also been used to eradicate MuH MRSA. The prevention of MU resistance by judicious use, and early action to minimize spread, is considered.

Leyden J J, Gans E H, Evaluation of the antimicrobial effects in vivo of Triaz(R) Gel (benzoyl peroxide special gel), Cleocin-T(R) Lotion (clindamycin phosphate lotion), and Azelex(R) Cream (azelaic acid cream) in humans. J-DERMATOLOGICAL-TREATMENT, 1997, 8: pp S7-S10.

In two recent, separate in vivo antimicrobial studies, orally administered Dynacin(R) (minocycline HCl) produced superior reduction of Propionibacterium acnes compared with doxycycline and tetracycline, and topically applied Triaz(R) (benzoyl peroxide special gel) produced comparably superior reduction in P. acnes compared with clindamycin phosphate lotion and azelaic acid cream. These findings stimulated interest in evaluating the in vivo antimicrobial efficacy of the combination of Dynacin :LOG mg twice daily orally, and topical Triaz 10% gel twice daily, each used daily for 6 weeks, with measurement of the residual antimicrobial effect 3 weeks post-dosage. After 3 weeks of treatment, there was a substantial, 2.5 log reduction in P. acnes from a baseline log count of 6.21 (1 112 000 organisms) to 3.52 (3311 organisms). After 6 weeks on this combination therapy, the reduction in P. acnes was dramatic; a count of log 2.24 or only 173 organisms was found. All reductions were statistically significant compared with baseline (P=<0.01). At 3 weeks after therapy had ceased, the level of P. acnes was still reduced significantly (P=<0.01) compared with baseline.

Oh CW, et al. An ultrastructural study of the retention hyperkeratosis of experimentally induced comedones in rabbits: the effects of three comedolytics. J Dermatol. 1996 Mar; 23(3):169-80.

The precise pathologic processes of comedo formation in acne are not well understood. Retention hyperkeratosis may play an important role. To evaluate the effects of three topical comedolytics, 20% azelaic acid, 0.1% tretinoin and 5% benzoyl peroxide, on the retention hyperkeratosis of experimentally induced comedones (EIC), an ultrastructural study was done. After formation of EIC with 50% oleic acid in paraffin oil on the external ears of rabbits, each comedolytic was applied for 4 weeks. Biopsies were taken

every week and, using a Hitachi H-600 transmission electron microscope, morphologic observations were done in the upper portion of the follicular epithelium. In EIC, after application of each comedolytic, the markedly thinned horny layer was loosely adhered by extremely few desmosomes and desmosomal bodies. The number and size of tonofilaments and keratohyaline granules decreased, but the number of variable sized Odland bodies increased in the upper epidermis. These findings appeared 1 week after application of either azelaic acid or benzoyl peroxide, and 3 weeks after application of tretinoin. For the first 2 weeks of tretinoin application, EIC showed rather compact hyperkeratosis with more desmosomes and desmosomal bodies than before. Azelaic acid tretinoin and benzoyl peroxide increased the number of Odland bodies, and the horny cells became less adhesive. This lysis of retention hyperkeratosis resulted in comedolysis. During 4 weeks of treatment with these three comedolytics, only tretinoin normalized the keratinization process.

Bojar RA, Cunliffe WJ, Holland KT Disruption of the transmembrane pH gradient--a possible mechanism for the antibacterial action of azelaic acid in Propionibacterium acnes and Staphylococcus epidermidis. J Antimicrob Chemother. 1994 Sep;34(3):321-30.

The effect of the topical acne treatment azelaic acid on the transmembrane proton gradient (Δ pH) of *Propionibacterium acnes* and *Staphylococcus epidermidis* was studied in vitro at external pH values found on human skin (pH 4.0-6.0). Bacteria were grown in defined media using continuous culture and Δ pH was estimated by measuring the accumulation of [¹⁴C] benzoic by the cells using flow dialysis. In both *P. acnes* and *S. epidermidis* the addition of 30 mM azelaic acid and the membrane active inhibitors nigericin (150 μ M) and CCCP (150 μ M) resulted in a rapid release of [¹⁴C] label into the dialysate indicating the dissipation of Δ pH between external pH values of 4.0-6.0. The addition of 60 mM NaCl as an iso-osmotic control and 150 μ M valinomycin did not induce the release of [¹⁴C] label. The addition of 30 mM azelaic acid reduced the Δ pH of *P. acnes* by 44% at external pH 4.0 and 28% at external pH 6.0. In *S. epidermidis* 30 mM azelaic acid reduced Δ pH by 88% at external pH 5.0 and 20% at external pH 6.0. Rapid loss of viability occurred in suspensions of *P. acnes* and *S. epidermidis* containing 30 mM azelaic acid at pH 4.0 with no viable cells recovered after 60 min incubation. At pH 6.0 little change in viable numbers of *P. acnes* and *S. epidermidis* were observed over a 2 h incubation period

Farmery M R, Jones C E, Eady E A, Cove J H, Cunliffe W J TI: In vitro activity of azelaic acid, benzoyl peroxide and zinc acetate against antibiotic-resistant propionibacteria from acne patients J-DERMATOL-TREAT, 1994, 5/2: 63-65

The minimum inhibitory concentrations (MICs) of three broad-spectrum antibacterial agents used in the therapy of acne were estimated for antibiotic-sensitive and antibiotic-resistant propionibacteria by agar dilution on one-quarter strength Brain Heart Infusion agar. Azelaic acid was the least active of the compounds tested under the conditions used with MICs of 2000-4000 μ g/ml (10.6-21.3 mM) for both sensitive and resistant strains. The inhibitory activity of benzoyl peroxide and zinc acetate was similar with MICs of 64-128 μ g/ml (0.26-0.53 mM) for the former and 32-64 μ g/ml (0.17-0.35 mM) for the latter against all 55 propionibacterial strains tested irrespective of resistance phenotype. These results confirm that all three agents are as active against antibiotic-resistant propionibacteria as against fully sensitive strains. It is recommended that these agents are prescribed either concomitantly with, or immediately following, courses of oral or topical antibiotics for acne in order to minimize the selection and dissemination of antibiotic-resistant strains of propionibacteria.

Brasch J, Friege B. Dicarboxylic acids affect the growth of dermatophytes in vitro. Acta Derm Venereol. 1994 Sep;74(5):347-50.

Azelaic acid is a dicarboxylic acid with known antimycotic activity. In this study we have used an agar dilution technique to test the effect of six other dicarboxylic acids (sebacic, undecanedioic, dodecanedioic, tridecanedioic, tetradecanedioic and hexadecanedioic acid, 10^{-4} - 10^{-2} mol/l, pH 5.5) on in vitro growth of *Trichophyton (T.) rubrum*, *T. mentagrophytes* and *Microsporum (M.) canis*. Furthermore, the fungicidal activity of 10^{-2} mol/l undecanedioic and sebacic acid was tested using a *T. rubrum* growth assay. Undecanedioic acid proved fungistatic at 10^{-2} mol/l for all species and fungicidal for *T. rubrum*. A minor fungistatic effect on *T. rubrum* and *T. mentagrophytes* was also seen with the other acids at this concentration. *M. canis* was inhibited only by high concentrations of four acids, whereas low concentrations of all six agents resulted in enlarged thallus diameters. We conclude that among dicarboxylic acids fungistatic activity is not limited to azelaic acid. Undecanedioic acid appears promising for further investigations.

Brasch J, Christophers E. Azelaic acid has antimycotic properties in vitro. Dermatology. 1993;186(1):55-8.

Azelaic acid is a therapeutic agent with well-known antibacterial properties, but its antimycotic effect has not yet been investigated systematically. In this study we have used an agar dilution technique to test the inhibitory effect of azelaic acid upon common dermatophytes, *Scopulariopsis brevicaulis*, *Candida albicans*, *Candida glabrata* and *Pityrosporum ovale*. As a result, the growth of dermatophytes and *S. brevicaulis* was suppressed by 0.56% azelaic acid and that of *P. ovale* by 1%. By 4% azelaic acid *C. glabrata* was inhibited completely, but *C. albicans* still maintained some growth. The antimycotic effect of azelaic acid occurred at pH values between 4.8 and 5.5, whereas its disodium salt had no such effect at pH 6.1. Considering the favorable pharmacological data of azelaic acid, our results give reason to investigate the antimycotic effect of this agent in vivo.

Passi S. Pharmacology and pharmacokinetics of Azelaic acid. Rev. Contemp. Pharmacother. 1993; 4: 441-447

Azelaic acid is a naturally-occurring 9-carbon atom saturated dicarboxylic acid which is devoid of toxicity, teratogenicity and mutagenicity. Following administration by different routes to humans and experimental animals it is predominantly and rapidly eliminated in the urine, but partly metabolized via ω -oxidation and partly decarboxylated. Its biological activities are multiple and diverse and its mechanism of action is quite complex and differentiated. *In vitro* azelaic acid is a competitive inhibitor of tyrosinase and other oxidoreductase enzymes and systems, e.g., mitochondrial enzymes of the respiratory chain, such as NADH-dehydrogenase, succinic dehydrogenase, and reduced ubiquinone-cytochrome C oxidoreductase, microsomal NADPH-cytochrome P450 reductase, thioredoxin reductase and 5-alpha-reductase. It also inhibits anaerobic glycolysis and yeast hexokinase. In addition, it has been demonstrated that it inhibits DNA polymerase, DNA synthesis and protein synthesis. By virtue of this it: (a) shows a spectrum of antimicrobial activity, both *in vitro* and *in vivo*, against a variety of aerobic and anaerobic microorganisms, without inducing resistant mutants', (b) has a modulating influence on the process of epidermal keratinization-, and (c) exerts a time- and dose-dependent anti-proliferative and cytotoxic activity against a variety of cultured tumoural cells and may have a potential as a general anti-tumour agent. Azelaic acid decreases the release of reactive oxygen species from neutrophils and has a strong scavenging activity against the extremely reactive and cytotoxic hydroxyl radicals. Recent investigations on the biogenesis of azelaic acid indicate that in man it is an end-product of chemical, physical or biological oxidative attacks on both free and esterified essential fatty acids and might play a physiological role as a natural anti-oxidant. All these data help to explain the multiple and diverse biological activities displayed both *in vitro* and *in vivo* by azelaic acid, and its therapeutic efficacy on skin disorders of different aetiologies.

Bojar AR, Holland KT. Azelaic acid: a review of its antimicrobial properties. Rev Contemp Pharmacother 1993; 4: 403-414.

Maple PA, Hamilton-Miller JM, Brumfitt W. Comparison of the in-vitro activities of the topical antimicrobials azelaic acid, nitrofurazone, silver sulphadiazine and mupirocin against methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother. 1992 Jun;29(6):661-8.

The *in-vitro* activities of the topical agents azelaic acid, nitrofurazone, silver sulphadiazine and mupirocin have been determined against 80 strains of MRSA collected from worldwide sources. MICs were determined by agar dilution (with an inoculum of approximately 5.0×10^5 cfu) in Iso-Sensitest agar, and MBCs were measured by replica-plating from MIC plates using velvet pads. The agents tested were uniformly active against MRSA, mupirocin being the most active (MIC₅₀ 0.15 mg/L) followed by nitrofurazone (MIC₅₀ 19 mg/L), silver sulphadiazine (MIC₅₀ 85 mg/L) and azelaic acid (MIC₅₀ 850 mg/L). Concentrations of azelaic acid, nitrofurazone and silver sulphadiazine close to the MIC were bactericidal, but mupirocin was only bactericidal at concentrations substantially greater than the MIC. In time-kill experiments, azelaic acid and nitrofurazone were gradually bactericidal, silver sulphadiazine was rapidly bactericidal and mupirocin was not bactericidal. Silver sulphadiazine killed sulphonamide-sensitive and sulphonamide-resistant strains equally rapidly. No resistant mutants were found to azelaic acid, nitrofurazone or silver sulphadiazine in an inoculum of 10^9 cfu, but two strains yielded (frequency: 1.0×10^{-9}) mutants resistant to mupirocin. Our *in-vitro* results suggest azelaic acid, nitrofurazone and silver sulphadiazine could be of use for clearing staphylococcal carriage.

Bojar RA, Holland KT, Cunliffe WJ. The in-vitro antimicrobial effects of azelaic acid upon Propionibacterium acnes strain P37. J Antimicrob Chemother. 1991 Dec;28(6):843-53.

The in-vitro antimicrobial activity of azelaic acid a new topical acne treatment, upon Propionibacterium acnes strain P37 was studied. In phosphate buffer at pH 6.0 500 mM azelaic acid had bactericidal activity whilst the addition of nutrients reduced susceptibility. Bactericidal activity was greatly enhanced by reducing the pH to 5.6. In a simple defined medium growth was inhibited by 100 microM azelaic acid. The accumulation of ¹⁴C azelaic acid was pH and temperature dependent with maximum uptake occurring at pH 4.6, 30 degrees C. Valinomycin, nigericin and CCCP (membrane-active inhibitors of energy transduction) inhibited uptake and azelaic acid was not accumulated by non-viable cells. The degradation of azelaic acid was repressed by glucose, and acetic acid was the major end-product of azelaic acid degradation in glucose depleted media. The incorporation of radiolabelled precursors into protein, DNA and RNA were inhibited in a dose dependent manner, and 50% inhibition occurred at 313, 3639 and 9226 microM respectively. The synthesis of proteins was shown to be significantly more sensitive to the action of azelaic acid than both RNA and DNA synthesis.

Akamatsu H, Komura J, Asada Y, Miyachi Y, Niwa Y. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. Arch Dermatol Res. 1991;283(3):162-6.

It has been shown that acne, hyperpigmentation and lentigo malignant are more or less related pathogenetically to reactive oxygen species (ROS). It has recently been reported that azelaic acid is effective in treating these conditions and that it possesses anti-enzymatic and antimitochondrial activity, including cytochrome-P450 reductase and 5 alpha-reductase in microsomal preparations with nicotinamide adenine dinucleotide phosphate (NADPH). We therefore investigated the effects of azelaic acid on human neutrophil functions, such as chemotaxis, phagocytosis and ROS generation. ROS generation in a cell-free system was also assessed. The results revealed that neutrophil chemotaxis and phagocytosis as well as ROS generated in a xanthine-xanthine-oxidase system were not significantly changed in the presence of azelaic acid. However, azelaic acid markedly decreased O₂⁻ and OH⁻ generated by neutrophils. It may be concluded that the reported clinical effectiveness of azelaic acid is partly due to its inhibitory action on neutrophil-generated ROS, leading to a reduction both in oxidative tissue injury at sites of inflammation and in melanin formation.

Passi S, Picardo M, Zompetta C, De Luca C, Breathnach AS, Nazzaro-Porro M. The oxyradical-scavenging activity of azelaic acid in biological systems. Free Radic Res Commun. 1991;15(1):17-28.

We have previously shown that azelaic acid, a C9 dicarboxylic acid, as disodium salt (C(9)2Na) is capable of inhibiting significantly the hydroxylation of aromatic compounds and the peroxidation of arachidonic acid due to reactive hydroxyl radicals (HO[·]). In this paper we have investigated the ability of C(9)2Na to inhibit the oxyradical induced toxicity towards two tumoral cell lines (Raji and IRE1) and normal human fibroblasts (HF). Oxyradicals were generated either by the addition of polyphenols to the medium, or by direct irradiation of phosphate buffered-saline in which cells were incubated from 15 min prior to incubation in normal medium. The effects of C(9)2Na were compared with those obtained by mannitol (MAN), superoxide dismutase (SOD) and catalase (CAT). C(9)2Na, MAN, SOD and CAT significantly decreased the polyphenol toxicity towards cell lines cultured up to 24 h. After 48 h of incubation the above compounds lost the capability of protecting cells from polyphenol toxicity. This suggests that the toxic role of oxyradicals (O₂⁻, H₂O₂, HO[·]) persists for about 24 h and, subsequently other toxic mechanisms must be involved, which are not affected by oxyradical scavengers. SOD and CAT did not show any protective effect on UV induced cytotoxicity, while both C(9)2Na and MAN were capable of reducing significantly the UV damage towards cell lines, even after 48 h incubation. This can be explained by the fact that UV cytotoxicity depends mainly on the generation of HO[·], that can be "scavenged" by C(9)2Na or MAN, but not by SOD or CAT. C(9)2Na and MAN were not significantly degraded in the period during which they afford protection against HO[·].

Passi S, Picardo M, De Luca C, Breathnach AS, Nazzaro-Porro M. Scavenging activity of azelaic acid on hydroxyl radicals "in vitro". Free Radic Res Commun. 1991;11(6):329-38.

Azelaic acid is an aliphatic dicarboxylic acid (HOOC-(CH₂)₇-COOH) which has recently been shown to have some practical therapeutic applications in skin diseases of different etiologies. It possesses diverse biological activities and its mechanisms of action are still under investigation. Azelaic acid, as disodium salt

(C(9)2Na), at concentrations from 0.05 mM to 1.0 mM is capable of inhibiting significantly the hydroxylation of 1-tyrosine to 1-DOPA due to hydroxylradicals (HO.) produced by Fenton reaction. Similarly C(9)2Na significantly inhibits the heterogeneous photocatalytic oxidation of toluene to cresols, and the peroxidation of arachidonic acid (C20:4,n6), due to HO. formed by dissolved oxygen in the presence of UV-irradiated semiconductor TiO₂ (photo-Fenton type reaction). C(9)2Na decomposition and its by-products formation are quantifiable only at high HO. concentrations. On the contrary, C(9)2Na is not a scavenger of O₂· generated by xanthine-xanthine oxidase system. Under the same experimental conditions, mannitol behaves like C(9)2Na. These data indicate that HO. scavenging capacity of C(9)2Na in vitro, and represent a useful tool for further investigations on the mechanisms of action of azelaic acid in biological systems.

Angius AG, Barbareschi M, Cattaneo M, Monti M, Caputo R. Evaluation of the anti-comedo effect of azelaic acid using the technique of horny layer biopsy and scanning electron microscopy. G Ital Dermatol Venereol. 1990 Aug;125(7-8):XXXIII-XXXVI. (Italian)

Hyperkeratosis of the follicular channel is the most common finding in acne skin. The hyperkeratosis may represent an altered keratinization process or the consequence of the abnormal sebum production and excretion. Several review demonstrated the anti-comedo activity of azelaic acid in acneic skin. This action may be due either to an anti-hormonal effect or to a change in keratin production. The aim of this work is to investigate the anti-comedo activity of 20% azelaic acid cream topically applied in a group of teen-agers affected by acne. A horny layer biopsy with cyanoacrylate glue was performed before and after four months of treatment with azelaic acid cream in ten acne patients. About 1 cm square horny layer biopsy was metallized and observed at the scanning electron microscopy to count the number of comedos. With this method we detected a reduction of about 26% of the comedos after four months of azelaic acid treatment. The result we obtained is in accordance with previous works about the anti-comedo activity of azelaic acid.

Passi S, Picardo M, De Luca C, Nazzaro-Porro M. Mechanism of azelaic acid action in acne. G Ital Dermatol Venereol. 1989 Oct;124(10):455-63. Italian.

The physiopathologic mechanism of acne seems to be dependent on four main factors: a) sebum production and excretion; b) type of keratinization of the follicular channel; c) microbial colonization of the pilosebaceous unit and d) inflammatory reaction of the perifollicular area. Azelaic acid is effective in the treatment of acne because it possesses an activity against all of these factors. Azelaic acid is a competitive inhibitor of mitochondrial oxidoreductases and of 5 alpha-reductase, inhibiting the conversion of testosterone to 5-dehydrotestosterone. It also possesses bacteriostatic activity to both aerobic and anaerobic bacteria including Propionibacterium acnes. Azelaic acid is an anti-keratinizing agent, displaying antiproliferative cytostatic effects on keratinocytes and modulating the early and terminal phases of epidermal differentiation.

Detmar M, et al. Effects of azelaic acid on proliferation and ultrastructure of mouse keratinocytes in vitro. J Invest Dermatol. 1989 Jul;93(1):70-4.

Topert M, Rach P, Siegmund Pharmacology and toxicology of azelaic acid. Acta Derm Venereol Suppl (Stockh). 1989;143:14-9.

The results of general pharmacological studies on metabolism, smooth muscles, renal function, cardiovascular and neurotropic effects do not contra-indicate the specific surface use of azelaic acid. From specific pharmacologic studies it is assumed that azelaic acid exerts its therapeutic effect in acne by an antimicrobial, probably bacteriostatic, effect on acne-relevant microorganisms such as Propionibacterium acnes and, in addition, by a strong comedolytic effect. In numerous studies it has been demonstrated that azelaic acid is not toxic.

Galhaup I. Azelaic acid: mode of action at cellular and subcellular levels. Acta Derm Venereol Suppl (Stockh). 1989;143:75-82.

Azelaic acid (AZA) has been reported to have an inhibitory effect on DNA synthesis of melanoma cell lines. In order to elucidate the mechanism(s) underlying this inhibitory effect, I elected to study the effects of AZA and, for control purposes, adipic acid (ADA) on DNA synthesis rate of nuclei isolated from melanoma cells and keratinocytes cultured in the presence of different concentrations of the dicarboxylic acids. Before

doing so, I found, by autoradiography, that [3H]AZA is incorporated into the nuclei in a time-dependent manner. AZA, and to a lesser extent ADA, caused a dose-dependent inhibition of DNA synthesis, regardless of whether these substances were present in cell cultures before isolation of nuclei, or were incubated with already isolated nuclei. In searching for the target for this inhibitory effect on nuclear DNA synthesis, I found that AZA, and to a lesser extent ADA, is a potent inhibitor of both bacterial DNA polymerase and of multienzyme complexes isolated from cultured melanoma cells and keratinocytes. These data suggest that the inhibitory effect of the dicarboxylic acids AZA and ADA on DNA synthesis of several cell lines is due to the interference of these substances with the activation of enzymes (e.g. DNA polymerases) required for DNA synthesis.

Mayer-da-Silva A, Gollnick H, Detmar M, Gassmuller J, Parry A, Muller R, Orfanos CE. Effects of azelaic acid on sebaceous gland, sebum excretion rate and keratinization pattern in human skin. An in vivo and in vitro study. Acta Derm Venereol Suppl (Stockh). 1989;143:20-30.

The effects of azelaic acid (AZA) on the epidermis of 47 individuals (12 with normal skin, 15 with seborrheic skin and 20 suffering from acne) and on in vitro cultured keratinocytes are reported. Topical application of a 20% AZA cream significantly improved the lesions of acne patients, but failed to induce clinically detectable changes in normal or seborrheic epidermis. Complementary investigations clearly showed that AZA treatment failed to induce specific changes in sebum composition, excretion rate, or in the size of sebaceous glands, but modified epidermal keratinization. Keratohyalin granules and tonofilament bundles were reduced in size and number, mitochondria were swollen and the rough endoplasmic reticulum of malpighian keratinocytes enlarged. The infundibular epidermis of acne individuals showed marked reduction of the horny layer thickness, widening of the horny cell cytoplasm, transitional corneal cells, normalization of filaggrin distribution, and the comedo contained few bacteria and spores. In vitro, AZA exerted marked time- and dose-dependent antiproliferative cytostatic effects on cultured keratinocytes, with a 50% inhibitory dose of 20 mM, decreased some keratinocyte proteins (highly soluble fractions S2, keratohyalin macroaggregate R2, and non-cross-linked fibrous protein S4) and a 95 kD and a 35 kD protein of the cytosolic fraction. Mitochondria were frequently damaged and the rough endoplasmic reticulum enlarged. Our results indicate that AZA is an antikeratinizing agent, displaying antiproliferative cytostatic effects on keratinocytes and modulating the early and terminal phases of epidermal differentiation.

Holland KT, Bojar RA, Cunliffe WJ. The interaction of azelaic acid with *Propionibacterium acnes*. J Invest Dermatol 1989; 92: 446.

Holland KT, Bojar RA. The effect of azelaic acid on cutaneous bacteria. J Dermatol Treat 1989; 1: 17-19.

Stamatiadis D, Bulteau-Portois MC, Mowszowicz I. Inhibition of 5 alpha-reductase activity in human skin by zinc and azelaic acid. Br J Dermatol. 1988 Nov;119(5):627-32.

The effects of zinc sulphate and azelaic acid on 5 alpha-reductase activity in human skin were studied using an in vitro assay with 1,2[3H]-testosterone as substrate. When added at concentrations of 3 or 9 mmol/l, zinc was a potent inhibitor of 5 alpha-reductase activity. At high concentrations, zinc could completely inhibit the enzyme activity. Azelaic acid was also a potent inhibitor of 5 alpha-reductase; inhibition was detectable at concentrations as low as 0.2 mmol/l and was complete at 3 mmol/l. An additive effect of the two inhibitors was observed. Vitamin B6 potentiated the inhibitory effect of zinc, but not of azelaic acid, suggesting that two different mechanisms are involved. When the three substances were added together at very low concentrations which had been shown to be ineffective alone, 90% inhibition of 5 alpha-reductase activity was obtained. If this inhibition is confirmed in vivo, zinc sulphate combined with azelaic acid could be an effective agent in the treatment of androgen related pathology of human skin.

Bojar RA, Holland KT, Leeming JP, Cunliffe WJ. Azelaic acid: its uptake and mode of action in *Staphylococcus epidermidis* NCTC 11047. J Appl Bacteriol. 1988 Jun;64(6): 497-504.

In vitro tests using *Staphylococcus epidermidis* as a model have shown that at pH 5.6 the micro-organisms are sensitive to azelaic acid, whilst at pH 6.0 and 7.0 the cells become progressively resistant, especially with nutrients present. In a simple defined medium the growth rate was reduced at 1 mmol/l and growth inhibited at 25 mmol/l. The uptake of azelaic acid was pH dependent, higher transport at lower pH values, and required viable cells. Azelaic acid, 457 $\mu\text{mol/l}$ gave 50% inhibition of protein synthesis and this mechanism could account for the bactericidal and bacteristatic effects. DNA and RNA were affected slightly by 100 mmol/l azelaic acid, and respiration by 500 mmol/l.

Mayer-da Silva A, Gollnick H, Imcke E, Orfanos CE. Azelaic acid vs. placebo: effects on normal human keratinocytes and melanocytes. Electron microscopic evaluation after long-term application in vivo. Acta Derm Venereol. 1987;67(2):116-22.

The effects of topically applied 20% azelaic acid (AA) on normal human epidermis were investigated vs. placebo in a double blind study by electron microscopy in 15 volunteers. After 3 months of local application twice daily, the pattern of epidermal keratinization was found altered in skin treated with AA. In particular, the number and thickness of tonofilament bundles and the number of keratohyaline granules seemed decreased; the remaining granules were smaller, occasionally showing irregular electron densities. The perinuclear endoplasmic reticulum and the cytoplasmic cisternae were enlarged and swollen mitochondria were regularly observed in most malpighian keratinocytes. Thorough quantitative evaluation of the number and distribution of melanocytes by a MOP-videoplan computer system showed no differences between verum and placebo sites, although, the mean number of melanocytes had increased in both, as compared to the untreated controls taken before onset of therapy. No significant qualitative changes of the normal melanocytes were found. These findings indicate that azelaic acid may influence the differentiation of normal human keratinocytes by reducing the synthesis of keratin precursors and may, therefore, act as a mild antikeratinizing agent, whereas, the pigmentary system in normal human epidermis does not show any specific change after 3 months of treatment with AA.

Detmar M, Muller R, Stadler R, Orfanos CE. Dicarboxylic acids inhibit the growth of keratinocytes in vitro. Hautarzt. 1986 Nov;37(11):625-7. German.

The antiproliferative effect of three straight-chained saturated dicarboxylic acids was examined with neonatal mouse keratinocyte cultures. Adipic acid (C6), azelaic acid (C9), and sebacic acid (C10) were added to the cultures in concentrations ranging from 1 to 50 mmol/l. Proliferation was assayed by liquid-scintillation counting of ^3H -thymidine incorporation into DNA and by autoradiography. Fifty percent inhibition of ^3H -thymidine incorporation was observed with 50 mmol/l adipic acid, 20 mmol/l azelaic acid, and 10 mmol/l sebacic acid, respectively. The antiproliferative effect was completely reversible after cessation of treatment. Moreover, treated cultures then showed a rebound effect with increased DNA synthesis. These results show that dicarboxylic acids exert reversible antiproliferative effects on keratinocytes.

Leeming JP, Holland KT, Bojar RA. The in vitro antimicrobial effect of azelaic acid. Br J Dermatol. 1986 Nov;115(5):551-6.

Various strains of cutaneous micro-organisms were tested in vitro for their survival rates in 0.5 mol/l (8.4% w/v) azelaic acid solution. All bacterial strains exhibited large reductions in viability (at least 40-fold) over a 24 h test period, but little response was noted with *Pityrosporum ovale*. The bactericidal effect of azelaic acid was reduced considerably in the presence of nutrients. Minimum inhibitory concentrations (MICs) and minimum bactericidal (or fungicidal) concentrations (MBCs) were also determined. MICs varied from 0.03 mol/l to 0.25 mol/l; MBCs were all either 0.25 mol/l or greater.

Gassmueller H, et al. Azelaic acid and sebum excretion rate. Br J Dermatol. 1985 Dec;113(6):800-2.

2.1.2 Pigmentation and tumor cells

Becker K, Gromer S, Schirmer R H, Mueller S, (Muller S) TI: Thioredoxin reductase as a pathophysiological factor and drug target. European Journal of Biochemistry, 2000, Vol/Iss/Pg. 267/20 (6118-6125)

Human cytosolic thioredoxin reductase (TrxR), a homodimeric protein containing 1 selenocysteine and 1 FAD per subunit of 55 kDa, catalyses the NADPH-dependent reduction of thioredoxin disulfide and of numerous other oxidized cell constituents. As a general reducing enzyme with little substrate specificity, it also contributes to redox homeostasis and is involved in prevention, intervention and repair of damage caused by H₂O₂-based oxidative stress. Being a selenite-reducing enzyme as well as a selenol-containing enzyme, human TrxR plays a central role in selenium (patho)physiology. Both dietary selenium deficiency and selenium oversupplementation, a lifestyle phenomenon of our time, appear to interfere with the activity of TrxR. Selenocysteine 496 of human TrxR is a major target of the anti-rheumatic gold-containing drug auranofin, the formal K(i) for the stoichiometric inhibition being 4 (n)M. The hypothesis that TrxR and extracellular thioredoxin play a pathophysiologic role in chronic diseases such as rheumatoid arthritis, Sjogren's syndrome, AIDS, and certain malignancies, is substantiated by biochemical, virological, and clinical evidence. Reduced thioredoxin acts as an autocrine growth factor in various tumour diseases, as a chemoattractant, and it synergises with interleukins 1 and 2. The effects of anti-tumour drugs such as carmustine and cisplatin can be explained in part by the inhibition of TrxR. Consistently, high levels of the enzyme can support drug resistance. TrxRs from different organisms such as *Escherichia coli*, *Mycobacterium leprae*, *Plasmodium falciparum*, *Drosophila melanogaster*, and man show a surprising diversity in their chemical mechanism of thioredoxin reduction. This is the basis for attempts to develop specific TrxR inhibitors as drugs against bacterial infections like leprosy and parasitic diseases like amebiasis and malaria.

Rodriguez-Vicente J, Vicente-Ortega V, Canteras-Jordana M. The effects of different antineoplastic agents and of pretreatment by modulators on three melanoma lines. Cancer. 1998 Feb 1;82(3):495-502.

BACKGROUND: The chemotherapy of melanoma patients must be improved because of the naturally poor response and acquired resistance of this disease. **METHODS:** The authors used mouse (B16F10) and human (SK-MEL-28 and SK-MEL-1) melanoma lines for in vitro treatment with melphalan, lomustine, fotemustine, and 4-hydroxyanisole (4-HA) alone, combined and after pretreatment with buthionine sulfoximine (BSO), ethacrynic acid (EA), and azelaic acid (AZA). **RESULTS:** Melphalan was the most effective individual drug, followed by lomustine, fotemustine, and 4-HA. The simultaneous administration of two agents was disappointing, although some combinations slightly improved the response compared with the individual treatments. Pretreatment with BSO enhanced the cytotoxicity of melphalan and lomustine 10-fold in B16F10 and 7.5-fold in SK-MEL-28, increasing the toxicity of fotemustine in all 3 lines. EA potentiated lomustine and fotemustine 9-fold and melphalan 5-fold in B16F10 and SK-MEL-28. AZA increased the effectiveness of lomustine and fotemustine in B16F10 and to a lower degree in the two human lines. 4-HA was the poorest drug for sensitization; only B16F10 BSO followed by 4-HA treatment demonstrated increased toxicity, and all other combinations with 4-HA were negative or antagonistic. There was a strong relationship between dopa oxidase activity and the toxicity of 4-HA. **CONCLUSIONS:** B16F10 was the most sensitive to all treatments and SK-MEL-1 the most resistant. Melphalan was the most active individual drug and 4-HA the least. Combinations of two drugs did not result in improved activity compared with drugs administered alone. Pretreatment with modulator seems to be a potential method for enhancing some treatments.

Parsons PG, Hansen C, Fairlie DP, West ML, Danoy PA, Sturm RA, Dunn IS, Pedley J, Ablett EM Tumor selectivity and transcriptional activation by azelaic bishydroxamic acid in human melanocytic cells. Biochem Pharmacol. 1997 Jun 1;53(11):1719-24.

Azelaic bishydroxamic acid (ABHA), a potent differentiating agent for lymphoid cells, was selectively toxic for 5 human tumor cell lines and transformed human melanocytes and keratinocytes (dose for 37% survival, D37, 30-100 microg/mL) compared with normal cells (melanocytes, fibroblasts; D37 > 300 microg/mL). Dendritic morphology was the only indicator found for increased differentiation, markers for the pigmentation pathway being unchanged or inhibited by ABHA. In contrast to hexamethylene bisacetamide and azelaic acid, ABHA significantly increased the HIV LTR, SV40 and c-fos promoter activities during a 24 hr treatment. Metallothionein promoter activity was enhanced by 5 hr treatment with ABHA in a sensitive melanoma cell line (MM96L) but was inhibited in a more resistant line (HeLa); c-fos promoter activity was inhibited in HeLa during this time. Transcription from a p53 binding response element was inhibited in

MM96L by a 24 hr ABHA treatment but enhanced in HeLa. ABHA may represent a structural prototype for designing more potent and selective anti-melanoma agents.

Rodriguez-Vicente J, et al. Azelaic acid has sensitizing effect in the chemotherapeutic treatment of several melanoma cell lines. *Pigment Cell Res.* 1996 Dec;9(6):317-25.

Chemotherapy for melanoma results in low response and must be reinforced with sensitizer compounds. We believed that azelaic acid (AZA) could modulate melanomas' resistance to antineoplastics. Therefore we tried to compare in vitro treatment with antineoplastics alone versus AZA treatment followed by antineoplastics. We carried out MTT assays to evaluate the cytotoxicity of melphalan, lomustine (CCNU), fotemustine, and 4-Hydroxyanisole (4-HA) on three melanoma lines (B16F10, SK-MEL-28, and SK-MEL-1), and the modulating effect of pretreatment with AZA (1 mM). AZA showed a dose-dependent antineoplastic activity on the three lines. Melphalan was the most active drug followed by CCNU, fotemustine, and 4-HA. The most sensitive line was B16F10 and the least sensitive was SK-mEL-1. Previous treatment with AZA of B16F10 reinforced the effect of melphalan (2.5 times), CCNU (10 times), and fotemustine (14 times); whereas for SK-MEL-28 and SK-MEL-1, only the cytotoxicity of CCNU and fotemustine increased. An antagonist effect was produced by 4-HA on all three lines. We concluded that AZA enhances in vitro cytotoxicity of CCNU and fotemustine.

Addo-Boadu K, Wojta J, Christ G, Hufnagl P, Pehamberger H, Binder BR. Azelaic acid decreases the fibrinolytic potential of cultured human melanoma cells in vitro. *Cancer Lett.* 1996 Jun 5;103(2):125-9.

Azelaic acid (AZA) has been used successfully in the treatment of lentigo maligna melanoma. Since it is generally accepted that the fibrinolytic potential of tumour cells is related to their malignant phenotype, it was the aim of this study to investigate the effect of AZA on the fibrinolytic potential of three different human melanoma cell lines (Bowes, GUBSB and MJZJ). Melanoma cells were incubated with AZA in doses ranging from 10^{-2} M to 4×10^{-2} M for 5, 8 and 24 h. The expression of tissue-type plasminogen activator (t-PA), urokinase-type PA (u-PA) and PA inhibitor-1 (PAI-1) in such treated cells was investigated by specific ELISAs on the protein level and by Northern blotting on the mRNA level. AZA caused a time and dose dependent decrease in the fibrinolytic potential of all three cell lines investigated by decreasing t-PA antigen in Bowes, by decreasing u-PA antigen in GUBSB and by increasing PAI-1 antigen in MJZJ cells, respectively. There was no significant difference between the viability of cells in control cultures and those treated with AZA. The effect of AZA on specific mRNA for t-PA in Bowes cells, u-PA in GUBSB and PAI-1 in MJZJ was consistent with its effect on the secretion of these fibrinolytic proteins by the respective cells. The results show that AZA decreases the fibrinolytic potential of the three human melanoma cell lines in vitro. This decrease may be operative in the mechanism by which AZA has been shown to affect malignant melanoma in vivo.

Lemic-Stojcevic L, Nias AH, Breathnach AS. Effect of azelaic acid on melanoma cells in culture. *Exp Dermatol.* 1995 Apr;4(2):79-81.

Using a clonogenic assay in vitro, it has been shown that exposure to azelaic acid (1-100 mM) for 24 hours has a dose-dependent effect on the survival of the colony-forming ability of murine (B16) and human (HMB2, and SK23) melanoma cells as compared with a non-melanotic non-tumoral Chinese hamster cell line (CHO). Both human cell lines were more sensitive to the diacid than the murine cells, and the HMB2 cells were more sensitive than the SK23 cells. These differences may be partly correlated with differences in pigmentation and doubling times between the three melanoma cell lines. The two human lines were more pigmented than the B16, and the SK23 more than the HMB2; the human lines had a longer doubling time than the others.

U-Taniguchi Y, et al. Cell cycle inhibition of HTLV-I transformed T cell lines by retinoic acid: the possible therapeutic use of thioredoxin reductase inhibitors. *Oncol Res.* 1995;7(3-4):183-9.

Adult T cell leukemia derived factor (ADF), which was first reported as a cytokine-like factor produced by human T lymphotropic virus I (HTLV-I)-transformed T cells, is a human homologue of thioredoxin (TRX). ADF/TRX has multiple functions including growth promoting, antiapoptotic and radical scavenging activities, and is also involved in a wide variety of intracellular processes as a dithiol reducing agent in cooperation with the NADPH-TRX reductase system. In HTLV-1(+) T cell lines, HuT 102 and MT-2, which

are ADF/TRX high producing cells, we found that the expression of ADF/TRX was dependent on the cell cycle and peaked at S phase. The reducing activity of ADF/TRX in these cells was also dependent on the cell cycle and elevated in S phase as determined by NADPH-dependent insulin degradation assay. Furthermore, inhibitors of TRX reductase, 13-cis-retinoic acid (13-cis-RA) and azelaic acid, inhibited the DNA synthesis of these cells. In contrast, the residual expression and reducing activity of ADF/TRX in HTLV-I(-) T cell lines did not show any significant correlation with the cell cycle. There was no distinct inhibitory effect of 13-cis-RA or azelaic acid on the growth of these ADF/TRX low producing cells. These results indicate that a high level of reducing activity of the ADF/TRX system may be required for the cell division of these virally transformed cells. This suggests that the TRX reductase inhibitors including retinoid derivatives have a potential therapeutic utility for treatment of HTLV-1(+) T cell leukemia without any effect on HTLV-I(-) cells.

Kvung Won Hzin, Ki Hong Lee, Ki Bum Myung. The effect of azelaic acid and retinoic acid on epidermal melanocytes in UVB-irradiated black mice. Kor J Dermatol 1992; 30 (4): 492-498.

Grammatico P, Scarpa S, Picardo M, Steindl K, Nazzaro-Porro M, Del Porto G. Karyotype modifications in human malignant melanoma cell cultures after treatment with azelaic acid. Mutat Res. 1993 Jul;300(2):119-23.

Azelaic acid (AzAc) is a C9 dicarboxylic acid which has recently been shown to have some therapeutic applications in skin diseases of different aetiologies. In order to study the in vitro activity of AzAc five human malignant melanoma primary cell cultures were treated for up to 60 days with 10 mM C9 2Na; the growth characteristics were defined by growth curve and the cytogenetics by Giemsa standard technique and GTG banding technique. Our data demonstrated an inhibition in replication of all five melanomas and the disappearance of the clones with chromosomal markers in four out of five melanomas after AzAc treatment.

Nazzaro-Porro M, et al. The depigmenting effect of azelaic acid. Arch Dermatol. 1990 Dec;126(12):1649-51.

Zaffaroni N, et al. Cytotoxic activity of azelaic acid against human melanoma primary cultures and established cell lines. Anticancer Res. 1990 Nov-Dec;10(6):1599-602.

The in vitro cytotoxic activity of azelaic acid was studied with 25 human melanoma primary cultures and with 5 established cell lines characterized by different contents of melanotic pigment. A dose-dependent antiproliferative effect was observed in both the experimental systems, even though cell lines displayed a slightly greater susceptibility to the compound, with ID50 values generally lower than those for fresh human tumors. Our results do not demonstrate a clear difference between melanotic and non-melanotic melanomas in sensitivity to azelaic acid. The early interference of azelaic acid on nucleic acid metabolism was investigated additionally with 15 human melanoma primary cultures. There were significant inhibitions of RNA and DNA synthesis in a remarkable percentage of tumors, at the highest concentrations of the compound. Moreover, cell proliferation of tumors that showed these antimetabolic effects was always significantly depressed by lower drug concentration as well as by the highest.

Wilkerson MG, et al. Azelaic acid esters do not depigment pigmented guinea pig skin. Arch Dermatol. 1990 Feb;126(2):252-3.

Schallreuter KU, Wood JW. A possible mechanism of action for azelaic acid in the human epidermis. Arch Dermatol Res. 1990;282(3):168-71.

Azelaic acid, and other saturated dicarboxylic acids (C9-C12), are shown to be competitive inhibitors of tyrosinase (KI azelaic acid = 2.73×10^{-3} M) and of membrane-associated thioredoxin reductase (KI azelaic acid = 1.25×10^{-5} M). The monomethyl ester of azelaic acid does not inhibit thioredoxin reductase, but it does inhibit tyrosinase, although double the concentration is necessary compared with azelaic acid (KI azelaic acid monomethyl ester = 5.24×10^{-3} M). Neither azelaic acid nor its monomethyl

ester inhibit tyrosinase when catechol is used as a substrate instead of L-tyrosine. Therefore, the weak inhibitory action of azelaic acid on tyrosinase appears to be due to the competition of a single carboxylate group on this inhibitor for the alpha-carboxylate binding site of the L-tyrosine substrate on the enzyme active site. Based on the inhibitor constant on tyrosinase, at least cytotoxic levels of azelaic acid would be required for the direct inhibition of melanin biosynthesis in melanosomes if this mechanism is responsible for depigmentation in the hyperpigmentation disorders lentigo maligna and melasma. Alternatively only $10(-5)$ M azelaic acid is required to inhibit thioredoxin reductase. This enzyme is shown to regulate tyrosinase through a feedback mechanism involving electron transfer to intracellular thioredoxin, followed by a specific interaction between reduced thioredoxin and tyrosinase. Furthermore, the thioredoxin reductase/thioredoxin system is shown to be a principal electron donor for the ribonucleotide reductases which regulates DNA synthesis.

Flamigni F, et al. Involvement of thiol transferase- and thioredoxin-dependent systems in the protection of 'essential' thiol groups of ornithine decarboxylase. *Biochem J.* 1989 Apr 1;259(1):111-5.

Ornithine decarboxylase (ODC), an enzyme with 'essential' thiol group(s), may be inactivated in vitro by removal of thiol reducing agents and re-activated by soluble factors from rat liver in the presence of NADPH or GSH. The NADPH- and GSH-dependent reducing systems were separated and resolved into three components, called factors A, B1 and B2, by chromatographic techniques. Factor B1 (Mr 12,000) could reactivate ODC in the presence of GSH and co-purified with thiol transferase activity. Factor B2 (Mr 12,000) and factor A (Mr approx. 110,000) were both needed to re-activate ODC in the presence of NADPH, and co-purified with thioredoxin and thioredoxin reductase activity respectively. In an attempt to investigate the physiological role of the 'essential' thiol group(s) of ODC, erythroleukaemia cells were incubated with NN-bis-(2-chloroethyl)-N'-nitrosourea, t-butyl hydroperoxide and vinblastine, which are known to increase the cellular GSSG/GSH ratio, azelaic acid, an inhibitor of thioredoxin reductase, and sodium arsenite, a strong inhibitor of the ODC-re-activating factors. All these compounds were able to decrease significantly the ODC activity induced in these cells. These results suggest that the thiol transferase- and thioredoxin-dependent systems may be physiologically relevant in maintaining ODC in the active, reduced, state.

Patzold HC, Breathnach AS, Robins EJ, Daridan ME, Bhasin YP, Ethridge LB, Nazzaro-Porro M, Passi S, Picardo M. Effect of dicarboxylic (C6 and C9) acids on a human squamous carcinoma cell line in culture. *Histol Histopathol.* 1989 Apr;4(2):167-71.

In tissue culture, azelaic acid (C9) has been shown to have an anti-proliferative and cytotoxic effect on human and murine malignant melanocytes, with inhibition of mitochondrial oxido-reductase enzymes and DNA synthesis, and damage to mitochondria. Recent reports of effects on differentiation of normal keratocytes have led to the present study of its effects on a squamous carcinoma cell line. Cells were exposed to single doses of disodium salts of azelaic (C9(2)Na) and adipic (C6(2)Na) acids at concentrations of $10(-2)$ M and $5 \times 10(-2)$ M for 48 hrs. Only C9(2)Na at $5 \times 10(-2)$ M for 4 hrs., and longer, significantly affected proliferation, and the cells exhibited massive swelling of mitochondria with loss of cristae. The results further confirm the probable value of azelaic acid as a general anti-tumoral agent rather than a specifically melanocytotoxic one. They could justify clinical studies on the effect of topical azelaic acid therapy on squamous cell carcinoma in vivo.

Breathnach AS, et al. Effect of dicarboxylic acids (C6 and C9) on human choroidal melanoma in cell culture. *Invest Ophthalmol Vis Sci.* 1989 Mar;30(3):491-8.

In cell culture, azelaic acid (C9) has been shown to have an antiproliferative and cytotoxic effect on human and murine malignant cutaneous melanocytes. Normal melanocytes are unaffected, as are normal choroidal melanocytes. Here, effects on cell kinetics and ultrastructure of cells of a human choroidal melanoma line have been studied. Cells were exposed to single doses of disodium salts of azelaic (C(9)2Na) and adipic (C(6)2Na) acids at concentrations of $10(-2)$ M and $5 \times 10(-2)$ M for 48 hr. C(9)2Na at $5 \times 10(-2)$ M had a significant effect on proliferation at 24 and 48 hr and this was not reversible on removal of diacid. At $5 \times 10(-2)$ M for 24 hr, C(6)2Na had no effect and at $5 \times 10(-2)$ M for 48 hr had an effect which was marginally significant, but reversible. Swelling and disruption of mitochondria was seen in cells exposed to C(9)2Na at $5 \times 10(-2)$ M for 1 hr and longer, but even at $10(-1)$ M, cells exposed to C(6)2Na were minimally affected. The results could encourage further investigations of the feasibility of azelaic acid therapy for uveal and ocular adnexal melanoma.

Nussgen AI, Fritz U, Graupe K, Breitbart EW, Schmiegelow P. Topographical analysis of proliferation ([3H]thymidine labelling index and mitotic index) as compared with tumour growth and tumour weight in xenotransplanted melanoma. Changes due to local and systemic application of azelaic acid. Acta Derm Venereol Suppl (Stockh). 1989;143:67-74.

Xenotransplanted human melanoma was investigated by measuring the increase in tumour volume and in final tumour weight (macroscopical parameters) and histomorphological parameters of cell proliferation: Mitotic index (MI) and autoradiographic [3H]thymidine labelling index (LI). A total of 87 tumours, derived from a human melanoma metastasis and a primary nodular melanoma respectively, were analysed by these methods in two series. Topical treatment of the tumours with azelaic acid cream resulted in a statistically significant reduction in the increase in tumour volume and, in the first series, in a clear decrease in final tumour weight and in the MI, as compared with controls. The LI was decreased only in the superficial region of the tumours, i.e. at the site of treatment. Subtumoral injection of azelaic acid (disodium salt solution) was the second route of local therapy. It was followed by a significant reduction in the increase in tumour volume, of final tumour weight (first series) and in the MI. The average LI was clearly smaller than in the controls, especially at the tumour base, which was the site of injection (local effect). Systemic (intravenous) injection of azelaic acid (same concentration of the disodium salt solution) had no negative effect on the increase in tumour volume or final tumour weight, but was followed by a clear reduction of the MI. The average LI of this group was significantly smaller than in the controls as well. This effect was most impressive in the perivascular regions of large and small vessels, which fact can be interpreted as a sort of local effect via the blood stream after systemic application of azelaic acid.

Breathnach AS, et al. Hyperpigmentary disorders--mechanisms of action. Effect of azelaic acid on melanoma and other tumoral cells in culture. Acta Derm Venereol Suppl (Stockh). 1989;143:62-6.

Azelaic acid has been shown to have a dose- and time-dependent inhibitory effect on both proliferation and cell viability of murine and human melanoma cells at a concentration of 10^{-3} M and higher. It also has an inhibitory effect on DNA synthesis and plasminogen activator activity, and causes swelling and vacuolation of mitochondria. These effects have also been observed with other tumoral cells in culture-lymphoma and leukaemia derived cell lines, and human squamous cell carcinoma. Normal cells in culture are not generally affected by exposure to azelaic acid. Tissue culture experiments have confirmed the clinical activity and efficacy of azelaic acid, and biochemical conclusions as to its mode of action.

Schallreuter KU, et al. Azelaic acid as a competitive inhibitor of thioredoxin reductase in human melanoma cells. Cancer Lett. 1987 Sep;36(3):297-305.

Azelaic acid has been shown to inhibit thioredoxin reductase (TR) at the surface of guinea pig and human skin, on cultures of human keratinocytes, melanocytes, melanoma cells, murine melanoma cells (Cloudman S91), and on purified enzymes from Escherichia coli, rat liver, and human melanoma. Human melanoma cells are more resistant to inhibition by azelaic acid than murine melanoma or human melanocytes. Kinetic studies with pure TRs indicate that azelaic acid is a reversible competitive inhibitor. Fluorescence spectroscopy has been used to show that azelaic acid does not interfere with electron transfer from NADPH to FAD on TR. However, azelaic acid does inhibit electron transfer from the dithiolate active site of this enzyme. Inhibition by azelaic acid is pH-dependent, requiring the dissociation of both carboxylate groups, and also the dissociation of the active site dithiol groups. Binding studies with [¹⁴C]azelaic acid at different pHs, indicate that inhibition is first due to the formation of a thioester on the active thiolate groups followed by transacylation of a basic amino acid residue in the active site. A comparative study of TR inhibition by C6, C9, C10 and C12 saturated dicarboxylic acids was also determined on guinea pig skin in vivo. These homologous dicarboxylic acids gave greater inhibition with increasing size (i.e. mol wt.).

Ward BJ, Breathnach AS, Robins EJ, Bhasin YP, Ethridge L, Nazzaro-Porro M, Passi S. Effect of L-carnitine on cultured murine melanoma cells exposed to azelaic acid. J Invest Dermatol. 1986 Apr;86(4):438-41.

The cytotoxic effect of azelaic acid on murine melanoma cells in culture is due, at least in part, to an antimitochondrial action. We investigated the possibility that the addition of carnitine to the medium may increase the transport of azelaic acid into the mitochondria and thereby increase its cytotoxic effect. Using

mitochondrial cross-sectional area measured from electron micrographs as a criterion for mitochondrial damage, we found that the addition of L-carnitine to the culture medium had no effect either alone or with a low (10^{-3} M) concentration of azelaic acid. At a high concentration (5×10^{-2} M) azelaic acid caused swelling and disruption of the mitochondria to such an extent that this was not increased by carnitine. At 10^{-2} M azelaic acid, however, some swelling of the mitochondria occurred which was significantly increased by the addition of carnitine. This indicates that carnitine-mediated transport of the diacid into the mitochondria had occurred. We conclude that carnitine may reduce the time or concentration needed for azelaic acid to have a toxic effect on the malignant melanocyte.

Geier G, Hauschild T, Bauer R, Kreysel HW. [Effect of azelaic acid on the growth of melanoma cell cultures in comparison with fibroblast cultures]. Hautarzt. 1986 Mar;37(3):146-8. German.

Azelaic acid, a linear C9 dicarboxylic acid, can effect a reduction in the growth of melanoma cells. This was shown in a comparison of two human melanoma cell cultures and cultured human skin fibroblasts. The cultures were observed for 24 days. The reduction in growth effected by azelaic acid showed significant differences concerning the dose-effect ratio in both melanoma cell lines observed. There was no inhibition of cell proliferation in the fibroblast cultures. Morphological and final trypan blue tests suggest that azelaic acid is not cytotoxic but cytostatic in a selective way.

Hu F, et al. Effects of dicarboxylic acids on normal and malignant melanocytes in culture. Br J Dermatol. 1986 Jan;114(1):17-26.

Robins EJ, et al. Ultrastructural observations on the effect of azelaic acid on normal human melanocytes and a human melanoma cell line in tissue culture. Br J Dermatol. 1985 Dec;113(6):687-97.

Leibl H, et al. Inhibition of DNA synthesis of melanoma cells by azelaic acid. J Invest Dermatol. 1985 Nov;85(5):417-22.

Pathak MA, et al. An evaluation of the effectiveness of azelaic acid as a depigmenting and chemotherapeutic agent. J Invest Dermatol. 1985 Sep;85(3):222-8.

Robins EJ, et al. Effect of dicarboxylic acids on Harding-Passey and Cloudman S91 melanoma cells in tissue culture. J Invest Dermatol. 1985 Sep;85(3):216-21.

Picardo M, et al. Activity of azelaic acid on cultures of lymphoma- and leukemia-derived cell lines, normal resting and stimulated lymphocytes and 3T3 fibroblasts. Biochem Pharmacol. 1985 May 15;34(10):1653-8.

Mensing H, Remier C, Schmidt KU. Chemotactic behaviour of melanoma cells *in vitro*: correlation with plasminogen activator activity and influence of azelaic acid. J Invest Dermatol 1984; 84: 44.

Passi S, Picardo M, Nazzaro-Porro M, Breathnach AS, Confaloni AM et al. Antimitochondrial effect of saturated medium chain length (C8 C13) dicarboxylic acids. Biochem Pharmacol 1984; 33: 103-108.

Nazzaro-Porro M, Passi S. Identification of tyrosinase inhibitors in cultures of *Pityrosporum*. J Invest Dermatol 1978;71: 205-218.

2.2 Kinetics and metabolism

Kroll C, Herrmann W, Stoesser R, Borchert H H, Maeder K TI: Influence of drug treatment on the microacidity in rat and human skin - An in vitro electron spin resonance imaging study Pharmaceutical Research, 2001, Vol/Iss/Pg. 18/4 (525-530) LG: English

Purpose. The possibilities of the noninvasive examination of microacidity in different depths of the skin in vitro was explored, and the impact of drug treatment on the pH inside the skin was studied. Methods. Spectral-spatial electron spin resonance imaging (ss-ESRI) and pH-sensitive nitroxides were used to obtain a pH map of rat and human skin in vitro. Results. The dermal application of therapeutically used acids, such as salicylic acid and azelaic acid, caused a plain change of microacidity (pH) inside the skin. Species-linked differences between rat and human skin samples with respect to penetration and microacidity were found. Conclusions. ESRI has been shown to be a new and completely noninvasive method to monitor microacidity in different skin layers and on the skin surface. This nondestructive method allows serial measurements on skin samples to be performed without any preparatory steps.

Malaisse W J, Greco A V, Mingrone G TI: Oxidation of 1,12-C-14| dodecanedioic acid by rat pancreatic islets. INTERNATIONAL-JOURNAL-OF-MOLECULAR-MEDICINE, 2000, V6, N4, OCT, pp 453-454

Several aliphatic dioic acids were recently reported to stimulate insulin release in isolated rat pancreatic islets incubated at close-to-physiological D-glucose concentrations. In order to gain insight into the mode of action of these acids in pancreatic islet B-cells, the oxidation of 1,12-C-14| dodecanedioic acid (5.0 mM) was now measured in rat islets. Expressed as pmol of 1, 12-C-14| dodecanedioic acid equivalent, the production of (CO₂)-C-14 was close to 1.0 pmol/islet per 120 min, representing about 8% of that attributable to the oxidation of D-U-C-14|glucose (8.3 mM). The dioic acid and the hexose failed to exert any significant reciprocal effect upon their respective oxidation rate. These findings support the view that the insulinotropic action of dodecanedioic acid, and presumably other aliphatic dioic acids, is causally linked to their capacity to act as nutrients in pancreatic islet cells.

Bertuzzi A, Mingrone G, Gandolfi A, Greco A V, Salinari S TI: Disposition of dodecanedioic acid in humans J-PHARMACOL-EXP-THER, 2000, Vol/Iss/Pg. 292/3 (846-852)

The disposition of dodecanedioic acid (C12) was investigated in six Overnight-fasting healthy male volunteers, who received a 165-min i.v. infusion of 42.45 mmol of C12 added to 150 μ Ci of (1-12-14C) C12. Blood samples were collected up to 360 min after the start of infusion, and concentration of serum labeled C12 was determined. Expired radioactivity (μ Ci/min) was measured up to 600 min and at 24 h. The 24-h C12 urinary excretion was around 5% of the administered amount. The percentage of C12 oxidized was 81.7 \pm 9.5% (mean \pm S.D.) of administered amount as estimated from the area under the curve of measured ¹⁴CO₂ expiration rate. C12 kinetics was described by assuming a single compartment. A saturable rate of C12 tissue uptake (model A) and a linear rate of tissue uptake (model B) were considered. The kinetics of CO₂ produced by C12 oxidation was described by a fast pathway acting in parallel to a slow pathway modeled by first order kinetics. Parameters of model B were estimated for each subject, whereas model A was identified by fitting the pooled data of all subjects. On the basis of estimates obtained from model B, an average calorie delivery of 500 kcal/day was predicted in the plateau phase for the infusion rate of our experiments. When estimated from model A, the maximal rate of tissue uptake was 0.38 \pm 0.08 mmol/min, with a maximal calorie delivery of 750 kcal/day. These results appear promising for C12 utilization in parenteral nutrition, because C12 elimination with urine is low, whereas tissue uptake and oxidation are rather efficient.

van Hoogdaem EJ. Transdermal absorption of topical anti-acne agents in man; review of clinical pharmacokinetic data. J Eur Acad Dermatol Venereol. 1998 Sep;11 Suppl 1:S13-9.

Apart from oral drug treatment, drug therapy in acne vulgaris comprises topical treatment with agents with a primarily keratolytic action (e.g. tretinoin and benzoylperoxide), and with antibiotics (clindamycin, erythromycin, and erythromycin-zinc complex). The acne grade in the particular patient usually determines the selection of the preferred route of administration, viz. topical or oral, or a combination of both, and topical treatment is usually preferred in mild to moderate acne. The fact that a topically applied compound may also become systemically available to a quantifiable extent, is not generally considered. AIM: The present paper reviews the clinical data on transdermal uptake of anti-acne agents in man, also with respect to their relevance for daily clinical practice. OUTCOME: The majority of published data on transdermal penetration of topical anti-acne agents focuses on the retinoid tretinoin, and on the antimicrobial agent clindamycin. This interest emerges from the fact that these agents have been associated with embryotoxicity/teratogenicity, and pseudomembranous colitis, respectively. For both compounds the extent of systemic availability after topical application is low, viz. 5-7% and 8%, respectively, at its highest. The height and variability in endogenous retinoid levels is very likely to outweigh any contribution of exogenously applied tretinoin, but a full consensus on the safe use of topical tretinoin in pregnancy is still lacking. With respect to clindamycin, the suggested association between its topical use and the occurrence of pseudomembranous colitis appears not to be of clinical relevance. In order to reduce systemic exposure to clindamycin as much as possible, topical application of clindamycin phosphate is to be preferred over clindamycin hydrochloride salt. Regarding other topical anti-acne agents, it has been suggested that topical zinc-erythromycin is to be preferred over erythromycin, both from clinical efficacy and safety viewpoints. With respect to the currently used compounds like benzoylperoxide, azelaic acid, and adapalene, available clinical pharmacokinetic data are scarce, and significant safety concerns did not emerge as yet. CONCLUSION: The limited transdermal uptake of topical anti-acne agents underpins their safe use in daily clinical practice. With respect to topical retinoids, formal consensus is lacking regarding their use in pregnancy.

Bojar RA, Cunliffe AG, Graupe K, Cunliffe WJ, Holland KT. Follicular concentrations of azelaic acid after a single topical application. Br J Dermatol. 1993 Oct;129(4):399-402.

Follicular concentrations of azelaic acid (AzA) were determined in vivo using a rapid, non-invasive method, after a single topical application of 20% (w/w) AzA cream, in order to establish whether the in vitro antimicrobial effects observed in previous studies are relevant in vivo. Preweighed amounts of 20% (w/w) AzA cream were applied over demarcated areas on the forehead and back of nine young adults, and samples were taken over a period of 5 h. AzA was removed from the skin surface by washing with acetone, and follicular casts were collected using cyanacrylate gel. The samples were centrifuged to remove particulate matter, and the supernatants derivatized for analysis by HPLC. Although the results showed wide-ranging variability, the follicular concentration increased as the amount present on the surface declined. The maximum follicular concentrations of AzA attained ranged from 7.5 to 52.5 ng (micrograms of follicular casts)⁻¹ and 0.5 to 23.4 ng (micrograms of follicular casts)⁻¹ in samples taken from the back and forehead, respectively. Assuming an average density of follicular material of 0.9 g ml⁻¹, the mean maximum follicular concentration attained on the back was between 36 and 251 mmol/l, and on the forehead was between 2 and 112 mmol/l, and indicates that the concentration of AzA attained in follicular casts after a single topical application is comparable with the concentration required to inhibit the growth of *Propionibacterium acnes* and *Staphylococcus epidermidis*, in vitro.

Passi S, Picardo M, De Luca C, Nazzaro-Porro M, Rossi L, Rotilio G. Saturated dicarboxylic acids as products of unsaturated fatty acids oxidation. Biochim Biophys Acta 1993; 1168: 190-198.

Passi S. Pharmacology and pharmacokinetics of Azelaic acid. Rev. Contemp. Pharmacother. 1993; 4: 441-447

Täuber U, Weiss C, Matthes H. Percutaneous absorption of azelaic acid in humans. Exp Dermatol. 1992 Nov;1(4):176-9.

Six healthy male volunteers received a single topical treatment with 5 g of an anti-acne cream containing 20% azelaic acid (AzA) onto the face, the chest and the upper back. One week later 1 g of AzA was given orally to the same subjects as aqueous microcrystalline suspension. Following the two treatments the renal excretion of the unchanged compound was measured. Analysis included ether extraction of the urine, derivatization of extract and HPLC with UV detection. After topical application 2.2 +/- 0.7%, and after oral administration 61.2 +/- 8.8% of the dose had been excreted unchanged with the urine. By comparing both amounts, the percutaneous absorption of AzA from the cream was assessed to 3.6% of the dermally applied dose.

Bertuzzi A, et al. Pharmacokinetic analysis of azelaic acid disodium salt. A proposed substrate for total parenteral nutrition. Clin Pharmacokinet. 1991 May;20(5):411-9.

Azelaic acid was the first dicarboxylic acid proposed as an alternative energy substrate in total parenteral nutrition. In this study, the pharmacokinetics of azelaic acid were investigated in 12 healthy volunteers, 7 receiving a constant infusion (10g over 90 min) and 5 a bolus dose (1g). The 24h urinary excretion and plasma concentration in blood samples taken at regular intervals were assayed by gas-liquid chromatography. Experimental data were analysed by a 2-compartment nonlinear model that describes both tubular secretion and cellular uptake in Michaelis-Menten terms. A high value of urinary excretion (mean 76.9% of infused dose) and a mean clearance of 8.42 L/h were found, suggesting the presence of tubular secretion. Estimating the population mean of the pharmacokinetic model parameters gave a maximal cellular uptake of 0.657 g/h. The model predicts that 90% of the maximal uptake should be reached in the plateau phase of a constant infusion of 2.2 g/h. The presence of extensive and rapid losses through urinary excretion, and the low estimated value of the maximal cellular uptake, indicate that azelaic acid is not suitable as an energy substrate for total parenteral nutrition.

Montgomery JA, Mamer OA, Colle E. Metabolism of deuterium-labeled nonanoic acids in the riboflavin-deficient rat model of multiple acyl-CoA dehydrogenase deficiency. Biol Mass Spectrom. 1991 Apr;20(4):179-85.

Riboflavin-deficient rats are used to study the metabolism of deuterium-labeled nonanoic acids under conditions mimicking the human disorder of multiple acyl-CoA dehydrogenase deficiency in which large amounts of ethyl-malonic, glutaric, adipic, suberic, 4-octenedioic, sebacic and 4-decenedioic acids are excreted. Both control and deficient rats convert the nonanoic acids to labeled azelaic and pimelic acids. The labeling pattern in pimelic acid is consistent with the omega-oxidation of nonanoic acids to azelaic acid followed by beta-oxidation to pimelic acid.

Tacchino RM, et al. Short-term infusion of azelaic acid vs intralipid in healthy subjects evaluated by indirect calorimetry. JPEN J Parenter Enteral Nutr. 1990 Mar-Apr;14(2):169-72.

Medium-chain dicarboxylic acids (MCDA) are usually considered byproducts of beta-oxidation when omega-oxidizable medium-chain monocarboxylic acids are accumulated, as in beta-oxidation impairment. However, evidence exists of a mitochondrial and cytoplasmatic peroxisomal carnitine independent beta-oxidation of these diacids. Our purpose was to evaluate whether MCDA could be used as source of calories. The metabolic response to intravenous administration of azelaic acid (AA) vs Intralipid (IL) was evaluated in six healthy overnight fasting male volunteers who received an infusion of 10 g of AA over 80 min and as a control 10 g of IL. AA reached a peak concentration at 80 min, (589 +/- 61 micrograms/ml) and was rapidly cleared from plasma (82 +/- 5 micrograms/ml at 240 min). Respiratory and metabolic parameters were evaluated by indirect calorimetry from the beginning of the infusion for 240 min. In both groups the CO₂ production (VCO₂) remained unchanged with no significant change from basal values. The O₂ consumption (VO₂ ml/min/m²) increased over basal values reaching a peak at the end of the infusion in both groups (AA from 119.4 +/- 16.9 to 143.0 +/- 27.6; IL from 124.7 +/- 16.8 to 152.3 +/- 29.5). Respiratory quotient (RQ) consequently decreased significantly (AA from 0.85 +/- 0.06 to 0.76 +/- 0.06; IL from 0.89 +/- 0.06 to 0.78 +/- 0.03) and calories derived from lipids increased. Metabolic rate (MR kcal/hr/m²) showed a slight increase (AA from 34.0 +/- 4.4 to 40.3 +/- 6.8; IL from 35.9 +/- 5.1 to 41.3 +/- 10.5). There was no significant difference between AA and IL treatment in all measurements.

Matsumoto M, et al. Organic acid and acylcarnitine profiles of glutaric aciduria type I. Acta Paediatr Jpn. 1990 Feb;32(1):76-82.

Urinary organic acid and acylcarnitine profiles from a 2-month-old boy were studied by gas chromatography-mass spectrometry and fast atom bombardment mass spectrometry. The patient excreted large amounts of glutaric acid and significant amounts of 3-hydroxyglutaric acid, glutaconic acid and glutarylcarnitine, and his serum glutaric acid level was markedly elevated. Thus he was chemically diagnosed as having glutaric aciduria type I (GAI). In addition to the above metabolites previously described in GAI, significantly increased excretion of 2-ketoglutaric acid, succinic acid, adipic acid, adipylylcarnitine, suberic acid and azelaic acid was found. 2-Ketoadipic acid methylsuccinic acid and ethylmalonic acid were also detectable, suberylcarnitine was not increased, and dehydroadipylylcarnitine was decreased in his urine. These results suggest that excess glutaryl-CoA causes the competitive inhibition of the dehydrogenation of adipylyl-CoA to dehydroadipylyl-CoA and results in an increase of adipic acid and adipylylcarnitine and a decrease of dehydroadipylylcarnitine. It is also suggested that oxidative decarboxylation of 2-ketoglutaric acid to succinyl-CoA is inhibited by high levels of glutaryl-CoA, and that the dehydrogenation of succinic acid to fumaric acid is inhibited owing to the increased glutaric acid derived from excess glutaryl-CoA. These results indicate that gas chromatography-mass spectrometry is the most appropriate and accurate method for the differential chemical diagnosis of GAI and glutaric aciduria type II.

Mingrone G, et al. Preliminary studies of a dicarboxylic acid as an energy substrate in man. JPEN J Parenter Enteral Nutr. 1989 May-Jun;13(3):299-305.

Azelaic acid (Az), a straight saturated chain nine carbon dicarboxylic acid, was administered in saline form to six healthy male volunteers by iv route. Serum levels of Az and urinary amounts of both azelaic and pimelic (C7) acids were measured by an improved gas liquid chromatographic method. Stoichiometric analysis of Az metabolism was compared with that of glucose and palmitic acid. The respiratory quotient (RQ) as well as the ATP/CO₂ ratio of Az were quite similar to that of palmitic acid. Therefore, Az oxidation is associated with a low cost of ATP synthesis in terms of carbon dioxide production. At the infusion rate used (7.5 g/hr) more than 50% of the administered dose was excreted in the urine. However, the remaining portion was cleared from the plasma in 200 min suggesting an uptake by body tissues which was also confirmed by indirect calorimetric analysis.

Passi S, Picardo M, Mingrone G, Breathnach AS, Nazzaro-Porro M. Azelaic acid--biochemistry and metabolism. Acta Derm Venereol Suppl (Stockh). 1989;143:8-13.

Medium chain length dicarboxylic acids (DA) from C8 to C13 are competitive inhibitors of tyrosinase in vitro. The introduction of electron acceptor groups or electron donor groups into the 2 and/or the 8 position of the molecule enhances or reduces respectively the inhibitory effects of DA. In addition to tyrosinase, DA can reversibly inhibit thioredoxin reductase, NADPH cytochrome P450 reductase, NADH dehydrogenase, succinic dehydrogenase and H₂CoQ-Cytochrome C oxidoreductase. Among DA, azelaic acid (AA, C9 dicarboxylic acid) is extensively used because: 1) it is much cheaper than other DA; 2) it has no apparent toxic or teratogenic or mutagenic effect; 3) when administered perorally to humans, at the same concentrations as the other DA, it reaches much higher serum and urinary concentrations. Serum concentrations and urinary excretion obtained with intravenous or intra-arterial infusions of AA are significantly higher than those achievable by oral administration. Together with AA, variable amounts of its catabolites, mainly pimelic acid, are found in serum and urine, indicating an involvement of mitochondrial beta-oxidative enzymes. Short-lived serum levels of AA follow a single 1 h intravenous infusion, but prolonging the period of infusion with successive doses of similar concentration produces sustained higher levels during the period of administration. These levels are consistent with the concentrations of AA capable of producing a cytotoxic effect on tumoral cells in vitro. AA is capable of crossing the blood-brain barrier: its concentration in the cerebrospinal fluid is normally in the range of 2-5% of the values in the serum.

Mingrone G, et al. Influence of sodium salts of saturated medium chain length (C6, C9, C10 and C12) dicarboxylic acids on the uterine horn of rat in vitro. Q J Exp Physiol. 1988 Mar;73(2):153-62.

The influence of the sodium salt of some dicarboxylic acids (adipic acid, C6; azelaic acid, C9; sebacic acid, C10; dodecandioic acid, C12) on both spontaneous and evoked activity of uterine horn of rats has been studied in vitro. Spontaneous activity of uterine muscle was inhibited by dicarboxylic salts (DS) causing the

total abolition of mechanical events at concentrations of 64×10^{-3} M-C6, 40×10^{-3} M-C9, 32×10^{-3} M-C10 and 24×10^{-3} M-C12. Dicarboxylic salts antagonized the maximal isometric contraction of the uterine horn induced by administration of acetylcholine, oxytocin or prostaglandins (PGF₂ alpha). The amount of antagonism was dependent upon the concentration of DS used. Dicarboxylic salt showed an aspecific inhibitory effect on the uterine horn which progressively increased with their chain length (C12 greater than C10 greater than C9 greater than C6). The results suggested that the inhibitory effects of DS on smooth muscle could be due to a cellular membrane hyperpolarization.

Breathnach AS, et al. Observations on cell kinetics and viability of a human melanoma cell line exposed to dicarboxylic acids in tissue culture. *Histol Histopathol.* 1986 Jul;1(3):235-9.

Cultures of human melanoma cell line B0008 were exposed to the disodium salts of azelaic acid (C9 2Na), adipic acid (C6 2Na) and dodecanedioic acid (C12 2Na) at 10^{-2} M and 5×10^{-2} M for 24 hrs. None of the diacid salts had a significant effect on growth rate or viability of the cells, at 10^{-2} M for 24 hrs nor had C6 2Na any effect at 5×10^{-2} M. At 5×10^{-2} M for 24 hrs, both C9 2Na, and C12 2Na had a significant effect in reducing both growth and viability. These effects were accompanied by morphological evidence of cell death, and swelling of mitochondria and accumulation of lipid droplets within cytoplasm of still viable cells.

Rocchiccioli F, et al. Medium- and long-chain dicarboxylic aciduria in patients with Zellweger syndrome and neonatal adrenoleukodystrophy. *Pediatr Res.* 1986 Jan;20(1):62-6.

Mingrone G, et al. Distribution of radiolabelled azelaic acid in eye membranes and fluids of rabbits. *Exp Pathol.* 1984;25(2):85-8.

Bargoni N, Tazartes O. On the effect of aliphatic saturated dicarboxylic acids on anaerobic glycolysis in chicken embryo. *Ital J Biochem* 1983; 32: 385-390

Mingrone G, Greco AV, Nazzaro-Porro M, Passi S. Toxicity of azelaic acid. *Drugs Exp Clin Res* 1983; 9: 447-455.

Passi S, et al. Metabolism of straight saturated medium chain length (C9 to C12) dicarboxylic acids. *J Lipid Res.* 1983 Sep; 24(9):1140-7.

**Maru U, et al. In vitro diffusion and skin penetration of azelaic preparations: study of correlations
J Pharm Belg. 1982 May-Jun;37(3):207-13.**

Saito K, et al. Steric course of deuterium incorporation from [2-²H₂]malonyl-CoA into fatty acids by fatty acid synthetases. *J Biochem (Tokyo).* 1981 Dec;90(6):1697-704.

Niwa T, et al. Pattern of aliphatic dicarboxylic acids in uremic serum including a new organic acid, 2,4-dimethyladipic acid. *Clin Chim Acta.* 1979 Nov 15;99(1):71-83.

Dousset N, et al. Azelaic acid transformation into monocarboxylic fatty acids in vivo in the rat. *Biochimie.* 1973;55(10):1279-85. French.

Bernhard K, et al. Azelaic acid as a normal constituent of human urine. Ger Med Mon. 1968 Apr;13(4):195.

Greub HR, et al. Azelaic acid, an additional constituent of human urine. Z Klin Chem Klin Biochem. 1967 Jul;5(4):217-8. German.

3. Chemistry

Scalia S, Bianchi A, Villani S, Guarneri M TI: Assay of underivatized azelaic acid in pharmaceutical and cosmetic products by HPLC PHARMAZIE, 1997, 52, N12,

A rapid HPLC procedure was developed for the assay of azelaic acid in pharmaceutical and cosmetic formulations without prior derivatization. After solid-phase extraction using disposable silica-based strong anion exchange cartridges, samples were analysed directly on a LiChrospher RP-IX reversed-phase column with spectrophotometric detection at 210 nm and acetonitrile/phosphate buffer as eluent. The recovery of azelaic acid from the different matrices was between 93.7 and 96.9%. The method is simple, reproducible and selective and it is suitable for routine analyses of commercial products.

Gatti R, et al. Analysis of aliphatic dicarboxylic acids in pharmaceuticals and cosmetics by liquid chromatography (HPLC) with fluorescence detection. J Pharm Biomed Anal. 1995 Apr;13(4-5):589-95.

2-Bromoacetyl-6-methoxynaphthalene has been found to be a useful prechromatographic fluorescent labelling reagent for the analysis of dicarboxylic acids. The derivatization reaction of azelaic acid and meglutol with this reagent yielded stable and highly fluorescent diesters which could be analysed by reversed-phase HPLC with fluorescence detection. According to the nature of the sample, the derivatization reaction could be carried out in acetonitrile or in an aqueous micellar system. The proposed methods proved to be suitable for the quality control of various complex pharmaceutical and cosmetic formulations of the azelaic acid and meglutol

Levai F, et al. Pre-column fluorescence derivatization using leucine-coumarinylamide for HPLC determination of mono- and dicarboxylic acids in plasma. Acta Physiol Hung. 1995;83(1):39-46.

A sensitive HPLC assay utilising a simple fluorescence pre-column labelling technique was developed for plasma level monitoring of different types of mono- and dicarboxylic acids. Carboxylic acids form mixed anhydrides with ethyl chloroformate in the presence of triethylamine; the mixed anhydrides further react with L-leucine-4-methyl-7-coumarinylamide, forming highly fluorescent and stable amides. Drugs with no chromophore (azelaic acid, and its longer carbon chain analogues) or weak UV absorption (artelnic acid, enalaprilat) were used as model compounds. The plasma samples were extracted using ion exchange solid phase cartridges. The separation was performed on an Axxiom C18 (5 microns, 4.6 x 250 mm) column. The detector wavelengths were set at 330 nm for excitation and 390 nm for emission.

Ferioli V, et al. Determination of azelaic acid in pharmaceuticals and cosmetics by RP-HPLC after pre-column derivatization. Farmaco. 1994 Jun;49(6):421-5.

This paper reports a RP-HPLC method for the determination in topics of azelaic acid, a keratolytic and anti-comedogenic agent widely used in the treatment of all types of acne. A derivatization step was needed prior to chromatographic analysis because the analyte is lacking in chromophore. A sample clean-up procedure by solid-phase extraction

Banerjee S, Trivedi GK, Srivastava S, Phadke RS. 2'-(3 alpha-Benzoyloxy-24-norcholan-23-yl)-2',4',4'-trimethyl-4',5'- dihydrooxazoline-N-oxyl as a potential spin probe for model membranes. Steroids. 1994 Jun;59(6):377-82.

A new steroidal proxyl (2,2,5,5-tetramethylpyrrolidine-N-oxyl) nitroxide (SPN), with the proxyl nitroxide moiety in the pendant side chain of the steroid, has been synthesized. Its localization in lipid bilayers was ascertained with the help of ¹H NMR and ³¹P NMR experiments. The effects of the nitroxide group in SPN incorporated into the bilayer on ¹³C relaxation times are interpreted qualitatively in terms of localization of the nitroxide group within the bilayer structure. The nitroxide SPN was used to monitor changes in membrane fluidity and permeability induced by local anaesthetics, mepivacaine and xylocaine and the antikeratinizing agent, azelaic acid. The results conclusively proved the applicability of the new steroidal proxyl nitroxide (SPN) as a potential spin probe for spin labeling studies.

Pattarino F, et al. Topical delivery systems for azelaic acid: effect of the suspended drug in microemulsion. Pharmazie. 1994 Jan;49(1):72-3.

Banerjee S, et al. Proxyl nitroxide of lithocholic acid: a potential spin probe for model membranes. Bioorg Med Chem. 1993 Nov;1(5):341-7.

Bennett MJ, et al. Azelaic and pimelic acids: metabolic intermediates or artefacts? J Inher Metab Dis. 1992;15(2):220-3.

Azelaic and pimelic acids are excreted in elevated amounts in urine in disorders of mitochondrial beta-oxidation and disorders of peroxisomal beta-oxidation, for which they are of significant diagnostic value. We have detected the presence of azelaic, pimelic and even-chain-length dicarboxylic acids (adipic, suberic and sebacic acids) arising artefactually as a result of storage of small sample volumes in plastic containers. Storage of samples for organic acid analysis in glass containers is recommended.

Baum G. Affinity chromatography of beta-galactosidase on controlled-pore glass derivatives. J Chromatogr. 1975 Jan 29;104(1):105-11.

4. Miscellaneous

Sasaki Guilherme L, Cruz Leonardo M, Gorin Philip A J, Iacomini Marcello {a} TI: Fatty acid composition of lipids present in selected lichenized fungi: A chemotyping study. Lipids, February, 2001, vol. 36, no. 2, p. 167-174

The total-lipid composition of 21 lichens of the ascomycetous genera *Cladonia* (11) and *Cladina* (1) of the family Cladoniaceae, *Cladia* (1), *Parmotrema* (3), *Ramalina* (2), *Leptogium* (1), *Cetraria* (1), and the basidiomycetous genus *Dictyonema* (1) was determined. Analyses of those of *Dictyonema glabratum* were carried out with a total extract and those obtained after successive extractions with various solvents. Each extract was partitioned between n-heptane/isopropanol and 1 M sulfuric acid, giving triglycerides (TG) in the upper phase. Extracts were methanolized and the resulting methyl esters were analyzed by gas chromatography-mass spectrometry. Methanolizates of TG unexpectedly contained esters of 9-oxo-decanoic, 9-methyl-tetradecanoic, 6-methyl-tetradecanoic, 3-hydroxy-decanoic, nonanedioic, and decanedioic acids, as well as common fatty acids. Fatty acid methyl ester profiles from the lichens were submitted to cluster analysis, and the resulting dendrogram showed a cluster consistent with *Cladonia* spp., suggesting an efficient aid to lichen taxonomy. The total carbohydrate content of each lipid extract was determined by a modified phenol-sulfuric acid method, which compensated for the presence of pigments.

Rimando A M, Olofsdotter M, Dayan F E, Duke S O TI: Searching for rice allelochemicals: An example of bioassay-guided isolation. AGRONOMY-JOURNAL, 2001, V93, N1, JAN-FEB, pp 16-20

A bioactivity-guided isolation method was developed with the objective of isolating the allelochemicals in rice (*Oryza sativa* L.). Roots of the allelopathic rice cultivar Taichung Native 1, grown hydroponically, were extracted and fractionated, with the activity of the fractions followed using a 24-well culture plate microbioassay. Some of the fractions obtained consisted of pure compounds, but none inhibited the growth of barnyardgrass *Echinochloa crusgalli* (L.) Beauv.], at the lower concentration at which they were tested. Identified compounds were azelaic acid; p-coumaric acid; 1H-indole-3-carboxaldehyde; 1H-indole-3-carboxylic acid; 1H-indole-5-carboxylic acid; and 1, 2-benzenedicarboxylic acid bis(2-ethylhexyl)ester. rho - Coumaric acid, a known allelochemical, inhibited the germination of lettuce (*Lactuca sativa* L.) seedlings at 1 mM. However, rho -coumaric acid was active against barnyardgrass only at concentrations higher than 3 mM. The two most active fractions obtained from the bioassay-guided isolation were still a mixture of compounds as analyzed by gas chromatography-mass spectrometry (GC-MS). Further fractionation is being done to isolate and identify the allelochemical(s) in these active fractions. This work has demonstrated the use of bioassay-guided isolation in identifying allelochemicals in rice and has correlated observed field activity with laboratory experiments.

Viallard V, et al. *Burkholderia graminis* sp. nov., a rhizospheric *Burkholderia* species, and reassessment of [*Pseudomonas*] phenazinium, [*Pseudomonas*] pyrrocinia and [*Pseudomonas*] glathei as *Burkholderia*. Int J Syst Bacteriol. 1998 Apr;48 Pt 2:549-63.

In a survey of soil and wheat or maize rhizoplane bacteria isolated using a medium containing azelaic acid and tryptamine as sole carbon and nitrogen sources, respectively, a large proportion of *Burkholderia*-like bacteria were found. Among them, a homogeneous group of strains was identifiable based on phenotypic properties, fatty acid composition, DNA-DNA hybridizations and 16S rDNA sequences. According to molecular data, this group belongs to the genus *Burkholderia* but its weak similarity to previously described species suggests that it belongs to a novel species. Closest 16S rDNA phylogenetic neighbours of this species are *Burkholderia caryophylli* and two previously named *Pseudomonas* species which clearly appear to be part of the *Burkholderia* genus and were thus named *Burkholderia glathei* comb. nov. and *Burkholderia phenazinium* comb. nov. Strains of the new species are oxidase- and catalase-positive, produce indole and gelatinase, and use L-xylose, lactose, rhamnose, trehalose, D-lyxose, L-arabitol, xylitol and D-raffinose as sole carbon source. This novel taxon is named *Burkholderia graminis*. In the course of this study, [*Pseudomonas*] pyrrocinia also proved to be a member of the *Burkholderia* genus.

Hodge JP, et al. Oxygen tolerance estimates in *Campylobacter* species depend on the testing medium. J Appl Bacteriol. 1994 Dec;77(6):666-73.

Oxygen tolerance of the microaerophile *Campylobacter jejuni* subsp. *jejuni* varied with different brands of complex media which were used for plating the dilute cell suspensions. The tryptone component was one factor. With some tryptones growth occurred at 21% oxygen whereas with others there was no growth at oxygen levels of 15% or higher. A chemically-defined, agar-solidified plating medium was used to estimate the oxygen tolerance of *Camp. jejuni* subsp. *jejuni*, *Camp. coli* and *Camp. fetus* subsp. *fetus*, and also to assess the effect of added scavengers of reactive oxygen intermediates on the oxygen tolerance. Some scavengers such as allopurinol, azelaic acid, caffeine, cimetidine, TEMPOL and pyruvate enhanced oxygen tolerance markedly whereas others such as carnosine, dimethyl thiourea, spermidine and superoxide dismutase had little effect.

Onsun N, Atilganoglu U, Nisanci P, Beycan I, Uras A R TI: Intralesional azelaic acid in common warts (3) Journal of Dermatological Treatment 1996, 7: 201-202

Zhang EJ, et al. [Chemical constituents from the bark of *Hibiscus syriacus* L]. Chung Kuo Chung Yao Tsa Chih. 1993 Jan;18(1):37-8, 63. Chinese.

Seven constituents (I-VII) were isolated from the bark of *Hibiscus syriacus* and identified as nonanedioic acid (I), suberic acid (II), 1-octacosanol (III), beta-sitosterol (IV), 1,22-docosanediol (V), betulin (VI) and erythrotriol (VII). VII was obtained from the plant for the first time, I, II, III and VI were isolated from Malvaceae plants for the first time.

Yang JS, et al. Chemical constituents of *Armillaria mellea* mycelium. VII. Isolation and characterization of chemical constituents of the acetone extract. Yao Hsueh Hsueh Pao. 1991;26(2):117-22. Chinese.

Eight compounds were isolated from the acetone extract of artificially cultured mycelium of *Armillaria mellea* (Vahl. ex Fr.) Quel. (Tricholomataceae). Three of them are protoilludane sesquiterpenoid aromatic esters. Their structures were elucidated by spectral data analysis as the known 4'-methylmelledonal (I) and two new compounds named armillaritin (II) and armillarivin (III). In addition, five known compounds were identified as D-erythritol, D-mannitol, azelaic acid, orsellinic acid and glycerin- α -monooleate

Chagnaud JL, Gosset I, Brochet B, Audhuy S, Geffard M. Monoclonal anti-conjugated azelaic acid antibody production: application to multiple sclerosis. Neuroreport. 1990 Oct;1(2):141-4.

We have previously reported the existence of anti-conjugated azelaic acid (Aze A) antibodies in the serum of patients with multiple sclerosis (MS). In order to demonstrate the specificity of these antibodies, we have produced a monoclonal antibody directed against Aze A conjugated by an acylation reaction to a protein. In competition experiments, with ELISA method, we demonstrated that a part of the antibodies, raised in rabbit after immunization by human immunoglobulins (Ig) of MS patients, recognized the antigen-combining site of our monoclonal anti-conjugated Aze A antibody. These results clearly demonstrate that a part of human Ig obtained from sera of MS patients shared common idiotopes with mouse monoclonal antibody raised against conjugated Aze A.

Jorand JP, Bounias M, Chauvin. The "survival hormones": azelaic and pimelic acids, suppress the stress elicited by isolation conditions on the steroids and phospholipids of adult worker honeybees. Horm Metab Res. 1989 Oct;21(10):553-7.

The kinetics of abdomen, haemolymph and thoracic-muscle steroid and phospholipid concentrations have been determined in adult worker-bees kept for 0 to 12 hrs starving in darkness, either grouped by 8 (controls) or strictly isolated, or isolated in presence of a piece of cotton impregnated with 1 microgram azelaic acid and 1 microgram pimelic acid, the so-called "survivones" which restore the lifespan of isolated bees. The dynamics of both steroids and phospholipids strongly deviates in isolated bees relatively to controls. The introduction of survivones completely restored the variations of haemolymph steroids of haemolymph and thorax phospholipids of isolated bees to exactly similar

Daverat P, Geffard M, Orgogozo JM. Identification and characterization of anti-conjugated azelaic acid antibodies in multiple sclerosis. J Neuroimmunol. 1989 Apr;22(2):129-34.

Human sera from patients with multiple sclerosis (MS) were tested using an enzyme-linked immunosorbent assay (ELISA) method on well plates coated with various dicarboxylic acid (C4 to C10) protein conjugates. Specific immunological binding was found with an azelaic acid (AzeA, C9) conjugate. The antibody titer was higher in the sera from the patients in acute relapse than with the progressive form, and higher than that from sera of patients with other neurological diseases and healthy subjects. Modifications of coating concentrations and of antibody dilutions, and experiments with preadsorption enabled determination of binding specificity. Competition experiments with related conjugates demonstrated that the AzeA residue was 167 times better recognized by antibodies from MS patients in acute relapse than those from controls. The suberic and sebacic acid conjugates which only differ from the AzeA conjugate by one methylene group were less well-recognized by MS sera (11 and 47 times, respectively) than the conjugate AzeA-BSA.

Rabinowitz JL, et al. Effect of 2 ppm ozone exposure on rat lung lipid fatty acids. Exp Lung Res. 1988;14(4):477-89.

Based on in vitro studies, the initial damage to lung cells by ozone exposure is believed to result in part from the breakdown of lipid polyunsaturated fatty acids to aldehydes, ozonides, and peroxides. The present study measured lipid breakdown products in lungs isolated from rats pretreated with [1-¹⁴C]acetate 12 h before exposure for 4 h to either air or 2 ppm ozone. Lipid fatty acid breakdown was indicated by a 112% increase in thiobarbituric acid-reactive substances on ozone exposure and by changes in chemical and radioactive measurements of mono- and dicarboxylic acids formed by treatment of lipid fractions with hydrogen peroxide. Ozone exposure resulted in a 63% increase in recovery of short-

chain fatty acids accounted for by increased recoveries of malonic acid by 37%, hexanoic acid by 47%, nonanoic acid by 118%, and azelaic acid by 107%. Recovery of glutaric acid was enhanced 15-fold by ozone exposure. Although decreases in tissue arachidonic acid could not be detected, oleic acid was significantly decreased by 36%. Recovery of radiolabel as short-chain fatty acids was increased by 65% on ozone exposure and was mainly accounted for by enhanced labeling of nonanoic and glutaric acid fractions. The failure to observe significant increases in ¹⁴C recovery in the other fractions suggested ozone-induced breakdown of unlabeled fatty acids. These results demonstrate the cleavage of unsaturated fatty acid double bonds following in vivo exposure of lungs to ozone. Breakdown of arachidonic and oleic acids was specifically identified by increased recoveries of glutaric and nonanoic acids, respectively.

Polis BD, et al. Studies on PGBx, a polymeric derivative of prostaglandin B1: I. Synthesis and purification of PGBx. *Physiol Chem Phys.* 1979;11(2):109-23.

Palassis J. The sampling and determination of azelaic acid in air. *Am Ind Hyg Assoc J.* 1978 Sep;39(9):731-6.