Solving an age-old problem

Western governments need to rethink their approach to dealing with an ageing population.

nature

ÄRZTE ZEITUNG.DE

Ärzte Zeitung, 24.03.2010

Kommentare (0)

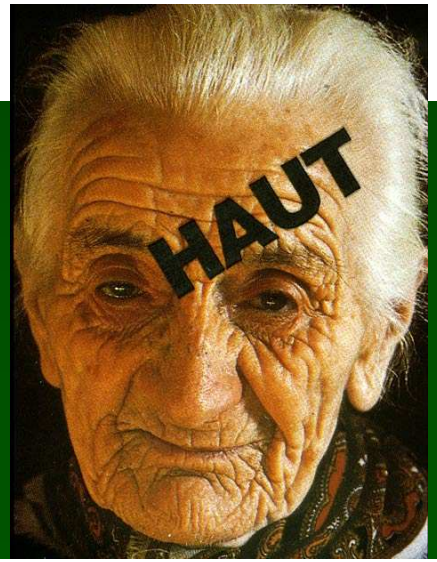
Haut und Haar altern bereits ab 30 Jahren

Hautverbesserungen sind ein Nebeneffekt des Hormonersatzes. Gegen die Haarveränderungen helfen topische Therapien.

Von Adela Žatecky

BERN. Das größte nichtreproduktive Zielorgan für Östrogene ist die Haut mit ihren Anhangsgebilden. Veränderungen an Haut und Haaren zählen daher zu den typischen Begleiterscheinungen der Menopause. Die dermatologischen Veränderungen gehören zwar nicht zu den Indikationsgebieten der Hormonersatztherapie, werden durch diese aber dennoch positiv beeinflusst.

Erst kommen die Falten, dann erschlafft die Haut



The NEW ENGLAND JOURNAL of MEDICINE

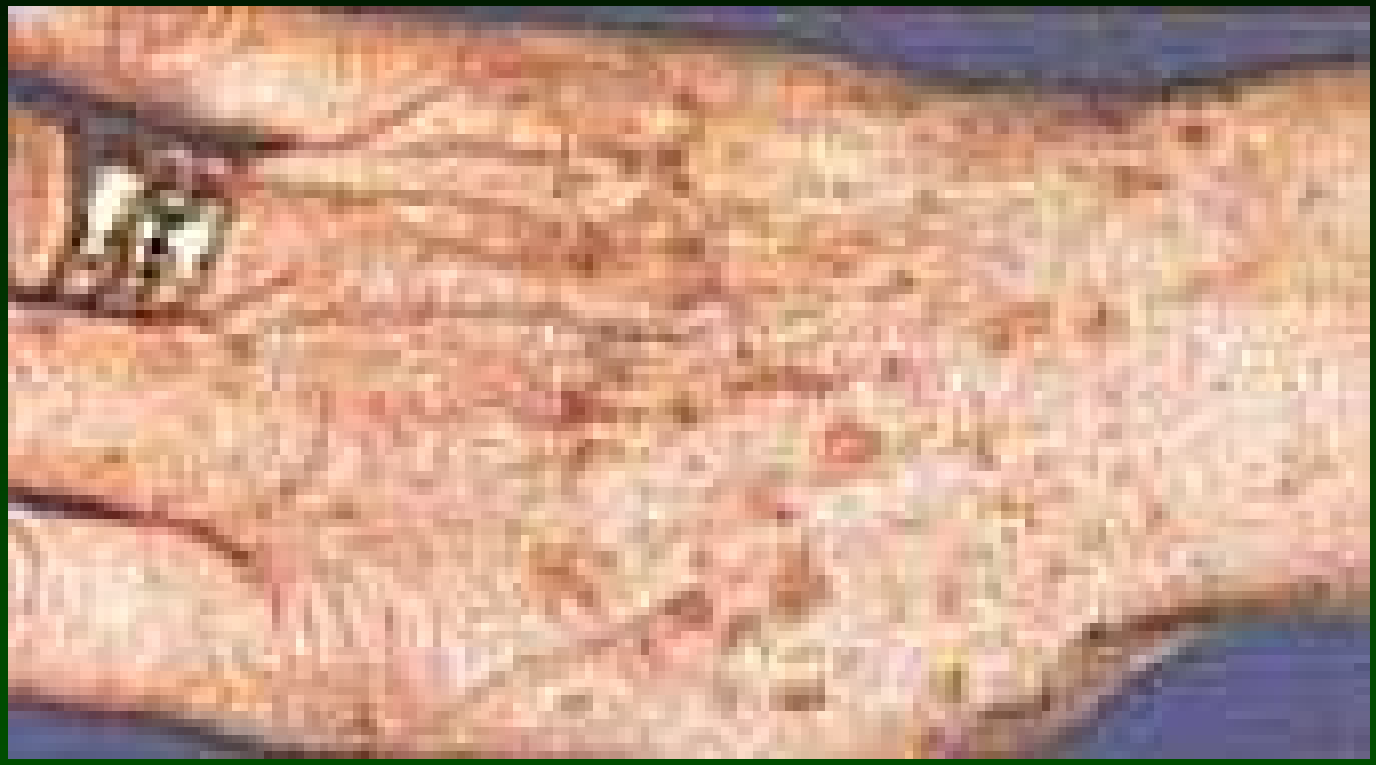
CLINICAL PRACTICE

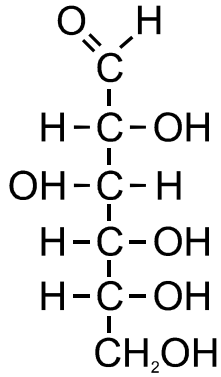
Treatment of Photoaging

Robert S. Stern, M.D.

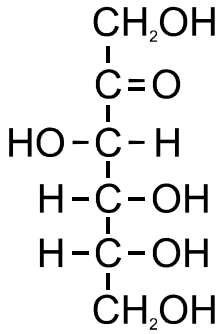
This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 45-year-old fair-skinned woman has noted increasing sallowness, roughness, fine wrinkles, and mottled hyperpigmentation on her face. She is bothered by these changes and is worried about the development of nonmelanoma skin cancer. What treatments may minimize skin aging and lower the risk of skin cancer?

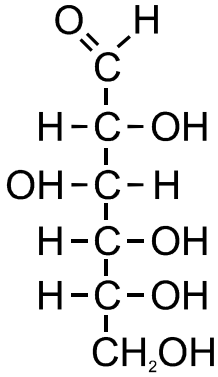




Glukose (Aldose)



Fruktose (Ketose)



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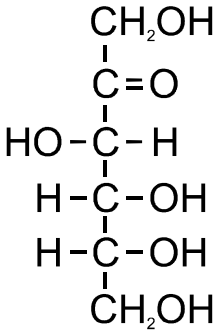

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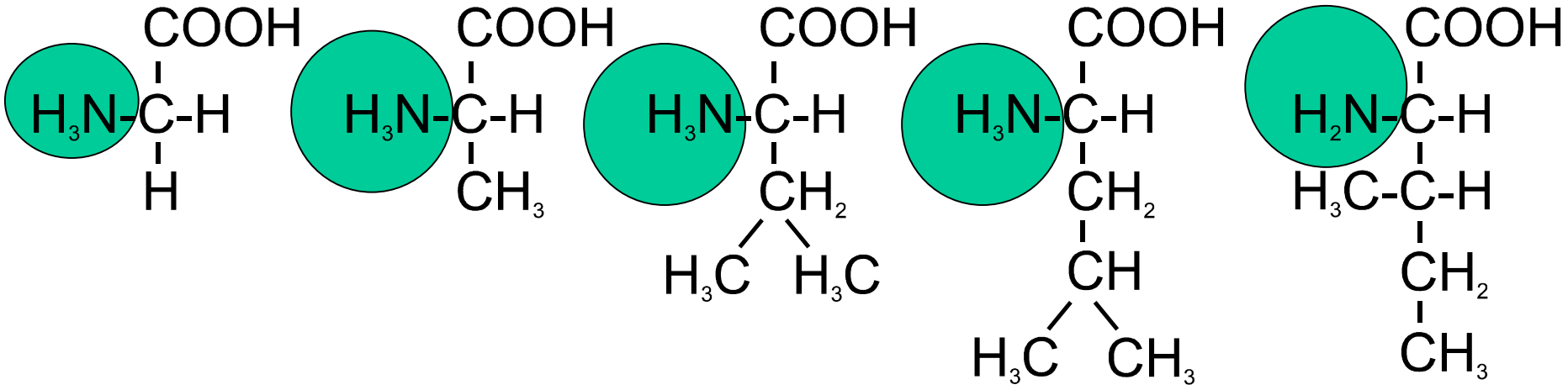
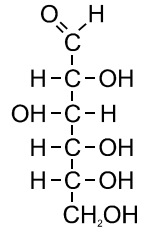


Glycin *Alanin* *Valin* *Leucin* *Isoleucin*



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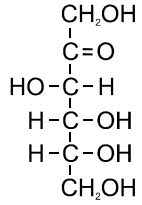

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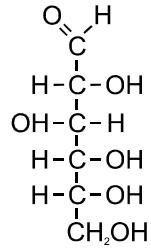

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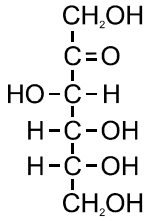

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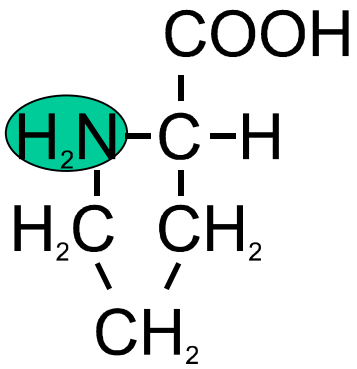
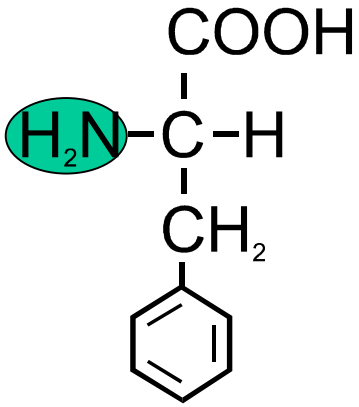
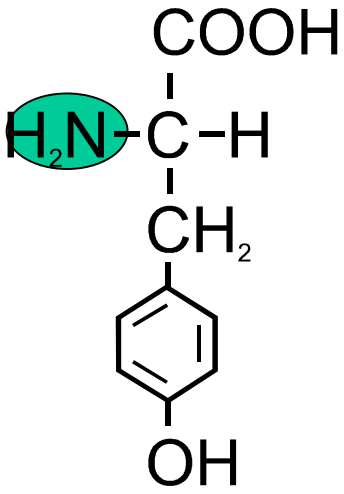


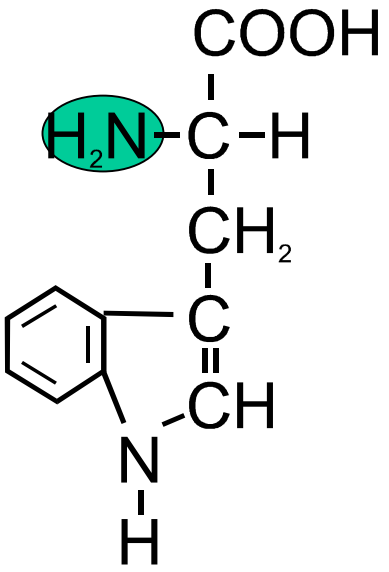
Prolin



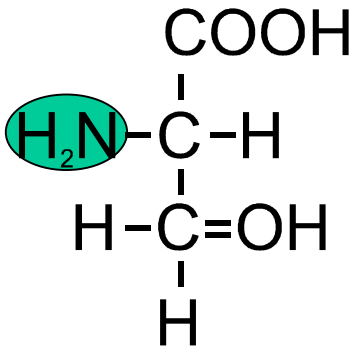
Phenylalanin



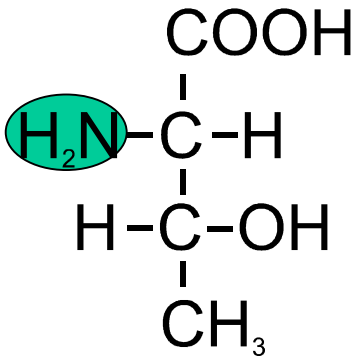
Tyrosin



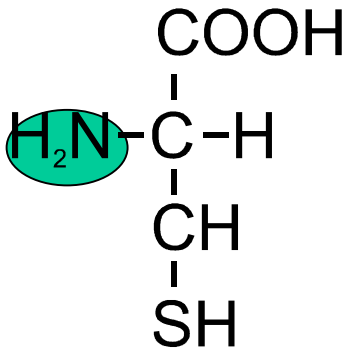
Tryptophan



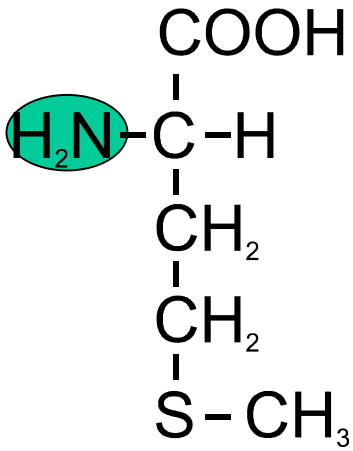
Serin



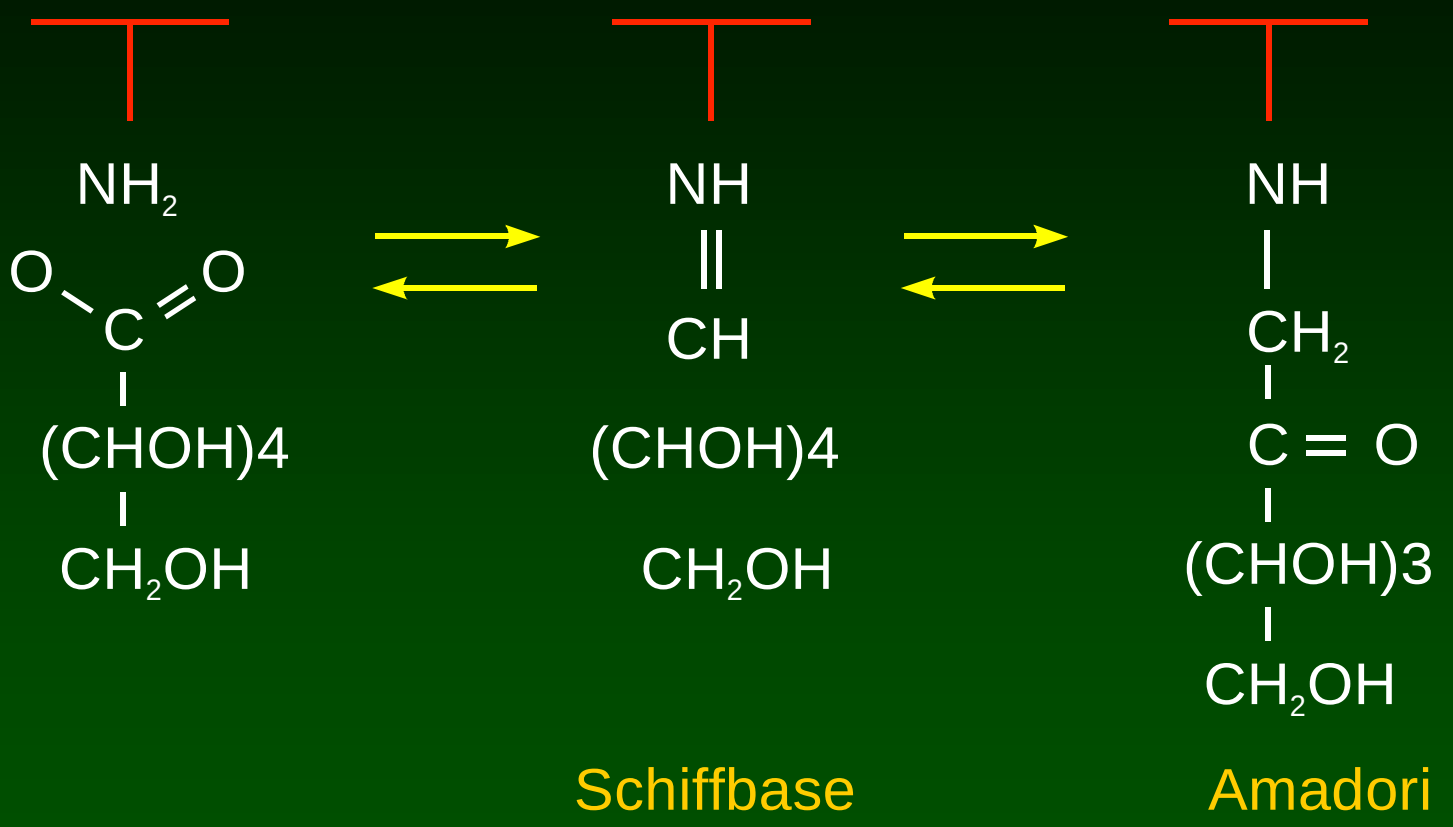
Threonin



Cystein



Methionin



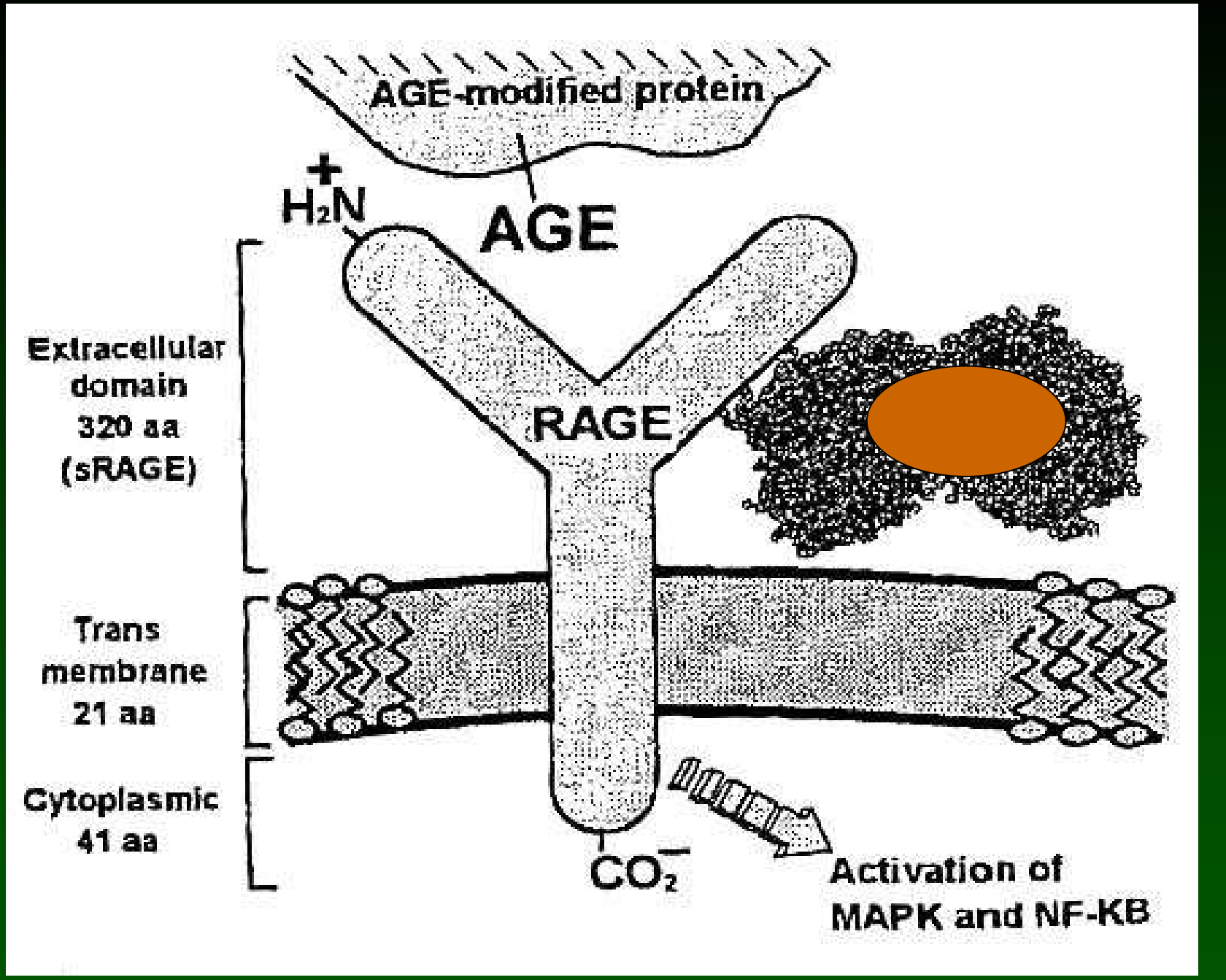
Clin Geriatr Med. 2002 Aug;18(3):383-405. Review

ALTERSBEDINGTE VERZUCKERUNG

MYELINSCHEIDEN

AUGENLINSE

HAUTKOLLAGEN


AGE-modified protein
+
H2N
AGE
RAGE
Extracellular domain 320 aa (sRAGE)
Trans membrane 21 aa
Cytoplasmic 41 aa
CO2−
Activation of MAPK and NF-KB

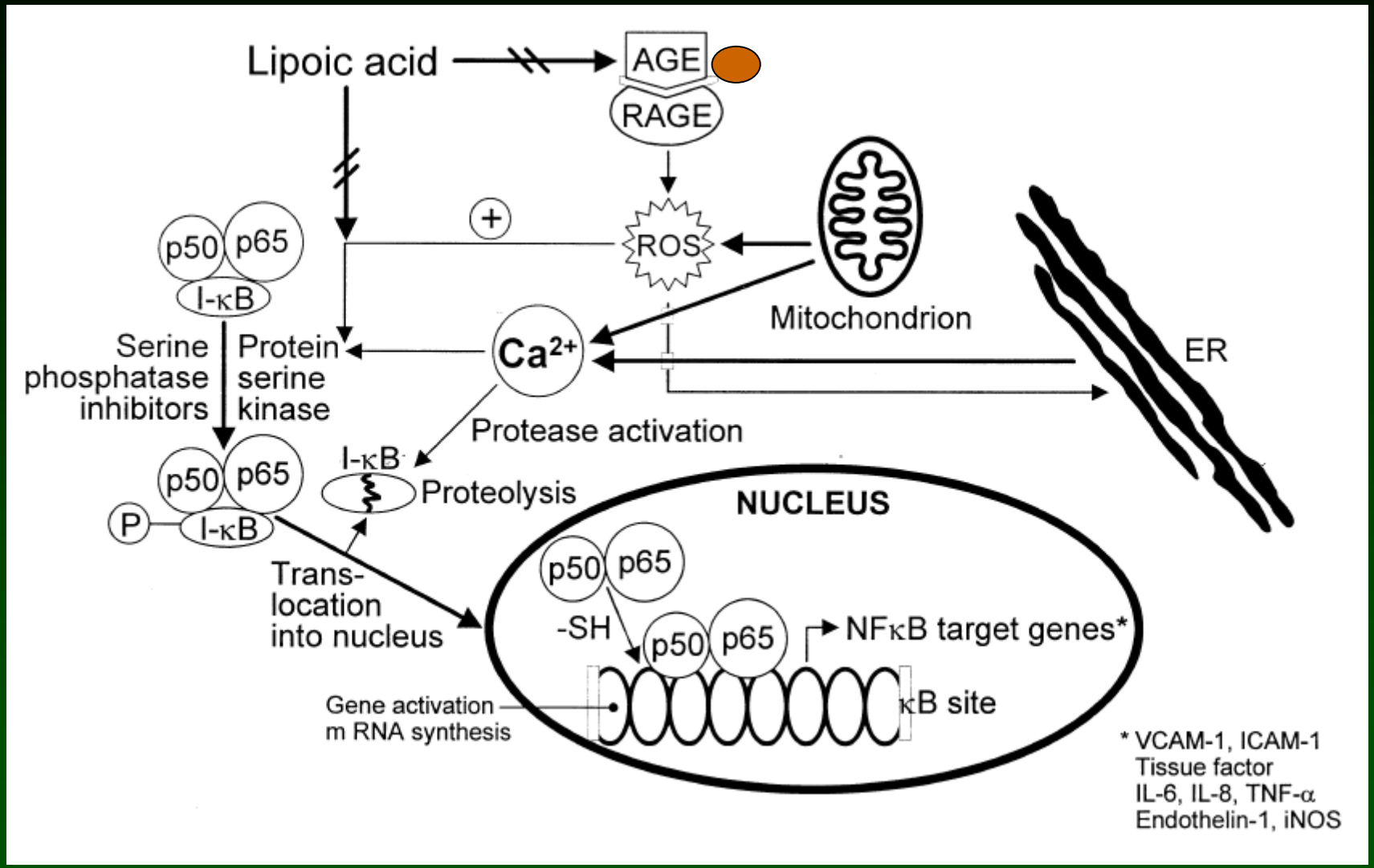
AGE

- INDUKTION PROINFLAMMATORISCHER PROTEINE

- VERLUST DER GEFÄSSELASTIZITÄT UND ANSPRECHBARKEIT AUF NO

- TISSUE FAKTOR UND NFKB ERHÖHT

Clin Geriatr Med. 2002 Aug;18(3):383-405. Review

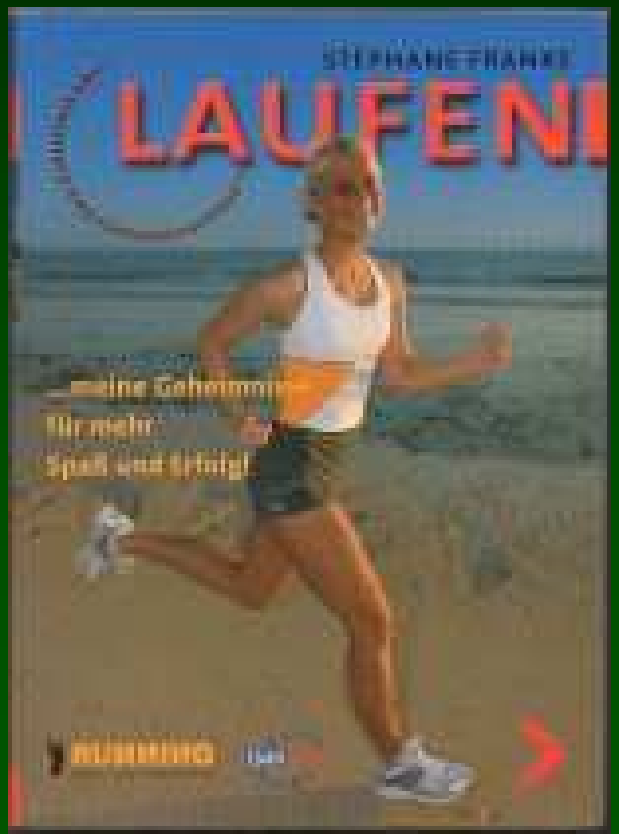

Lipoic acid
AGE
RAGE
p50
p65
I-κB
+
ROS
Mitochondrion
ER
Serine phosphatase inhibitors
Protein serine kinase
Ca2+
Protease activation
I-κB
Proteolysis
p50
p65
P
I-κB
NUCLEUS
Trans-location into nucleus
p50
p65
-SH
p50
p65
NFκB target genes*
Gene activation m RNA synthesis
κB site
* VCAM-1, ICAM-1
Tissue factor
IL-6, IL-8, TNF-α
Endothelin-1, iNOS

Vascular endothelial dysfunction in aging: loss of Akt-dependent endothelial nitric oxide synthase phosphorylation and partial restoration by (*R*)-α-lipoic acid

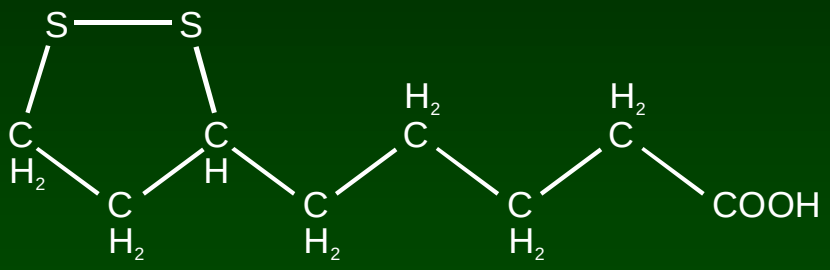
A.R. Smith and T.M. Hagen[1]

Department of Biochemistry and Biophysics and Linus Pauling Institute, 571 Weniger Hall, Oregon State University, Corvallis, OR 97331, U.S.A.

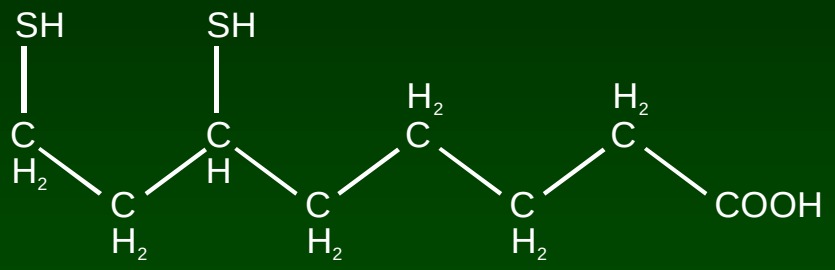
Molecular Mechanisms of Signalling



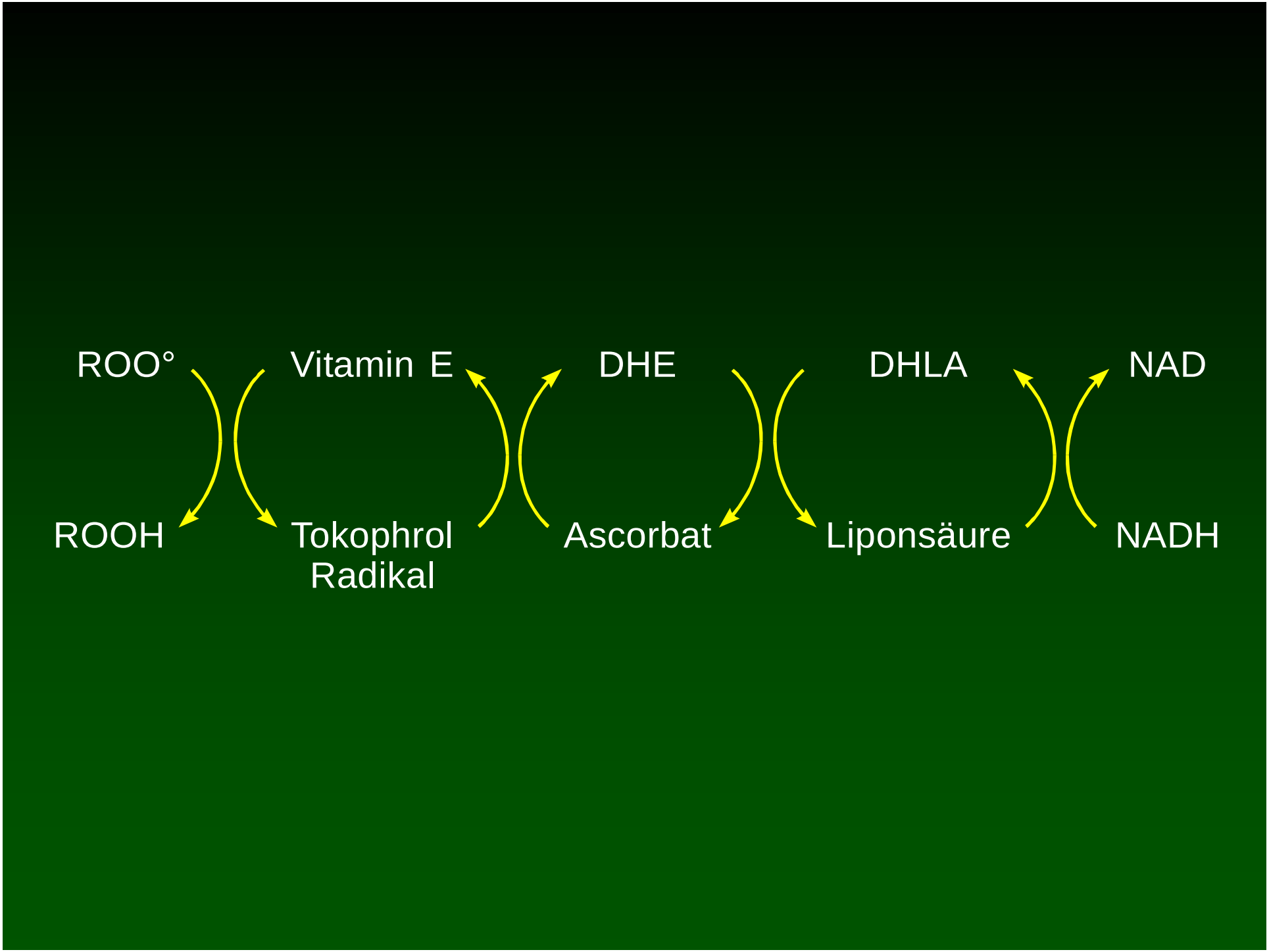
ℴ-Lipoic acid

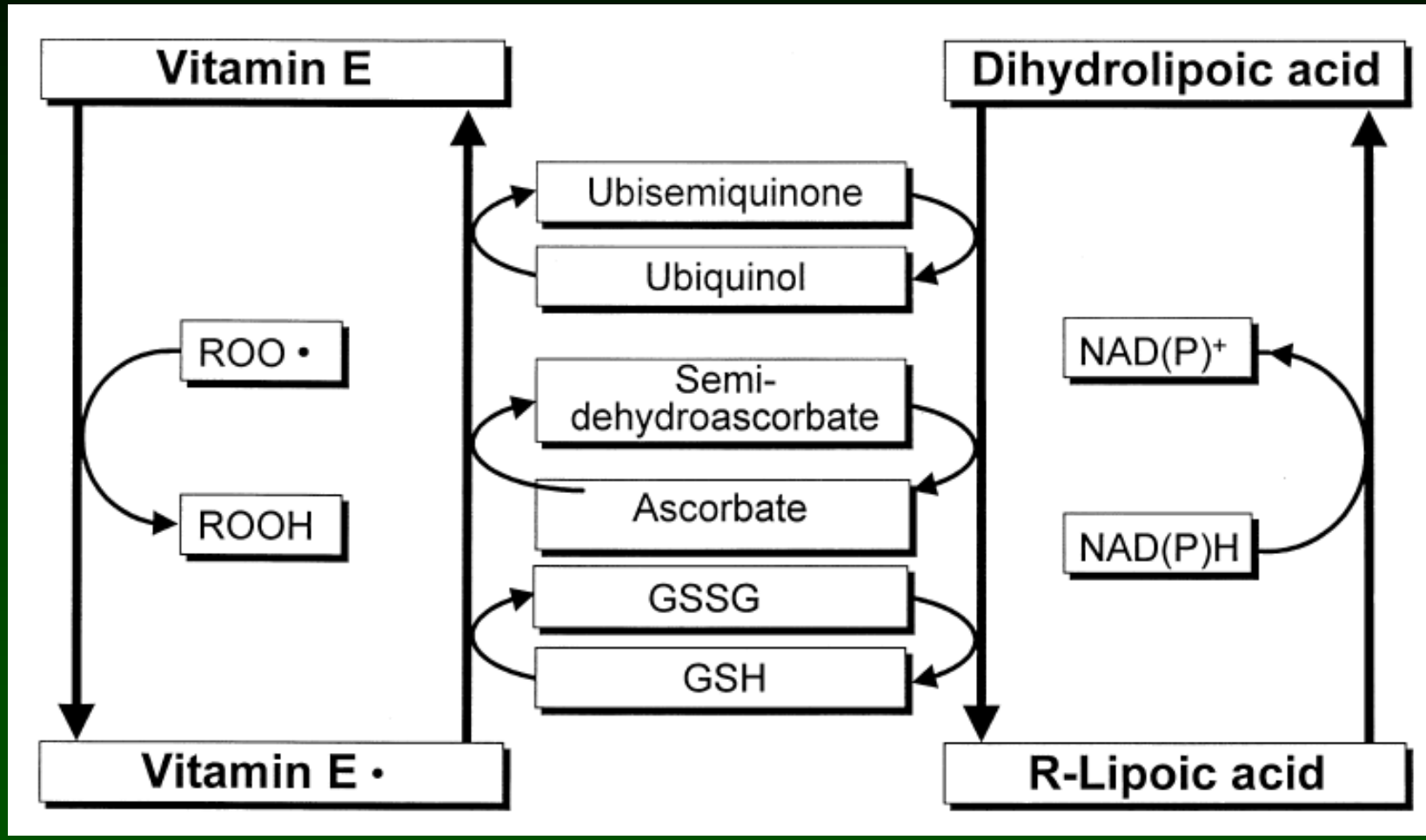


Dihydrolipoic acid



Radikalfänger
Glukosereduktion
Transkriptionsregulator


ROO°
Vitamin E
DHE
DHLA
NAD
ROOH
Tokophrol Radikal
Ascorbat
Liponsäure
NADH


Vitamin E
Dihydrolipoic acid
Ubisemiquinone
Ubiquinol
ROO •
Semi-
dehydroascorbate
NAD(P)+
ROOH
Ascorbate
NAD(P)H
GSSG
GSH
Vitamin E •
R-Lipoic acid

British Journal of Dermatology 2003; **149:** 841–849.

Therapeutics

Randomized, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% α-lipoic acid related to photoageing of facial skin

H.BEITNER

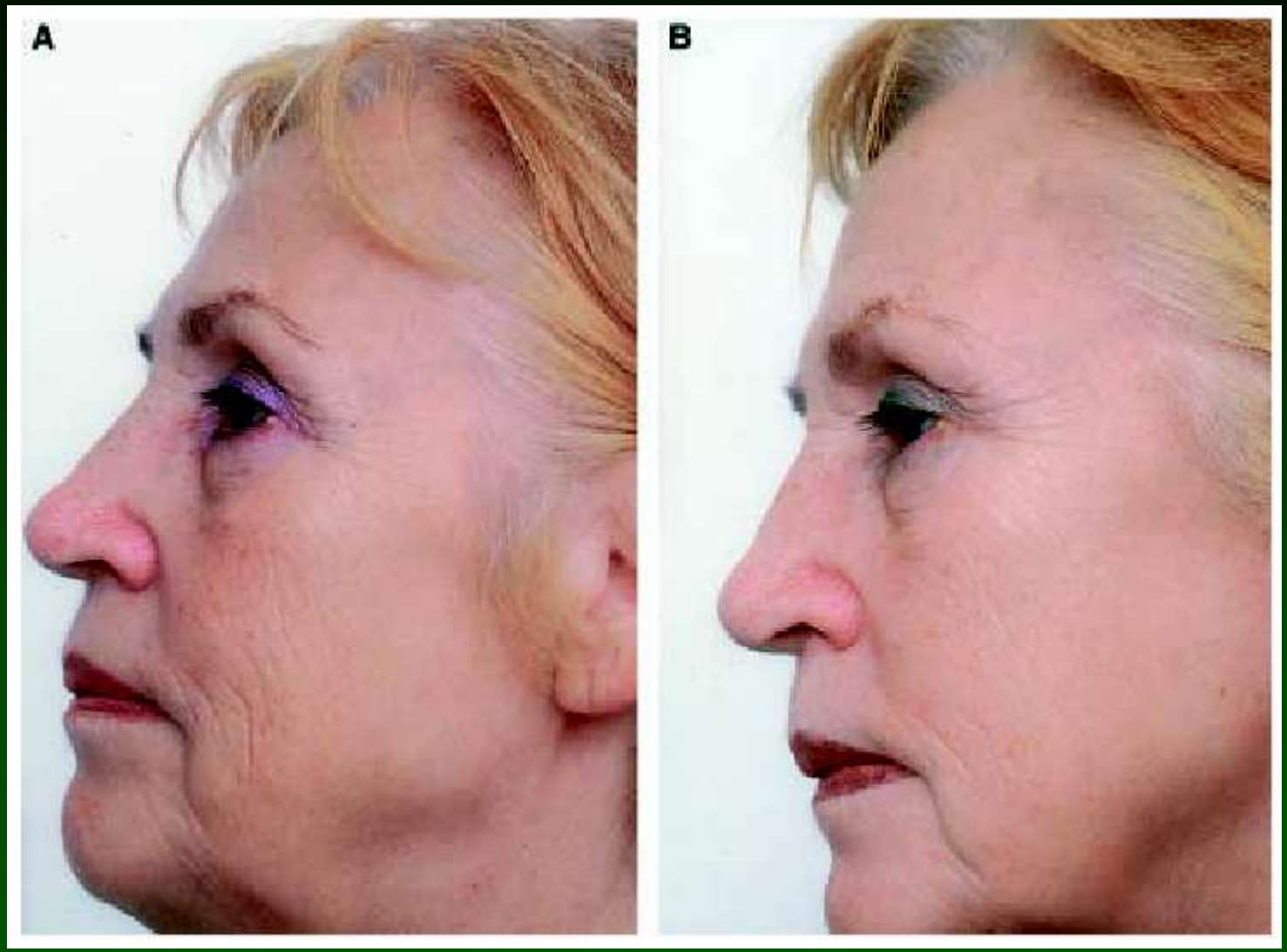
Department of Dermatology, Karolinska Hospital, 17176 Stockholm, Sweden

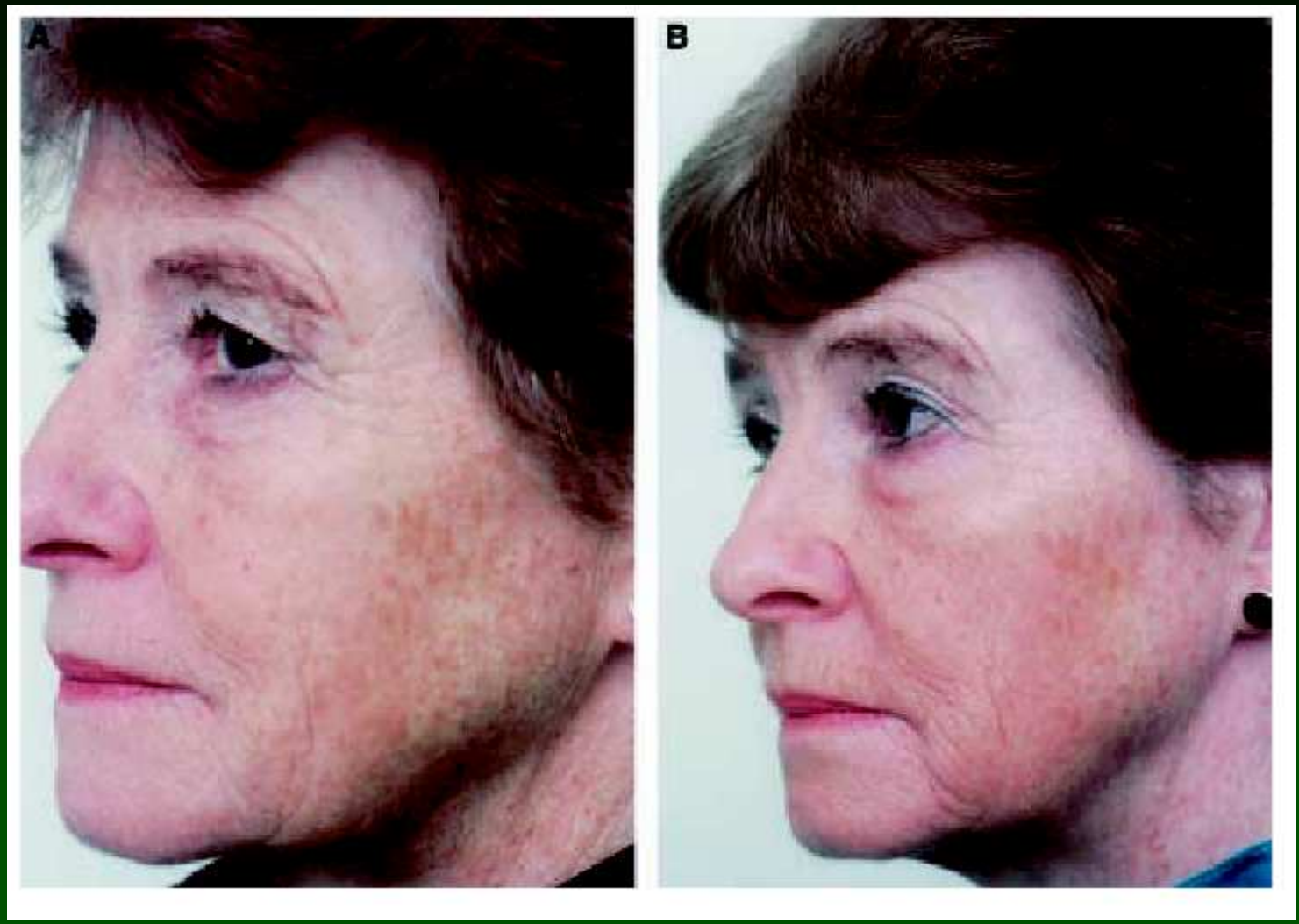
Br J Dermatol. 2003 Oct;149(4):841-9.

Randomized, placebo-controlled, double blind study on the clinical efficacy of a cream containing 5% alpha-lipoic acid related to photoageing of facial skin.

Beitner H.

CONCLUSIONS: It is indicated that 12 weeks of treatment with a cream containing 5% LA improves clinical characteristics related to photoageing of facial skin.


A
B


A
B

α LIPONSÄURE

AKNE-NARBEN

ROSAZEA

KOLLAGENVERLUST

TRÄNENSÄCKE


Skinrepair Maske
mit Alpha Liponsäure
für 10 Anwendungen 100ml
Ch.Nr.: 150311mk
zum alsbaldigen Gebrauch
Alte Leopoldsapotheke, Plankengasse 6, 1010 Wien


Hormonkosmetik
Prof.DDr.J.HUBER
Prinz Eugen-Strasse 16


Hormonkosmetik
Prof.DDr.J.HUBER
Prinz-Eugen-Strasse 16
Skinrepair Maske
mit Alpha Liponsäure
für 10 Anwendungen 100ml

REVIEW

Green tea and the skin

Stephen Hsu, PhD
Augusta, Georgia

Plant extracts have been widely used as topical applications for wound-healing, anti-aging, and disease treatments. Examples of these include ginkgo biloba, echinacea, ginseng, grape seed, green tea, lemon, lavender, rosemary, thuja, sarsaparilla, soy, prickly pear, sagebrush, jojoba, aloe vera, allantoin, feverwort, bloodroot, apache plume, and papaya. These plants share a common character: they all produce flavonoid compounds with phenolic structures. These phytochemicals are highly reactive with other compounds, such as reactive oxygen species and biologic macromolecules, to neutralize free radicals or initiate biological effects. A short list of phenolic phytochemicals with promising properties to benefit human health includes a group of polyphenol compounds, called catechins, found in green tea. This article summarizes the findings of studies using green tea polyphenols as chemopreventive, natural healing, and anti-aging agents for human skin, and discusses possible mechanisms of action. (J Am Acad Dermatol 2005;52:1049-59.)

J Am Acad Dermatol. 2005 Jun;52(6):1049-59.

The FASEB Journal express article10.1096/fj.02-0914fje. Published online August 1, 2003.

Dual mechanisms of green tea extract-induced cell survival in human epidermal keratinocytes

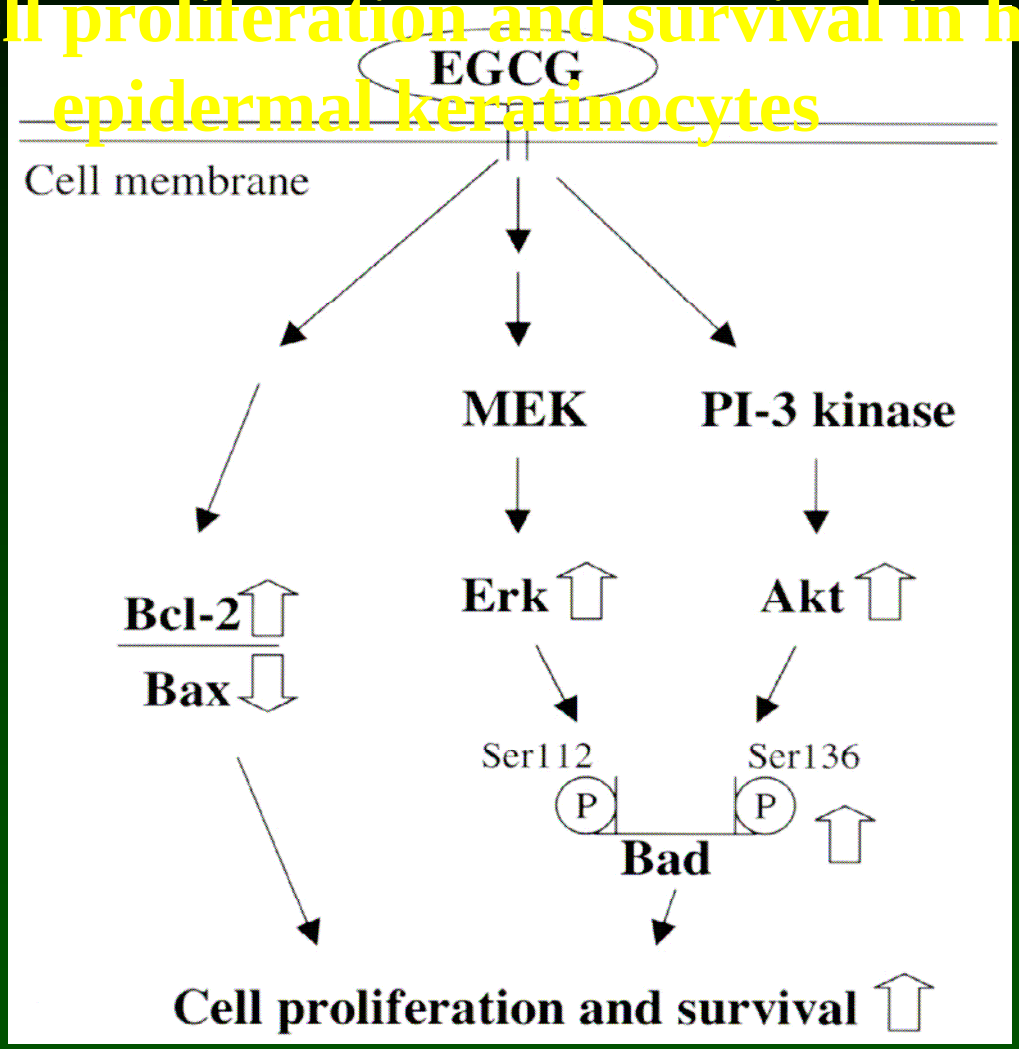
Jin Ho Chung, Ji Hyun Han, Eun Ju Hwang, Jin Young Seo, Kwang Hyun Cho, Kyu Han Kim, Jai Il Youn, and Hee Chul Eun

Department of Dermatology, Seoul National University College of Medicine, and Laboratory of Cutaneous Aging Research, Clinical Research Institute, Seoul National University Hospital, Seoul, Korea

Corresponding author: Hee Chul Eun, Department of Dermatology, Seoul National University Hospital, 28 Yongon-dong, Chongno-Gu, Seoul 110-744, Korea. E-mail:hceun@snu.ac.kr

FASEB J. 2003 Oct;17(13):1913-5. Epub 2003 Aug 1.

Proposed molecular mechanisms of EGCG-induced cell proliferation and survival in human epidermal keratinocytes



Chung JH et al. FASEB J. 2003 Oct;17(13):1913-5. Epub 2003 Aug 1.

EGCG promotes human keratinocyte survival, and inhibits ultraviolet light-induced apoptosis by dual mechanism, namely, by phosphorylating Bad protein through Erk and Akt pathways, respectively, and by increasing the Bcl-2 to Bax ratio

Kwon OS et al. Phytomedicine. 2007 Aug;14(7-8):551-5. Epub 2006 Nov 7.

Green Tea Polyphenols Prevent Ultraviolet Light-Induced Oxidative Damage and Matrix Metalloproteinases Expression in Mouse Skin

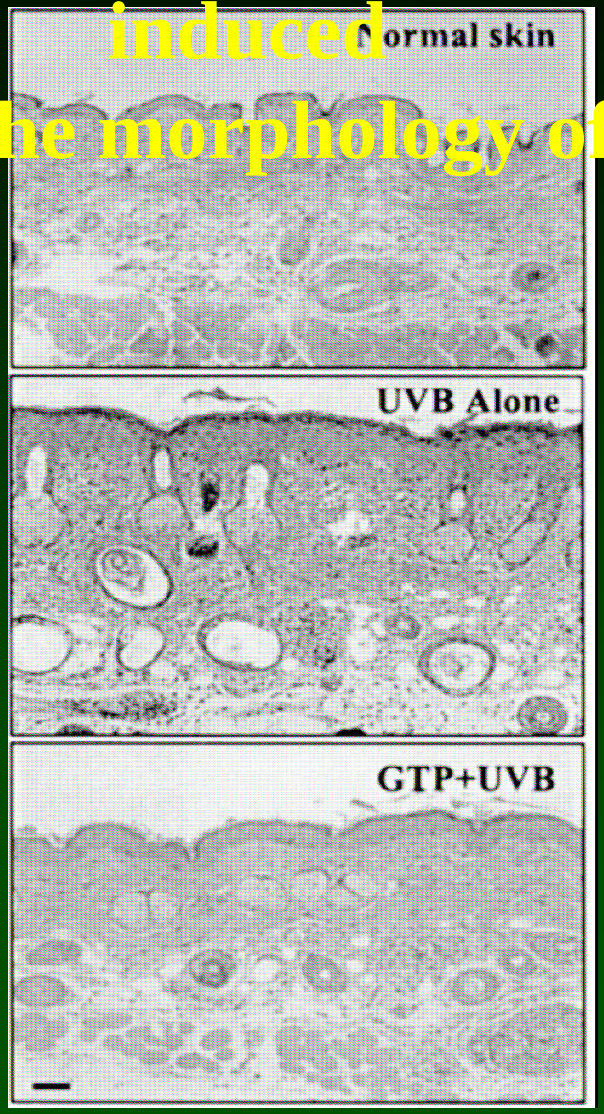
Praveen K. Vayalil,* Anshu Mittal,* Yukihiko Hara,¶ Craig A. Elmets,*†‡ and Santosh K. Katiyar*†‡§

*Department of Dermatology, University of Alabama at Birmingham, Birmingham, Alabama, USA; †Department of Environmental Health Sciences, University of Alabama at Birmingham, Birmingham, Alabama, USA; ‡Department of Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, Alabama, USA; §Center for Aging, University of Alabama at Birmingham, Birmingham, Alabama, USA; ¶Tokyo Food Techno Co. Ltd., Shizuoka, Japan

Chronic exposure of solar ultraviolet (UV) light to human skin results in photoaging. UV-induced oxidative damage and induction of matrix metalloproteinases (MMP) have been implicated in this process. Because polyphenols from green tea (GTP) prevent other cutaneous adverse effects of UV radiation we hypothesized that UV irradiation-induced oxidative damage and induction of MMP might be prevented *in vivo* in mouse skin by oral administration of GTP. GTP was administered in drinking water (0.2%, wt/vol) to SKH-1 hairless mice, which were then exposed to multiple doses of UVB (90 mJ per cm^2, for 2 mo on alternate days) following *in vivo* photoaging animal protocol. Treatment of GTP resulted in inhibition of UVB-induced protein oxidation *in vivo* in mouse skin, a hallmark of photoaging, when analyzed biochemically, by immunoblotting, and immunohistochemistry. GTP treatment also inhibited UVB-induced protein oxidation *in vitro* in human skin fibroblast HS68 cells, which supports *in vivo* observations. Moreover, oral administration of GTP also resulted in inhibition of UVB-induced expression of matrix degrading MMP, such as MMP-2 (67%), MMP-3 (63%), MMP-7 (62%), and MMP-9 (60%) in hairless mouse skin. These

J Invest Dermatol. 2004 Jun;122(6):1480-7.

Oral administration of GTP prevents UVB-induced damage to the morphology of the skin



Vayalil PK et al. J Invest Dermatol. 2004 Jun;122(6):1480-7.

Human hair growth enhancement in vitro by green tea epigallocatechin-3-gallate (EGCG)

O.S. Kwon, J.H. Han, H.G. Yoo, J.H. Chung, K.H. Cho, H.C. Eun, K.H. Kim*

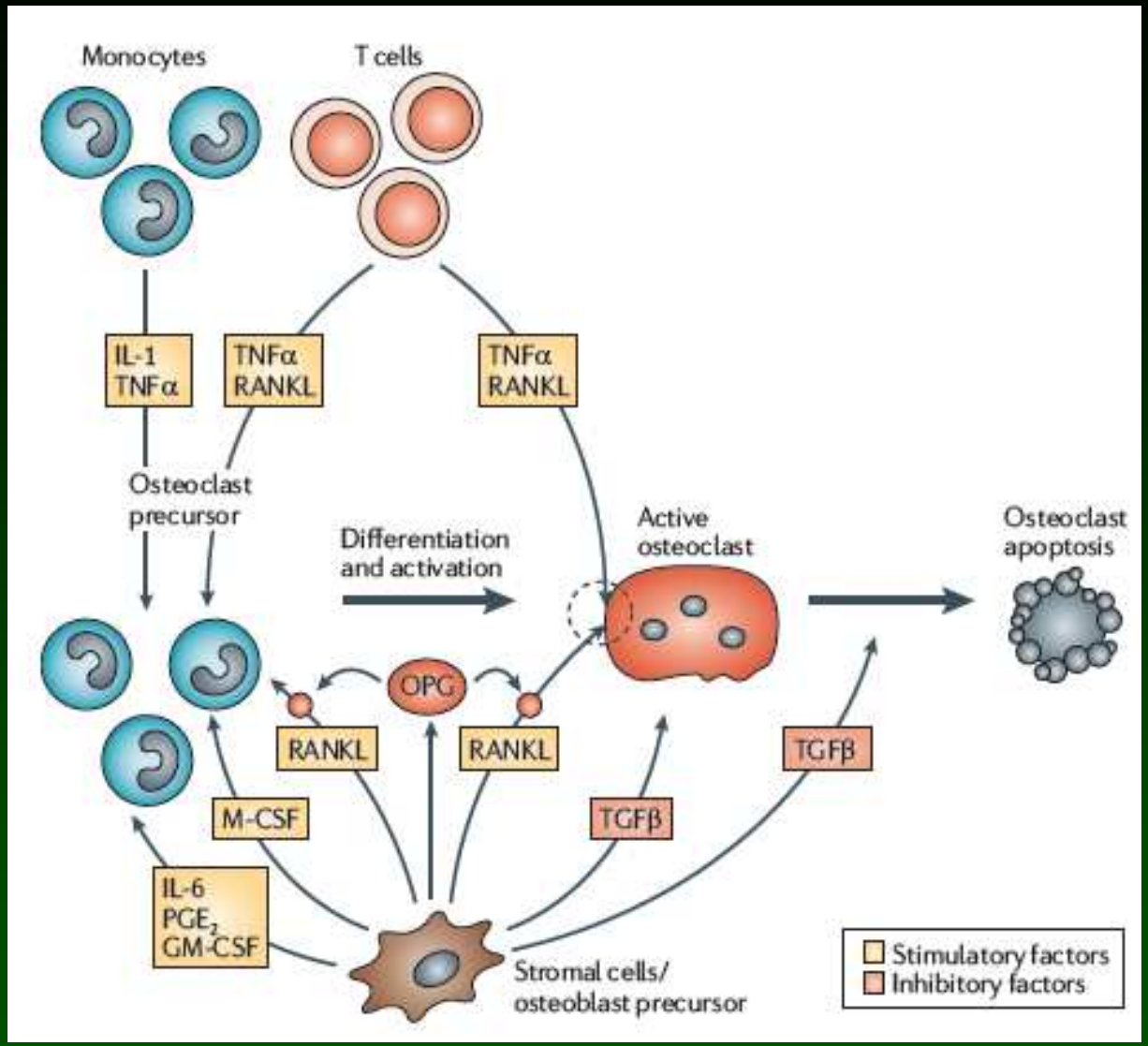
Department of Dermatology, Seoul National University College of Medicine, Laboratory of Cutaneous Aging and Hair Research, Clinical Research Institute, Seoul National University Hospital, Institute of Dermatological Science, Seoul National University, 110-744 Seoul, Republic of Korea

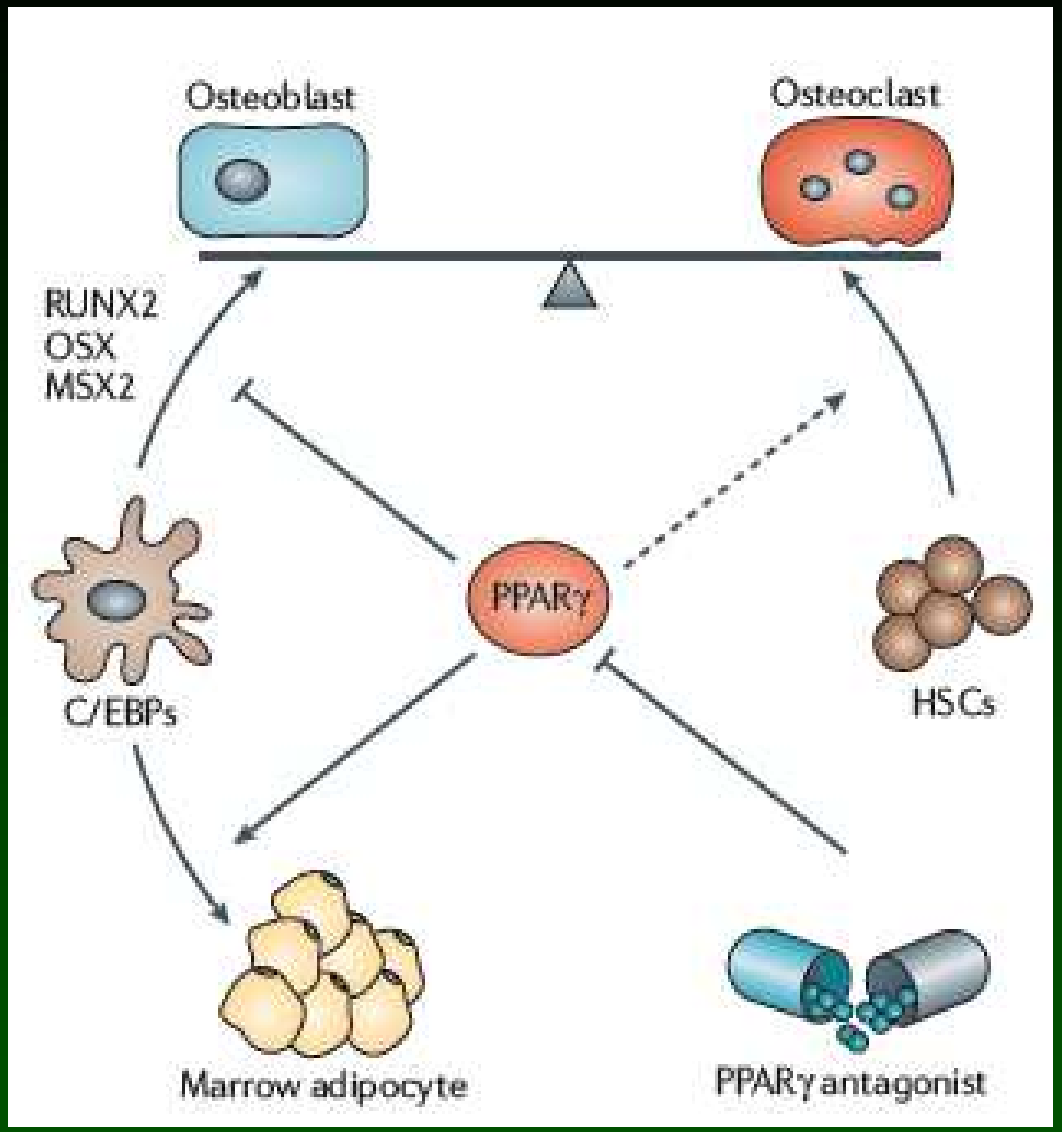
Phytomedicine. 2007 Aug;14(7-8):551-5. Epub 2006 Nov 7.


17 9:05AM

Emerging therapeutic opportunities for skeletal restoration

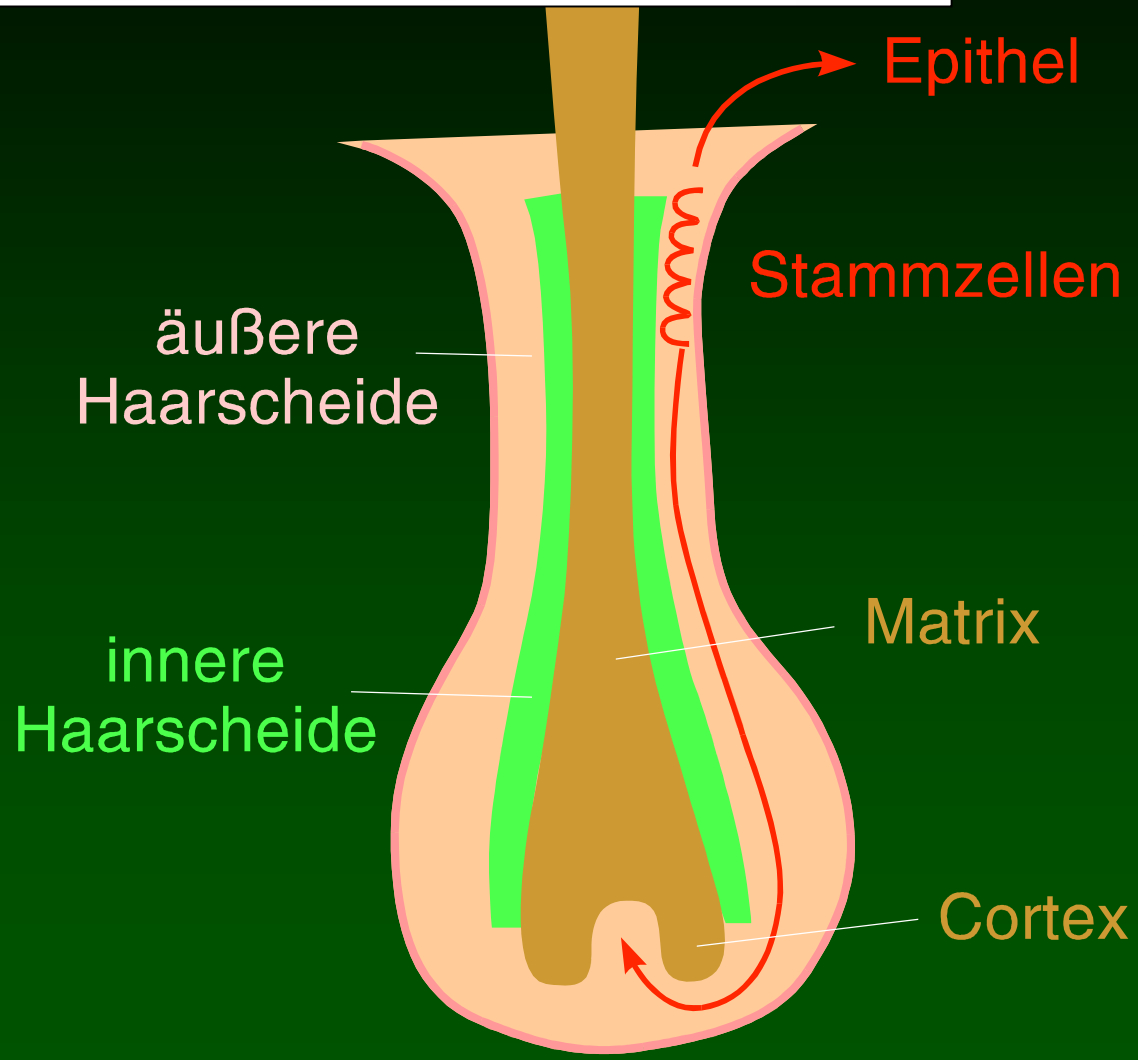
Masanobu Kawai[*‡||], *Ulrike I. Mödder*[§||], *Sundeep Khosla*[§] *and Clifford J. Rosen*[*]


Monocytes
T cells
IL-1
TNFα
TNFα
RANKL
TNFα
RANKL
Osteoclast
precursor
Differentiation
and activation
Active
osteoclast
Osteoclast
apoptosis
OPG
RANKL
RANKL
TGFβ
M-CSF
TGFβ
IL-6
PGE2
GM-CSF
Stromal cells/
osteoblast precursor
Stimulatory factors
Inhibitory factors

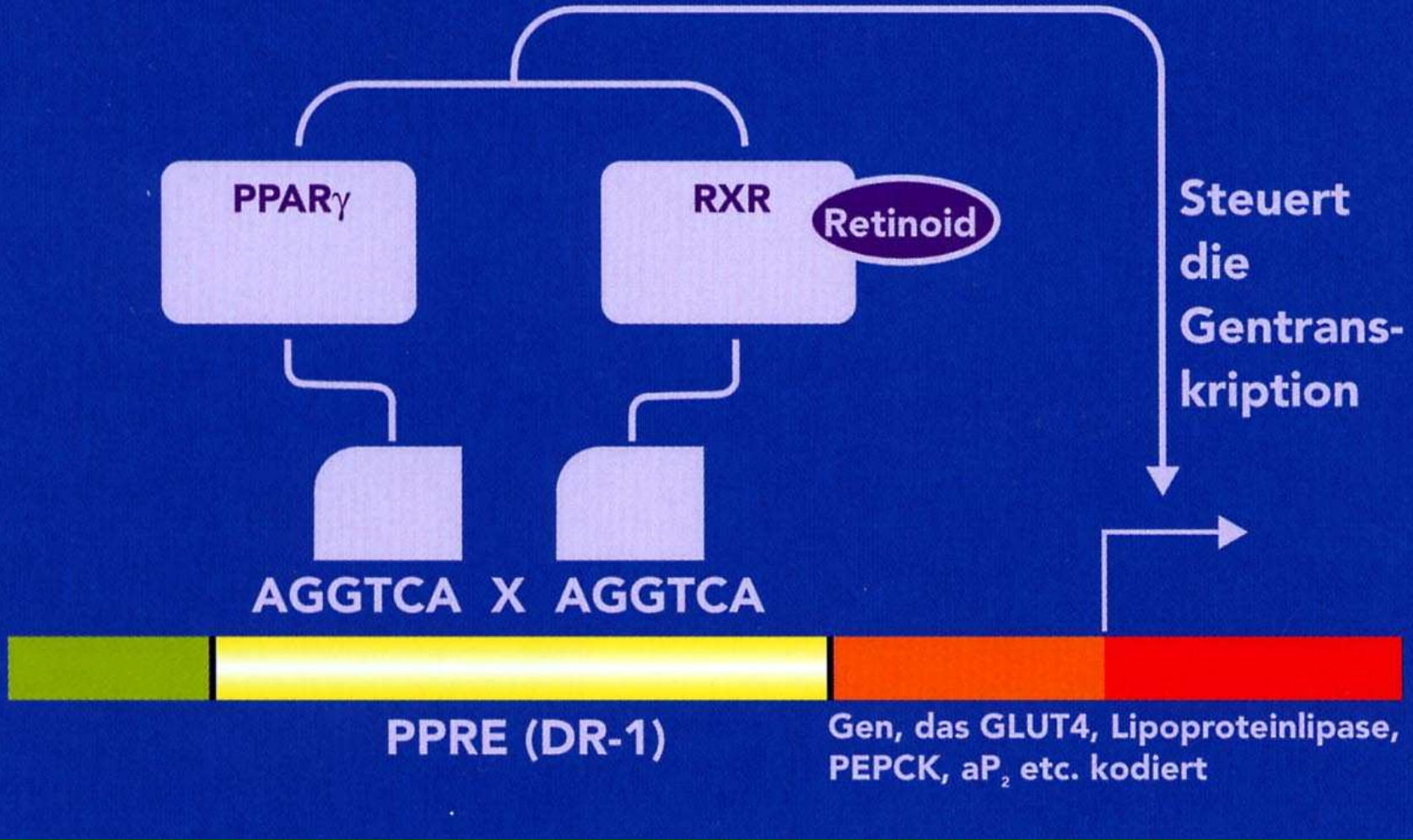

Osteoblast
Osteoclast
RUNX2
OSX
MSX2
PPARγ
C/EBPs
HSCs
Marrow adipocyte
PPARγ antagonist

Cell, Vol. 104, 233–245, January 26, 2001, Copyright ©2001 by Cell Press

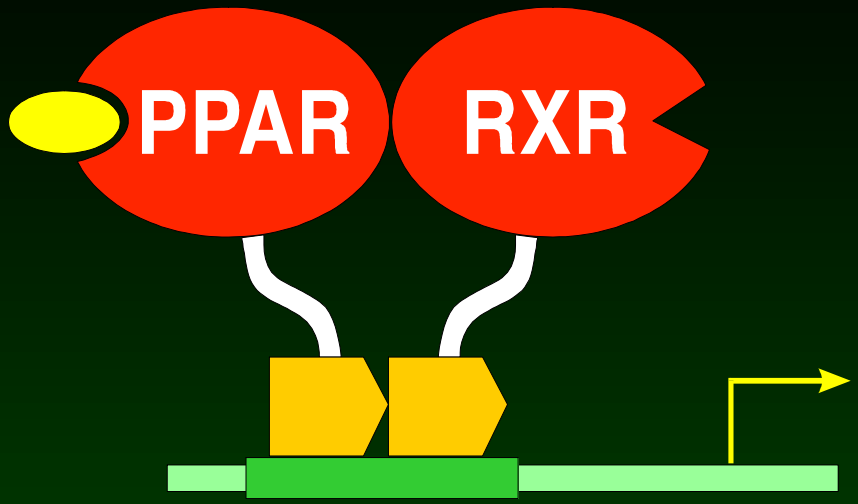
Morphogenesis and Renewal of Hair Follicles from Adult Multipotent Stem Cells



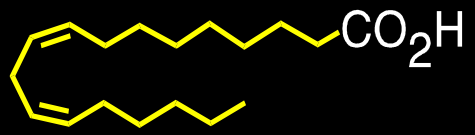
Die Aktivierung von PPARγ beeinflusst die Expression bestimmter Gene



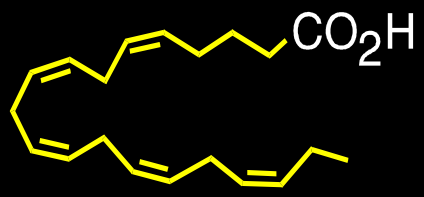
LIGANDEN



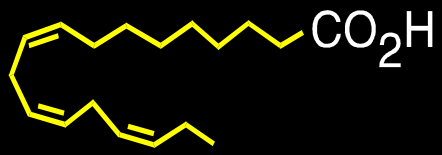
Pan-agonists



Linoleic acid



Eicosapentaenoic acid



Linolenic acid

PPARα-selective

PPARγ-selective

Aktivierung von PPAR alpha und PPAR gamma

Fischöl

Exercise

Fasting

Rosiglitazon

J. Biol. Chem. 273, 29577

Natural ligands

Polyunsaturated fatty acid (ω3)

- α-linolenic acid
- Eicosapentaenoic acid
- Docosahexaenoic acid

Prostaglandins J_2 (PGJ_2)

- 15-deoxy-$\Delta^{12,14}$-PGJ_2
- Δ^{12}-PGJ_2

Synthetic ligands

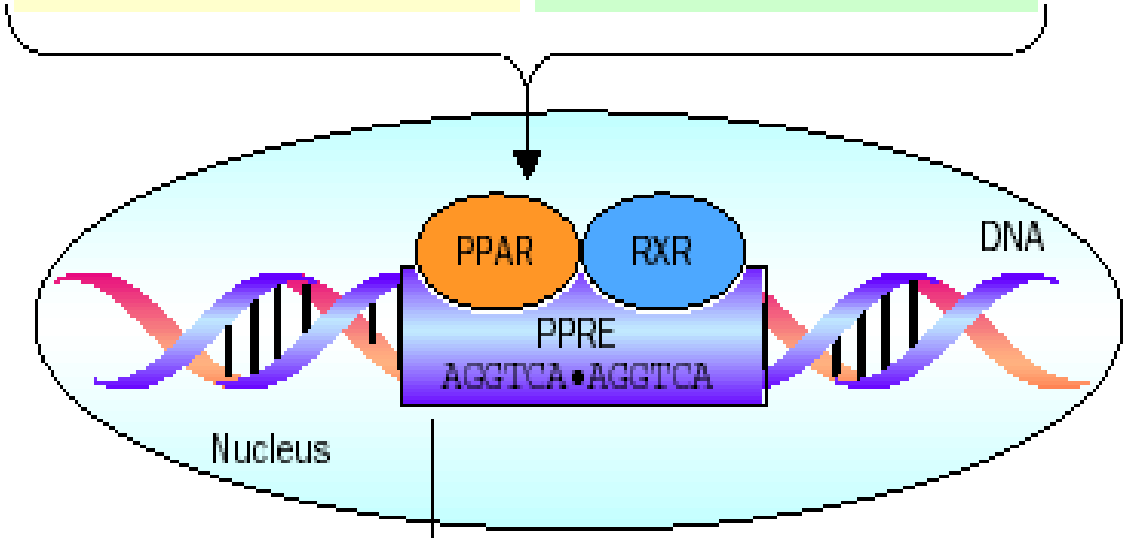
Thiazolidinediones

Non-steroidal anti-inflammatory drugs

- Indomethacin
- Ibuprofen
- Fenoprofen

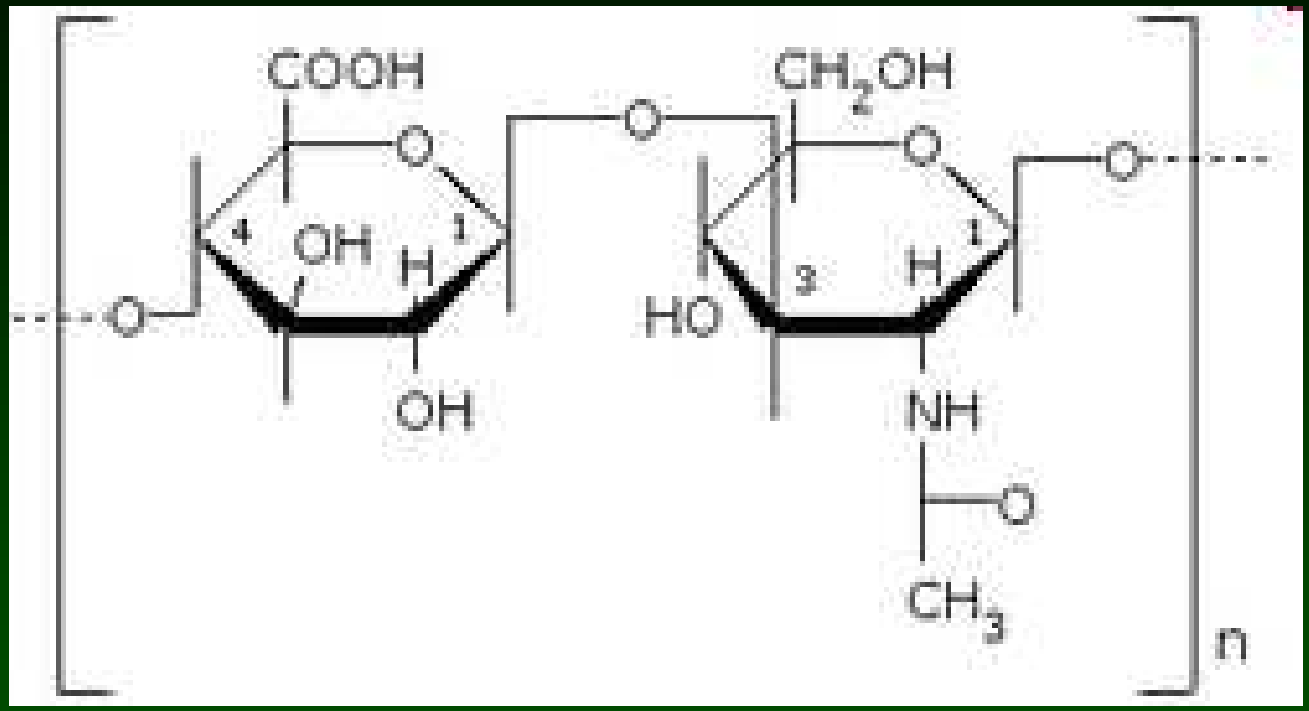
L-tyrosine-derived compounds

- Fluoromethyloxycarbonyl

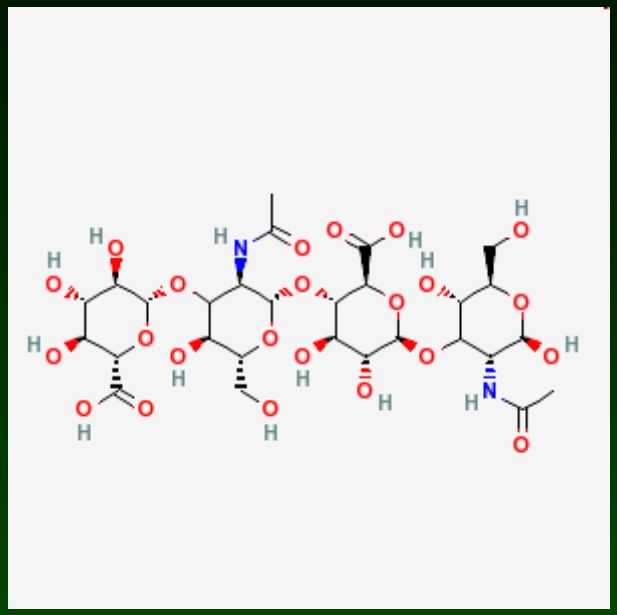


Regulation of genes implicated in control of

- Lipid metabolism
- Insulin sensitisation
- Carcinogenesis
- Inflammation

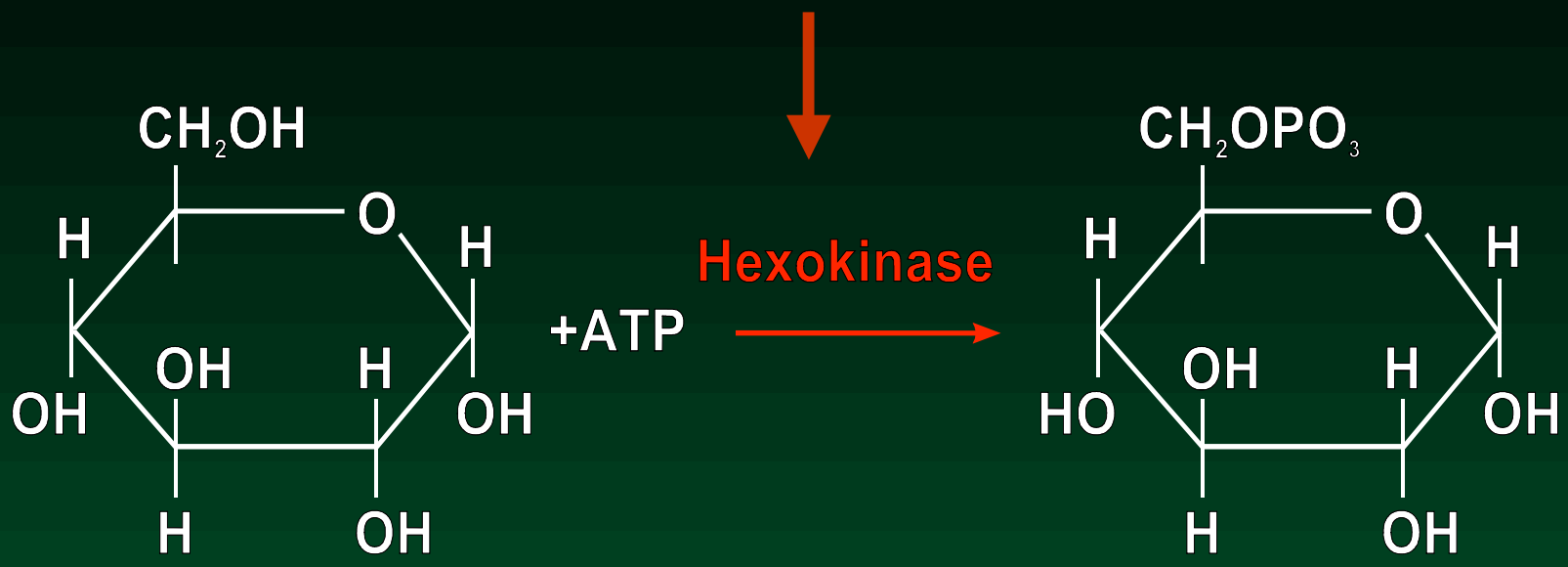


Die Hyaluronsäure besitzt die Fähigkeit, relativ zu ihrer Masse sehr große Mengen an Wasser zu binden (bis zu sechs Liter Wasser pro Gramm). Der Glaskörper des Auges z.B. besteht zu 98 % aus Wasser, das an nur 2 % Hyaluronsäure gebunden ist

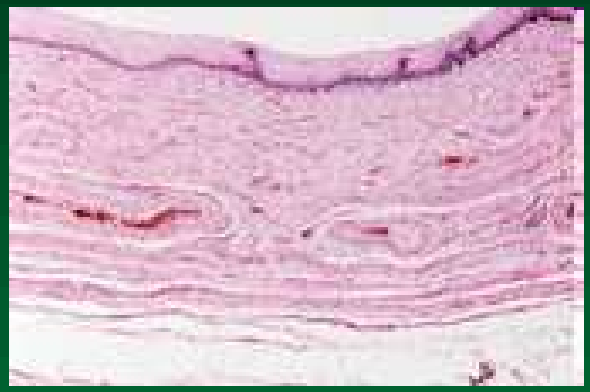


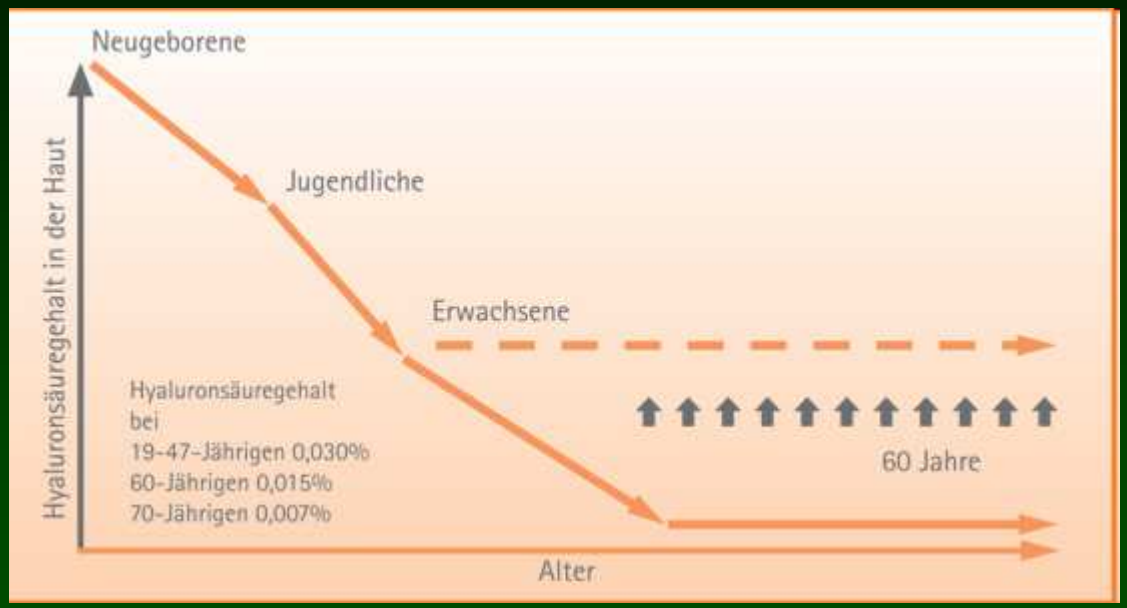
Hyaluronsäure besteht aus β-(1→4)-glykosidisch miteinander verknüpften Glukuronyl-β-(1→3)-N-Acetylglukosamin-Disaccharideinheiten, wobei bis zu 100.000 aufeinander folgen können

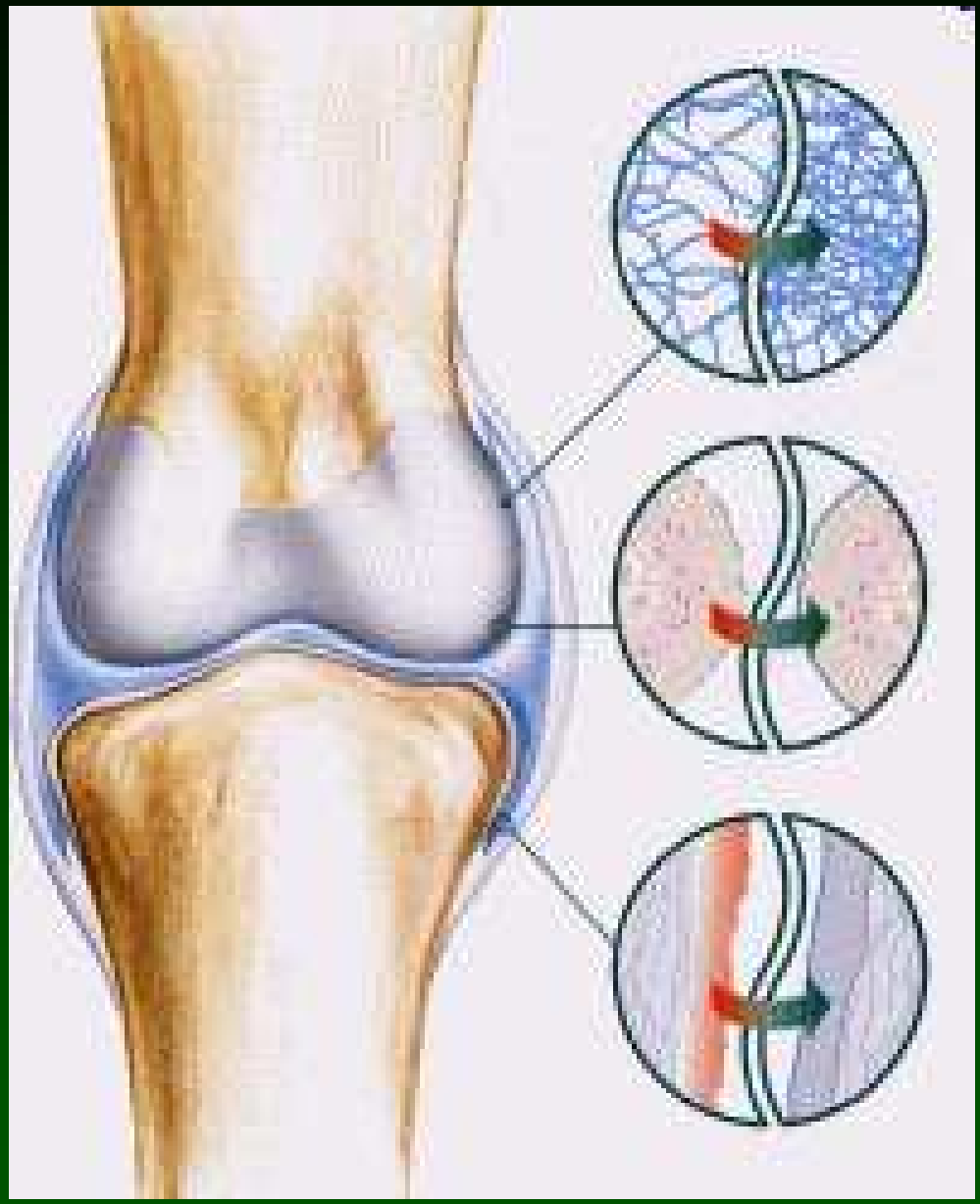
estrogen



Glukose




Neugeborene
Jugendliche
Erwachsene
60 Jahre
Hyaluronsäuregehalt in der Haut
Hyaluronsäuregehalt
bei
19-47-Jährigen 0,030%
60-Jährigen 0,015%
70-Jährigen 0,007%
Alter



Facial Rejuvenation mit neuen modularen Konzepten

Hyaluronsäure mit Langzeiteffekt – subdermale Anwendungstechnik bietet neue Möglichkeiten der Volumenaugmentation

Im Rahmen der 21. Münchner Fortbildungswoche für praktische Dermatologie und Venerologie, die vom 20. bis 25. Juli stattfand, referierte Dr. med. Michael Weidmann, (Facharzt für Dermatologie-Allergologie-Phlebologie, Augsburg) in einem Workshop über die neuen Varioderm® Hyaluronsäure-Filler. In einer anschließenden Live-Anwendung an zwei Patienten konnte er vor allem die Anwendung von Varioderm Subdermal darstellen. Dr. Weidmann wendet seit über zwölf Monaten die Produktlinie Varioderm an.

Den Patienten können heute umfassende Therapiekonzepte geboten werden, die dem Alterungsprozess der Haut effektiv entgegenwirken. Dabei finden vor allem

Der Unterschied von Varioderm® zu anderen Hyaluronsäurepräparaten

Dr. Weidmann erläuterte in seinem Vortrag zunächst die Abgrenzun-

New Hyaluronic Acid Filler for Subdermal and Long-lasting Volume Restoration of the Face

Michael J Weidmann

Klinik/Praxis am Forsterpark, Augsburg

Abstract

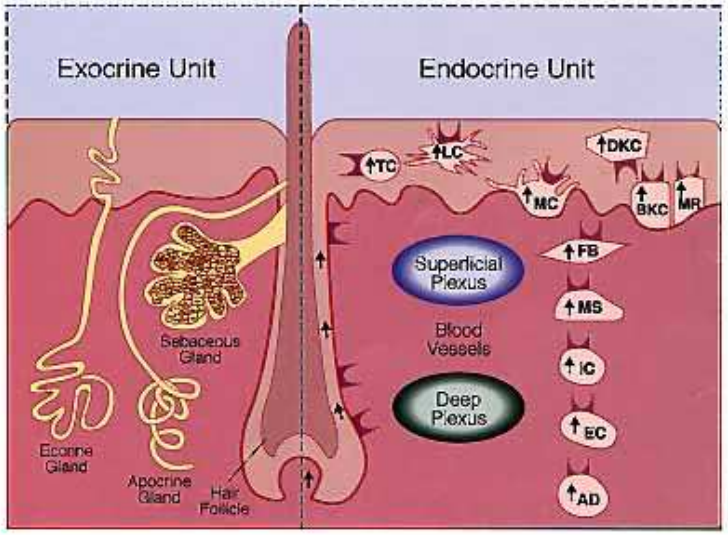
Over the past few years, the focus in the field of aesthetic medicine has gradually shifted towards minimally invasive procedures. As more and more patients are refusing to take prolonged absences from their work, the use of filler materials, botulinum toxin A, peelings, laser, fat implantation and other minor surgical corrections has significantly increased. Minimally invasive volume restoration of the face through long-lasting resorbable fillers is nowadays more attractive and important to patients.

Figure 5: Cheek Augmentation and Marionette Lines of a Patient Before and After Injection with Varioderm Subdermal 1ml (Before and After 12 Months)

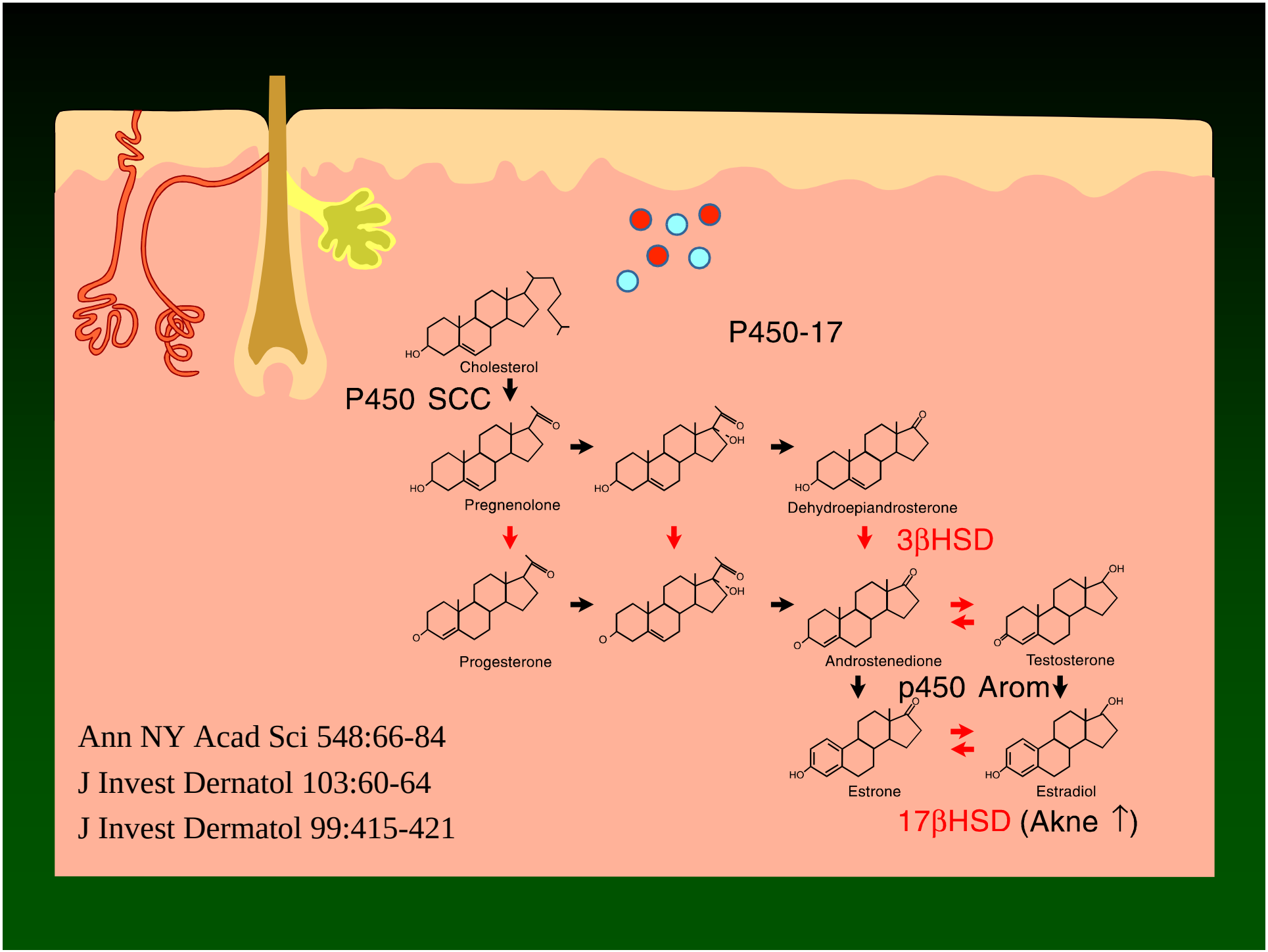
Figure 6: Injection with Varioderm Subdermal 2ml in the Naso-labial Folds (Before and After Nine Months)

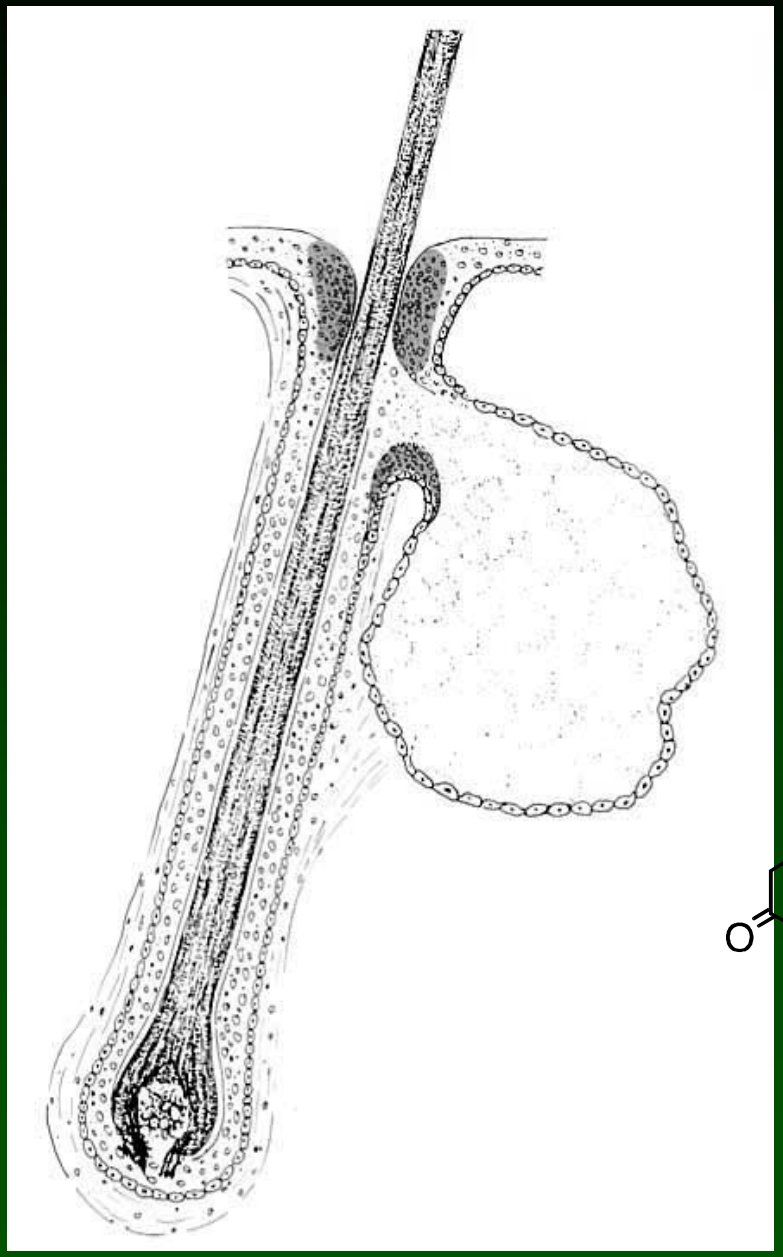
ENDOCRINE REVIEWS

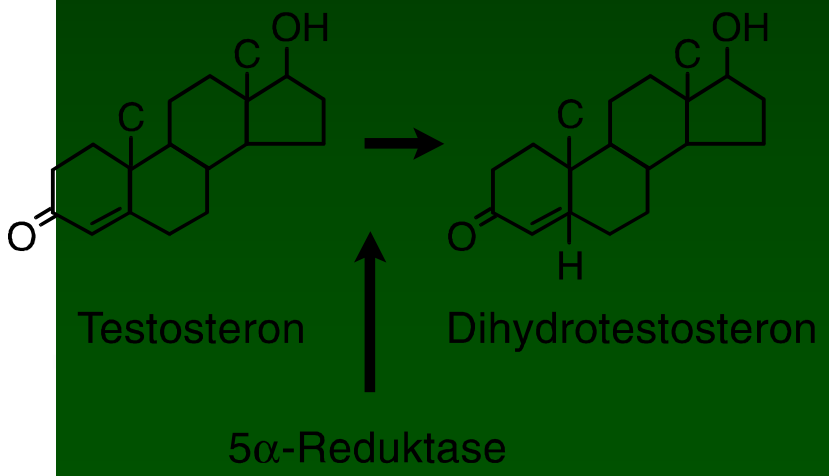
Volume 21, Number 5, October 2000

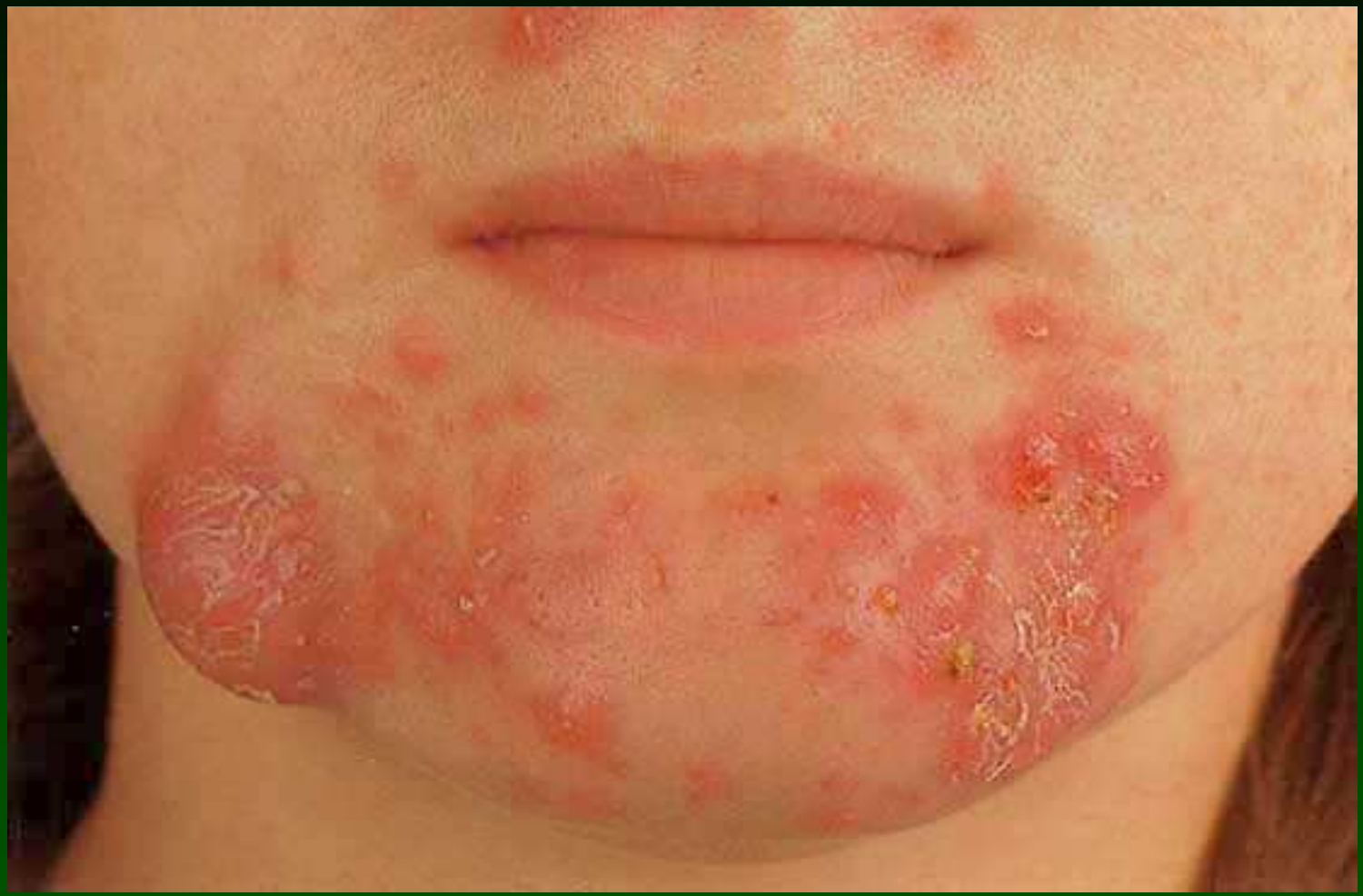


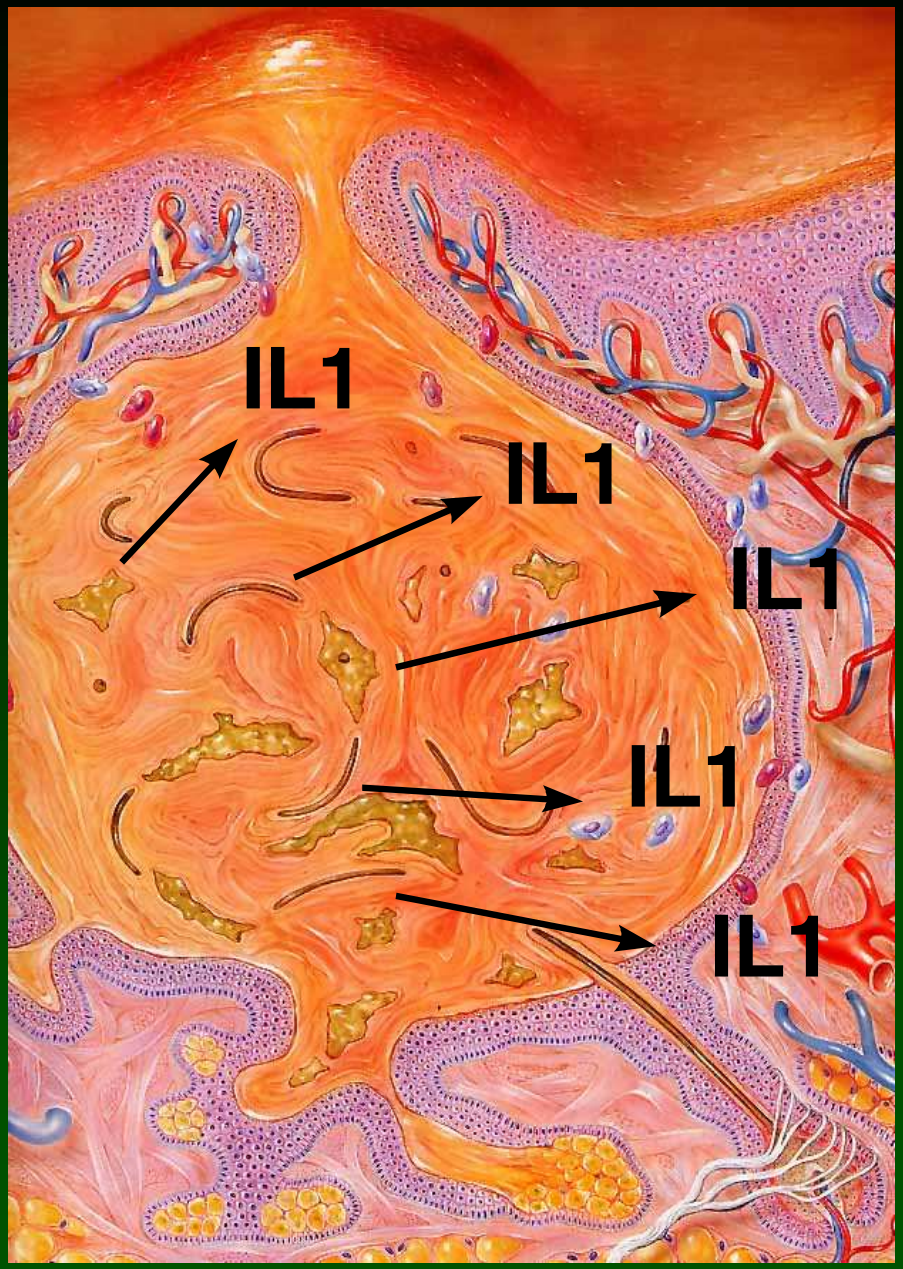
PUBLISHED BIMONTHLY BY THE ENDOCRINE SOCIETY


Cholesterol
P450-17
P450 SCC
Pregnenolone
Dehydroepiandrosterone
3βHSD
Progesterone
Androstenedione
Testosterone
p450 Arom
Estrone
Estradiol
17βHSD (Akne ↑)
Ann NY Acad Sci 548:66-84
J Invest Dernatol 103:60-64
J Invest Dermatol 99:415-421




OH
C
C
O
OH
C
C
O
H
Testosteron
Dihydrotestosteron
5α-Reduktase





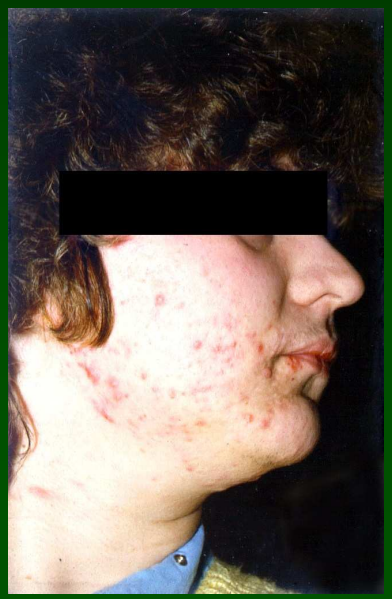
J Invest Dermatol 98 (6):895-901

STUDY

Topical Cyproterone Acetate Treatment in Women With Acne

A Placebo-Controlled Trial

Doris M. Gruber, MD; Michael O. Sator, MD; Elmar A. Joura, MD; Eva Maria Kokoschka, MD; Georg Heinze, MSc; Johannes C. Huber, MD, PhD



Arch Dermatol. 1998 Apr;134(4):459-63.

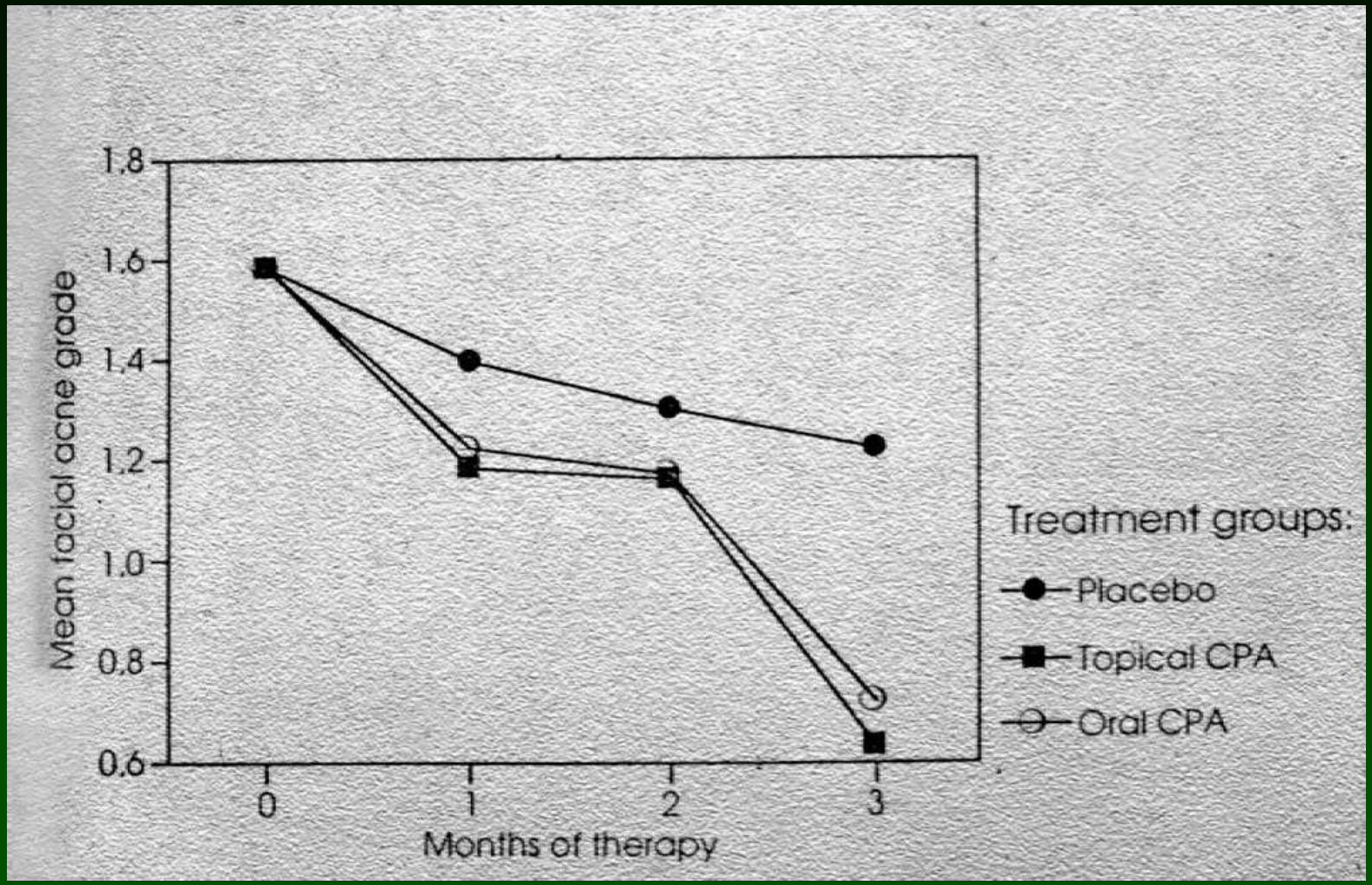
Traitement topique de l’acné

Rp./

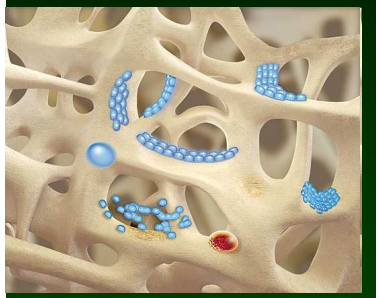
Cyproteronacetat	**0,30 g**
Salbengrundlage	**ad 50,00 g**

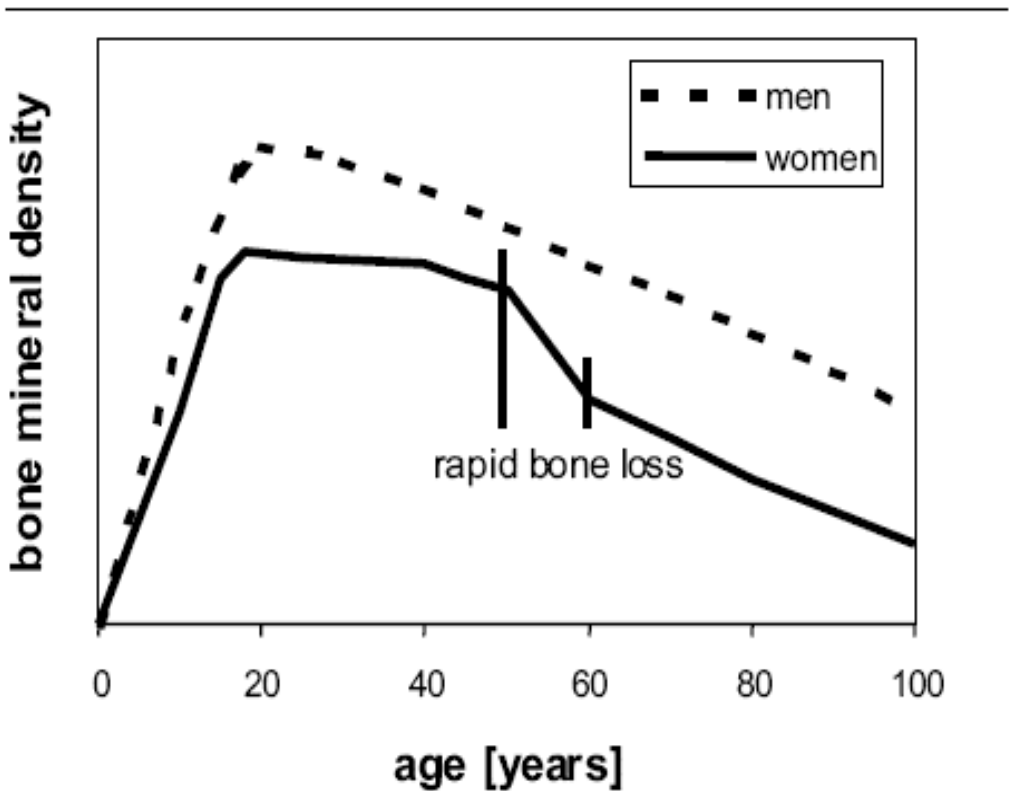
D.S. CPA-creame 0,6%

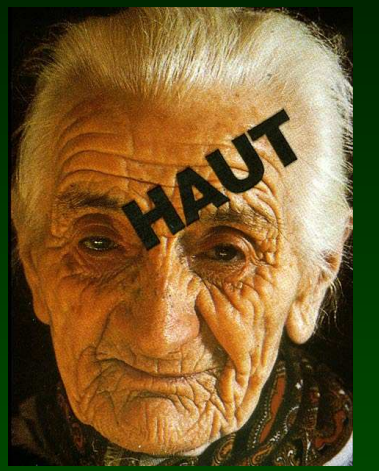
Arch Dermatol. 1998 Apr;134(4):459-63



Arch Dermatol. 1998 Apr;134(4):459-63







Internist (Berl). 2002 Dec;43(12):1529-30, 1533-43. Review.

There is a sharp gender difference in bone mass, but also in the decline of the bon mass. The most important point is the “rapid loss area” in the erly menopause. In this time window, we have to take special care for our female patients, in consulting but also in the diagnosis of high risk patients

CLIMACTERIC 2007;10:320–334

A prospective, randomized, double-blind, placebo-controlled study on the influence of a hormone replacement therapy on skin aging in postmenopausal women

P.-G. Sator, M. O. Sator, J. B. Schmidt, H. Nahavandi†, S. Radakovic, J. C. Huber* and H. Hönigsmann*

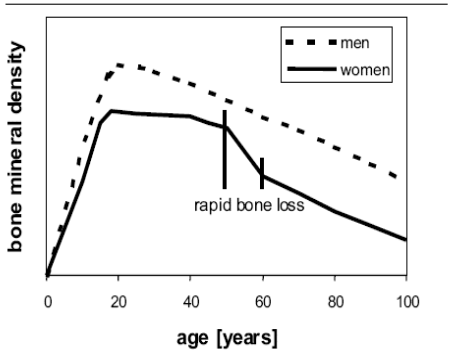
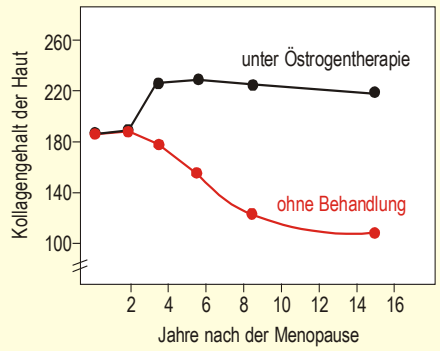


Fig. 1. Bone gain and bone loss in men and women. Adapted from R. Bartl, 2001 [9]



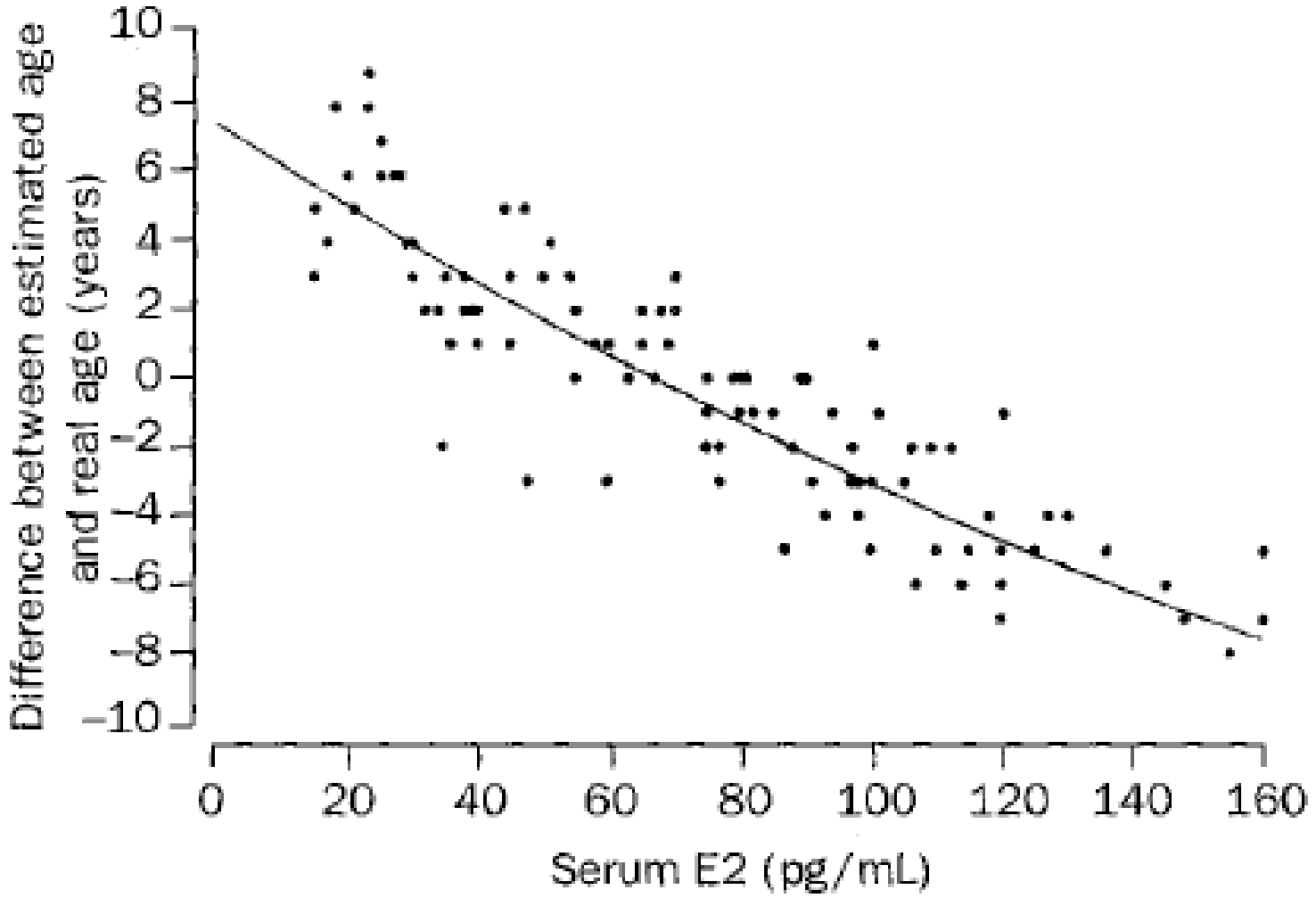
Oestrogen and age estimations of perimenopausal women

Ludwig Wildt, Teresa Sir-Petermann

We estimated the age of perimenopausal women at a first visit and measured the concentrations of oestradiol in serum. The accuracy of estimation of age strongly correlated with oestradiol concentrations: age was overestimated when oestradiol was low and underestimated when oestradiol was high.

The association between oestrogens and sexual attractiveness has been widely discussed in both scientific and popular literature.[1] However, the question how

Lancet. 1999 Jul 17;354(9174):224



Lancet. 1999 Jul 17;354(9174):224

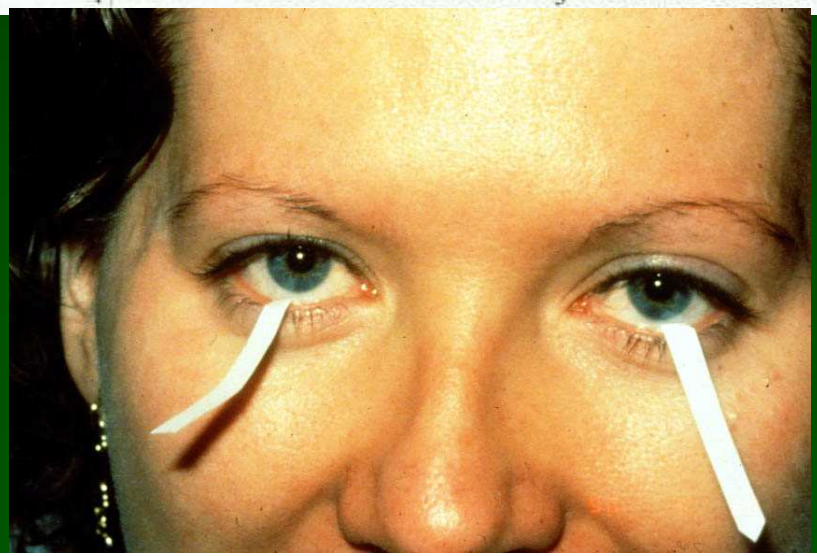
British Journal of Obstetrics and Gynaecology
January 1998, Vol. 105, pp. 100–102

Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol

***Michael O. Sator** *Registrar*, ***Elmar A. Joura** *Consultant/Lecturer*, ***Thomas Golaszewski** *Consultant*,
***Doris Gruber** *Registrar*, ***Peter Frigo** *Consultant*, ***Markus Metka** *Consultant*,
†Anton Hommer *Consultant*, ***Johannes C. Huber** *Professor*

**Department of Obstetrics and Gynaecology, Division of Endocrinology and Sterility Treatment, and* †*Department of Ophthalmology, University of Vienna, Austria*

Objective To investigate the effect of 17β-oestradiol ophthalmic drops in comparison with a traditional tear substitute in postmenopausal women with keratoconjunctivitis sicca.

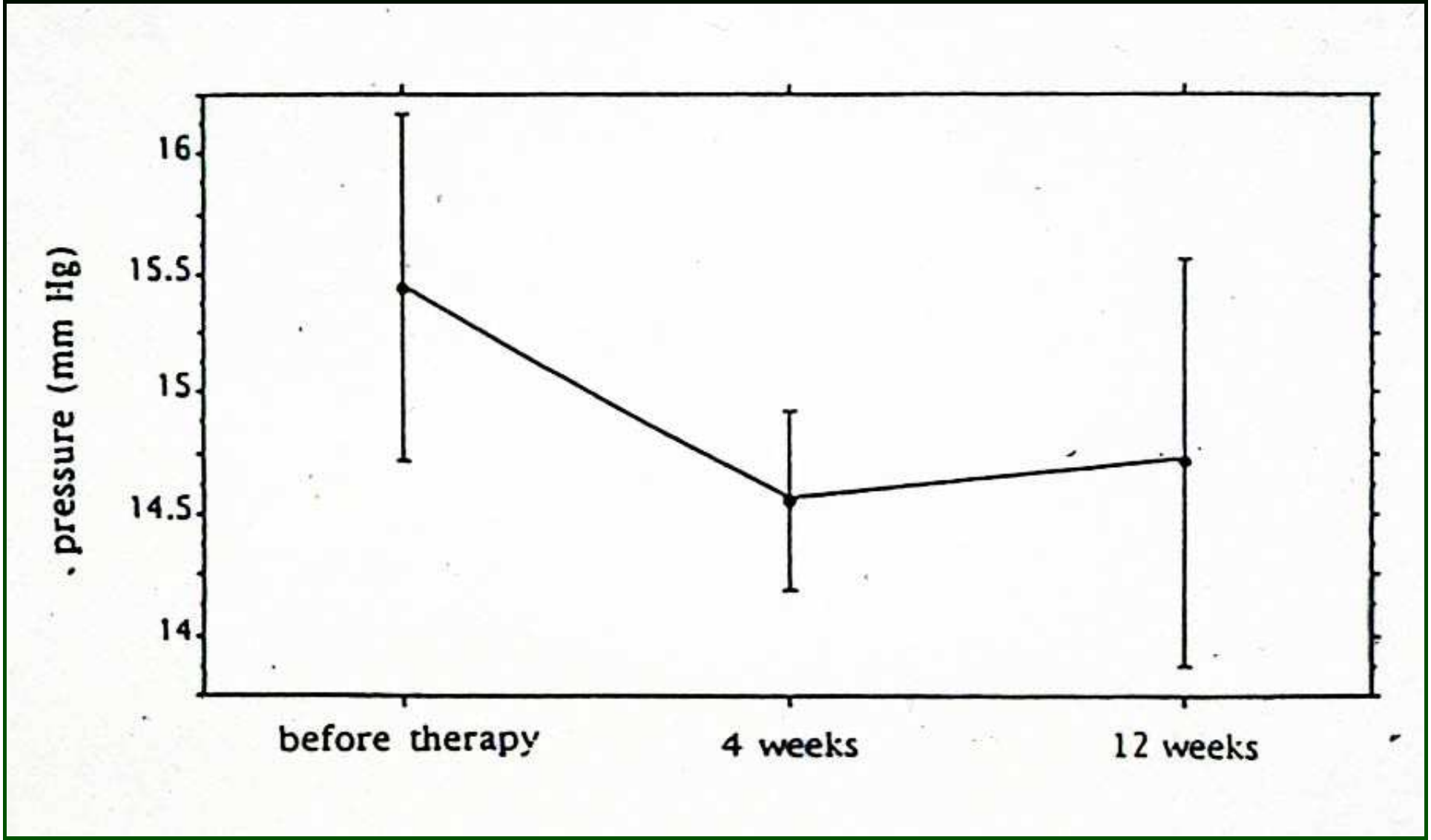


THE LANCET

Hormonal influences on intraocular pressure

Michael O Sator Doris M Gruber Elmar A Joura

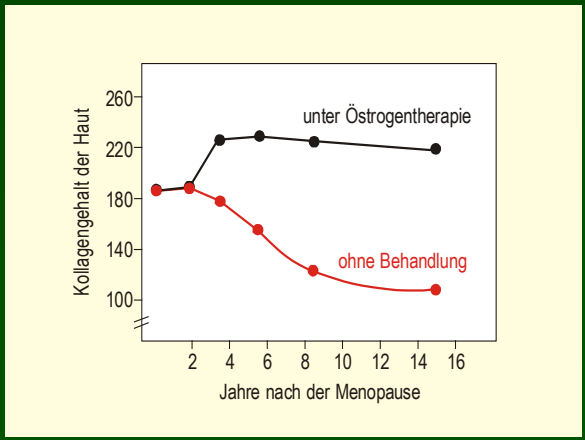
Reprinted from THE LANCET Saturday 14 September 1996
Vol. 348 No. 9029 Pages 761–762


pressure (mm Hg)
16
15.5
15
14.5
14
before therapy
4 weeks
12 weeks

Maturitas. 1987 Apr;9(1):1-5.

Skin collagen changes in post-menopausal women receiving oestradiol gel.

Brincat M, Versi E, O'Dowd T, Moniz CF, Magos A, Kabalan S, Studd JW.



Maturitas. 1994 Nov;20(1):25-30.

Treatment of skin ageing symptoms in perimenopausal females with estrogen compounds. A pilot study.

Schmidt JB, Binder M, Macheiner W, Kainz C, Gitsch G, Bieglmayer C.

CONTINUING MEDICAL EDUCATION

Estrogen and skin: The effects of estrogen, menopause, and hormone replacement therapy on the skin

Glenda Hall, MD, and Tania J. Phillips, MD, FRCPC
Boston, Massachusetts

J Am Acad Dermatol 2005;53:555-68

Table II. Summary of trails reviewing skin thickness in patients receiving hormone replacement therapy

Study group	Study design	Treatment period	No of women	Treatment groups	Outcome	Measurement tools
Brincat et al[53] 1985	Retrospective comparison	2-10 y	N = 52	50 mg estradiol/100 mg testosterone implant*	The skin of patients treated with estrogen was 30% thicker than those who had never taken estrogen	Radiologic assessment at the forearm
				versus		
			N = 66	no treatment		
Maheux et al[60] 1994	Randomized double-blind placebo-controlled	12 mo	N = 30	0.625 mg CEE	Increased skin thickness with 33% increase in dermis	Ultrasonography biopsy at the greater trochanter
				versus		
			N = 30	placebo		
			Total N = 60			
Callens et al[46] 1996	Open-label	Mean 4.8 y	N = 49	17β-estradiol gel or transdermal estradiol†	Increased skin thickness in all locations	Ultrasonography at 5 skin locations
			N = 49	versus		
			Total N = 98	no treatment		

CEE, Conjugated equine estrogen.
*Received 5 mg norethisterone for 7days every month.
†All received some form of progestin.

Table III. Review of studies evaluating skin collagen content in patients receiving hormone replacement therapy

Study group	Study design	Treatment period	No of women	Treatment groups	Outcome	Measurement tools
Brincat et al[55] 1987	Open-label	12 mo	N = 16	1.5 mg estradiol gel to lower abdomen	Increase in collagen at the the thigh[§] and abdomen	Biopsy below the greater trochanter with hydroxyproline extraction and subsequent calculation of collagen content.
				versus		
		6 mo	N = 22	50 mg estradiol implant	Increase in collagen	
				versus		
		6 mo	N = 20	50 mg estradiol implant and 100 mg testosterone implant	No overall increase in collagen	
				versus		
		6 mo	N = 20	100 mg estradiol implant	Increase in collagen[§]	Biopsy of abdomen also taken in the topical group.
			Total N = 78			
Castelo-Branco et al[58] 1992	Random allocation placebo-controlled	12 mo	N = 28	0.625 mg/d CEE in 25-d cycle*	1.8% increase in collagen	Biopsy specimens of the abdomen were processed in accordance with a previously described colorimetric method
				versus		
			N = 28	50 μg transdermal 17β-estradiol in 24-d cycle*	5.1% increase in collagen	
				versus		
			N = 32	0.625 mg/d CEE every day*	3.0% increase in collagen	
				versus		
			N = 30	No treatment	3.2% decline in collagen	
			Total N = 118			

CEE, Conjugated equine estrogens; *EM,* electron microscopy; *LM,* light microscopy; *PICP,* human type I procollagen.

*Also received 2.5 mg/d medroxyprogesterone acetate for the last 12 days of each cycle.

†Also received 1 mg cyproterone acetate for the last 10 days of each cycle.

‡Also received 1 mg norethisterone acetate daily.

§Not statistically significant.

Table III. Review of studies evaluating skin collagen content in patients receiving hormone replacement therapy

Study group	Study design	Treatment period	No of women	Treatment groups	Outcome	Measurement tools
Varila et al[61] 1995	Open-label	3 mo	Total N = 12	2.5 mg topical estradiol 1/2 lower abdomen versus Placebo cream contralaternal abdomen	Localized increase in collagen synthesis and morphologic improvement	LM/EM review of abdominal biopsy specimen; blister fluid analysis (PICP)
Haapasaari et al[63] 1997	Open-label, parallel group	12 mo	N = 15	2 mg/d 17β-estradiol every day‡	No difference among any of the groups in amount of collagen or the rate of collagen synthesis	LM/EM review of abdominal biopsy; blister fluid analysis;
				versus		
			N = 14	2 mg/d estradiol valerate every day		
				versus		
			N = 14 Total N = 43	No treatment		
Sauerbronn et al[59] 2000	Randomized double-blind placebo-controlled	6 mo	N = 21	2 mg estradiol† in 21-d cycle	6.5% increase in collagen	Biopsy of the medical upper arm, computerized image analysis of collagen fibers
				versus		
			N = 20 Total N = 41	Placebo	No change	

CEE, Conjugated equine estrogens; *EM*, electron microscopy; *LM*, light microscopy; *PICP*, human type I procollagen.

*Also received 2.5 mg/d medroxyprogesterone acetate for the last 12 days of each cycle.

†Also received 1 mg cyproterone acetate for the last 10 days of each cycle.

‡Also received 1 mg norethisterone acetate daily.

§Not statistically significant.

Ann Chir Gynaecol Suppl. 1987;202:39-41.

Local oestriol treatment improves the structure of elastic fibers in the skin of postmenopausal women.

Punnonen R, Vaajalahti P, Teisala K.

Br J Obstet Gynaecol. 1995 Dec;102(12):985-9.

The effect of topical oestradiol on skin collagen of postmenopausal women.

Varila E, Rantala I, Oikarinen A, Risteli J, Reunala T, Oksanen H, Punnonen R.

International Journal of Dermatology, Vol. 35, No. 9, September 1996

S. 669-74

PHARMACOLOGY AND THERAPEUTICS

TREATMENT OF SKIN AGING WITH TOPICAL ESTROGENS

JOLANTA B. SCHMIDT, M.D.,

MARTINA BINDER, M.D., GABRIELE DEMSCHIK, M.D.,

CHRISTIAN BIEGLMAYER, PH.D., AND ANGELIKA REINER, M.D.

American Journal of Pathology, Vol. 155, No. 4, October 1999

Topical Estrogen Accelerates Cutaneous Wound Healing in Aged Humans Associated with an Altered Inflammatory Response

Gillian S. Ashcroft,[*†‡] Teresa Greenwell-Wild,[*]
Michael A. Horan,[‡] Sharon M. Wahl,[*] and
Mark W. J. Ferguson[†]

Hormone replacement therapy and prevention of pressure ulcers and venous leg ulcers

David J Margolis, Jill Knauss, Warren Bilker

Pressure ulcers and venous leg ulcers are common chronic wounds. Oestrogens in the form of hormone replacement therapy (HRT) might have an effect on wound healing, but this possibility has not been studied in detail. Using a case-cohort study including elderly patients in the UK General Practice Research Database, we showed that patients who received HRT were less likely to develop a venous leg ulcer (age-adjusted relative risk 0·65 [95% CI 0·61–0·69]) or a pressure ulcer (0·68 [0·62–0·76]) than those who did not use HRT. Therefore, we believe that HRT could be beneficial for the prevention of these wounds.

Lancet 2002; **359:** 675–77

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2001; **10**: 245–251
DOI: 10.1002/pds.582

ORIGINAL REPORT

Is hormone replacement therapy protective for venous ulcer of the lower limbs?

Anick Bérard PhD*[1], Susan R. Kahn MD, MSc[2] and Lucien Abenhaim MD, ScD[2]

Secretory leukocyte protease inhibitor mediates non-redundant functions necessary for normal wound healing

GILLIAN S. ASHCROFT[1], KEJIAN LEI[1], WENWEN JIN[1], GLENN LONGENECKER[2], ASHOK B. KULKARNI[2], TERESA GREENWELL-WILD[1], HOLLIE HALE-DONZE[1], GEORGE MCGRADY[1], XIAO-YU SONG[1] & SHARON M. WAHL[1]

NATURE MEDICINE • VOLUME 6 • NUMBER 10 • OCTOBER 2000 • 1147-53

Estrogen accelerates cutaneous wound healing associated with an increase in TGF-β1 levels

GILLIAN S. ASHCROFT[1,2], JOANNE DODSWORTH[1], EGON VAN BOXTEL[2], ROY W. TARNUZZER[3], MICHAEL A. HORAN[2], GREGORY S. SCHULTZ[3] & MARK W.J. FERGUSON[1]

NATURE MEDICINE • VOLUME 3 • NUMBER 11 • November 1997 • 1209-15

Estrogen modulates cutaneous wound healing by downregulating macrophage migration inhibitory factor

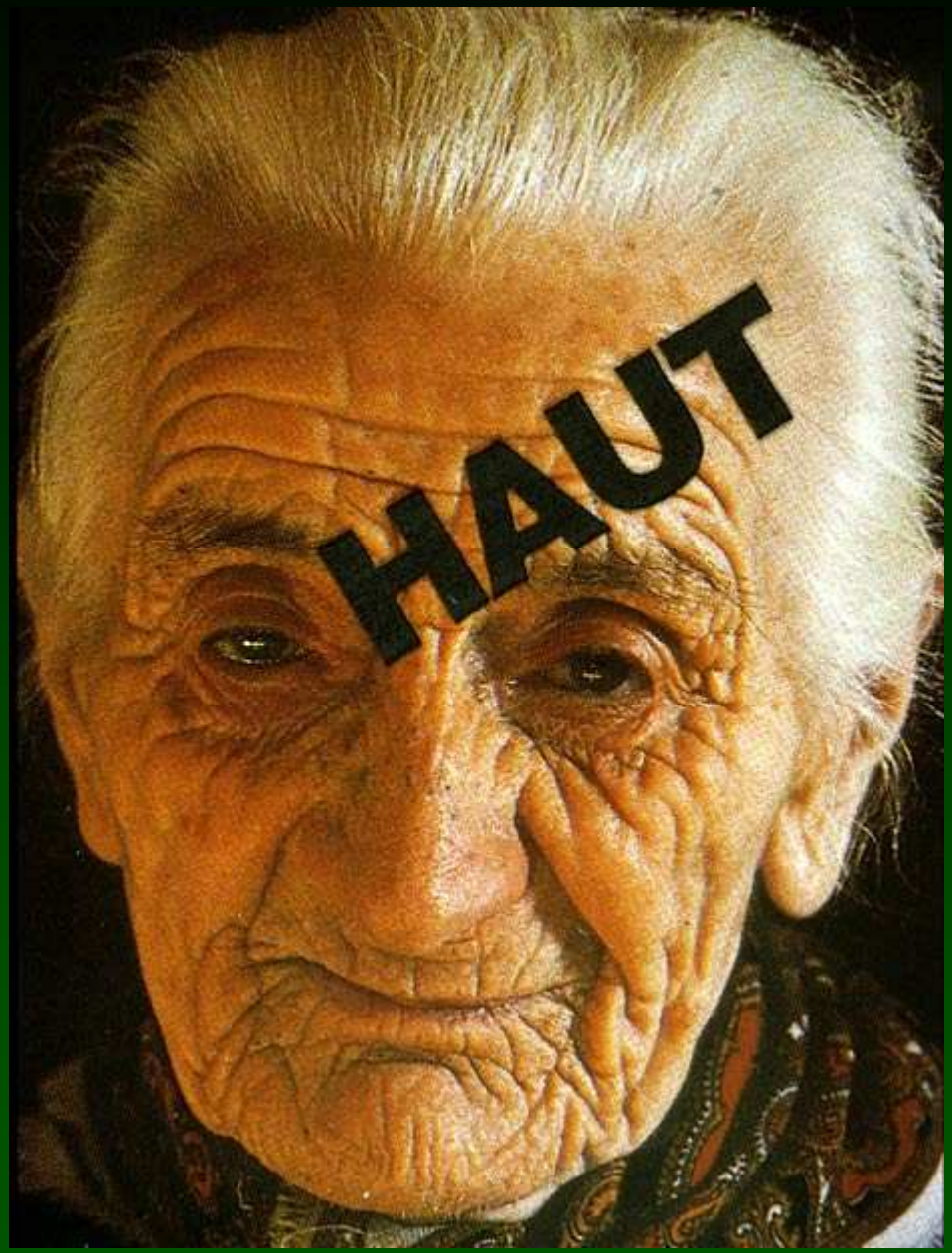
Gillian S. Ashcroft,[1] Stuart J. Mills,[1] KeJian Lei,[2] Linda Gibbons,[1] Moon-Jin Jeong,[2] Marisu Taniguchi,[3] Matthew Burow,[4] Michael A. Horan,[1] Sharon M. Wahl,[2] and Toshinori Nakayama[3]

J. Clin. Invest. **111**:1309–1318 (2003). doi:10.1172/JCI200316288.

Gynecol Endocrinol. 2001 Dec;15 Suppl 6:18-21.

Immunological and dermatological impact of progesterone.

Huber J, Gruber C.


HAUT

THERAPEUTICS

DOI 10.1111/j.1365-2133.2005.06685.x

Effects and side-effects of 2% progesterone cream on the skin of peri- and postmenopausal women: results from a double-blind, vehicle-controlled, randomized study

G. Holzer, E. Riegler, H. Hönigsmann, S. Farokhnia* and B. Schmidt

Division of Special and Environmental Dermatology, Medical University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria
**Pharmacy Department, General Hospital of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria*

Correspondence
Dr Gregor Holzer.
E-mail: gregor.holzer@meduniwien.ac.at

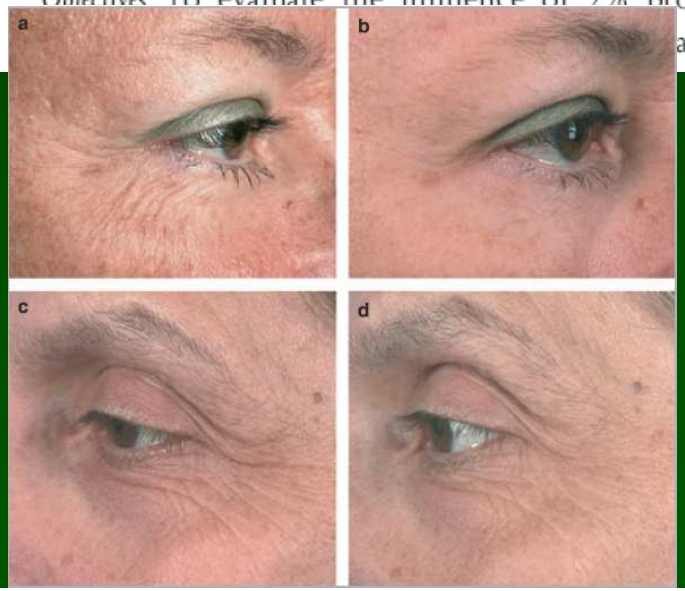
Accepted for publication
12 January 2005

Summary

Background For many years topical progesterone has been prescribed by gynaecologists as an antiageing and skin-firming treatment, without any clinical scientific evidence of its effects, tolerability and safety when applied to skin.

Objectives To evaluate the influence of 2% progesterone cream on function and

al women.



PATHOPHYSIOLOGY OF PREMATURE SKIN AGING INDUCED BY ULTRAVIOLET LIGHT

GARY J. FISHER, PH.D., ZENGQUAN WANG, PH.D., SUBHASH C. DATTA, PH.D., JAMES VARANI, PH.D., SEWON KANG, M.D., AND JOHN J. VOORHEES, M.D.

ABSTRACT

Background Long-term exposure to ultraviolet irradiation from sunlight causes premature skin aging (photoaging), characterized in part by wrinkles, altered pigmentation, and loss of skin tone. Photoaged

ULTRAVIOLET irradiation from the sun has deleterious effects in human skin, including sunburn, immune suppression,[1] cancer, and premature aging (photoaging). Sunburn and immune suppression occur acute-

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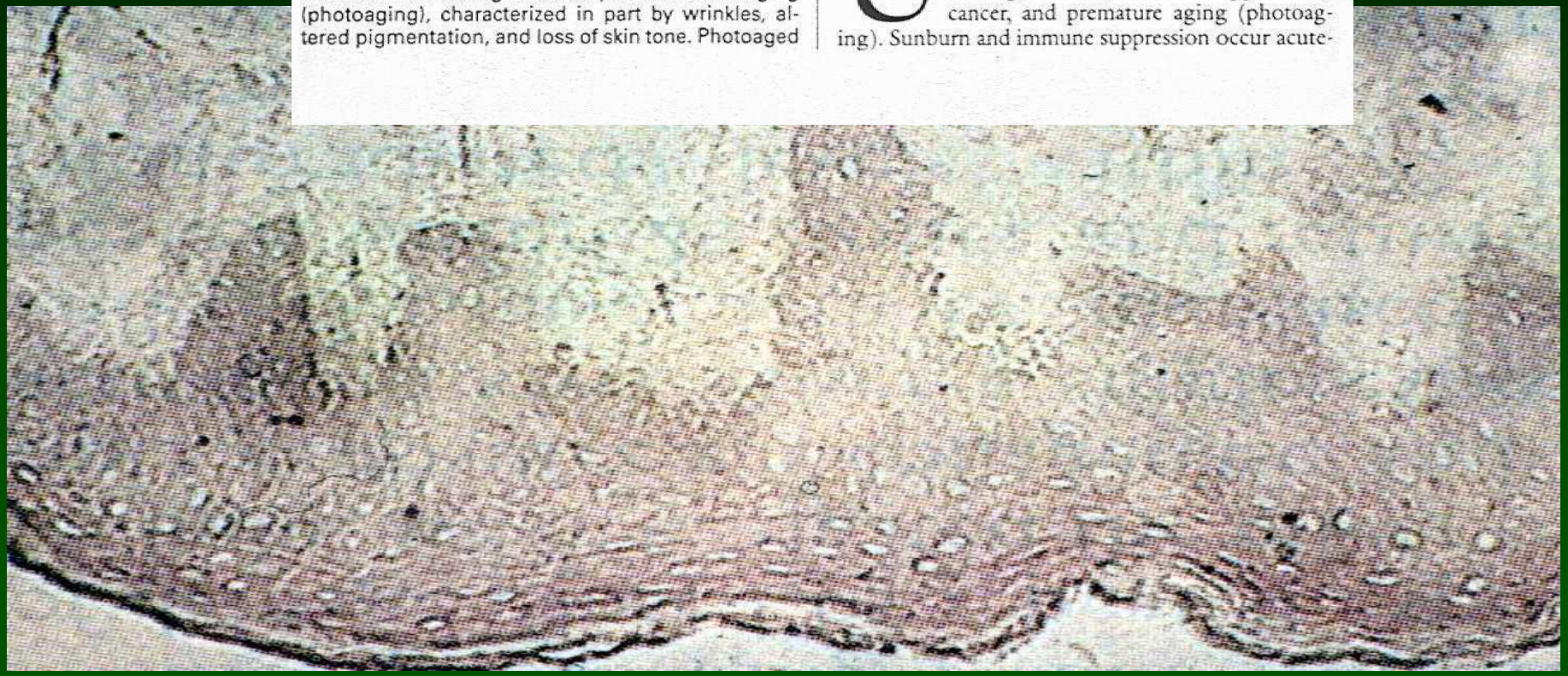

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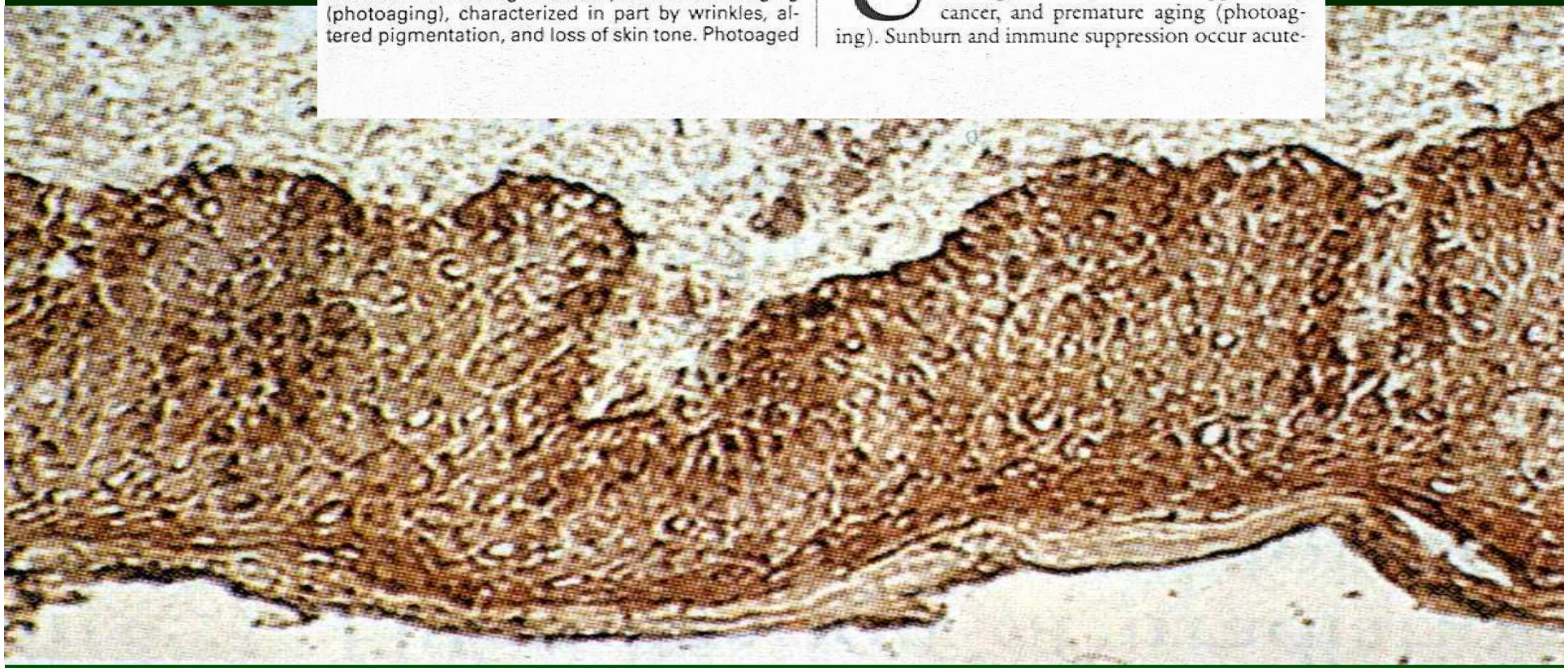
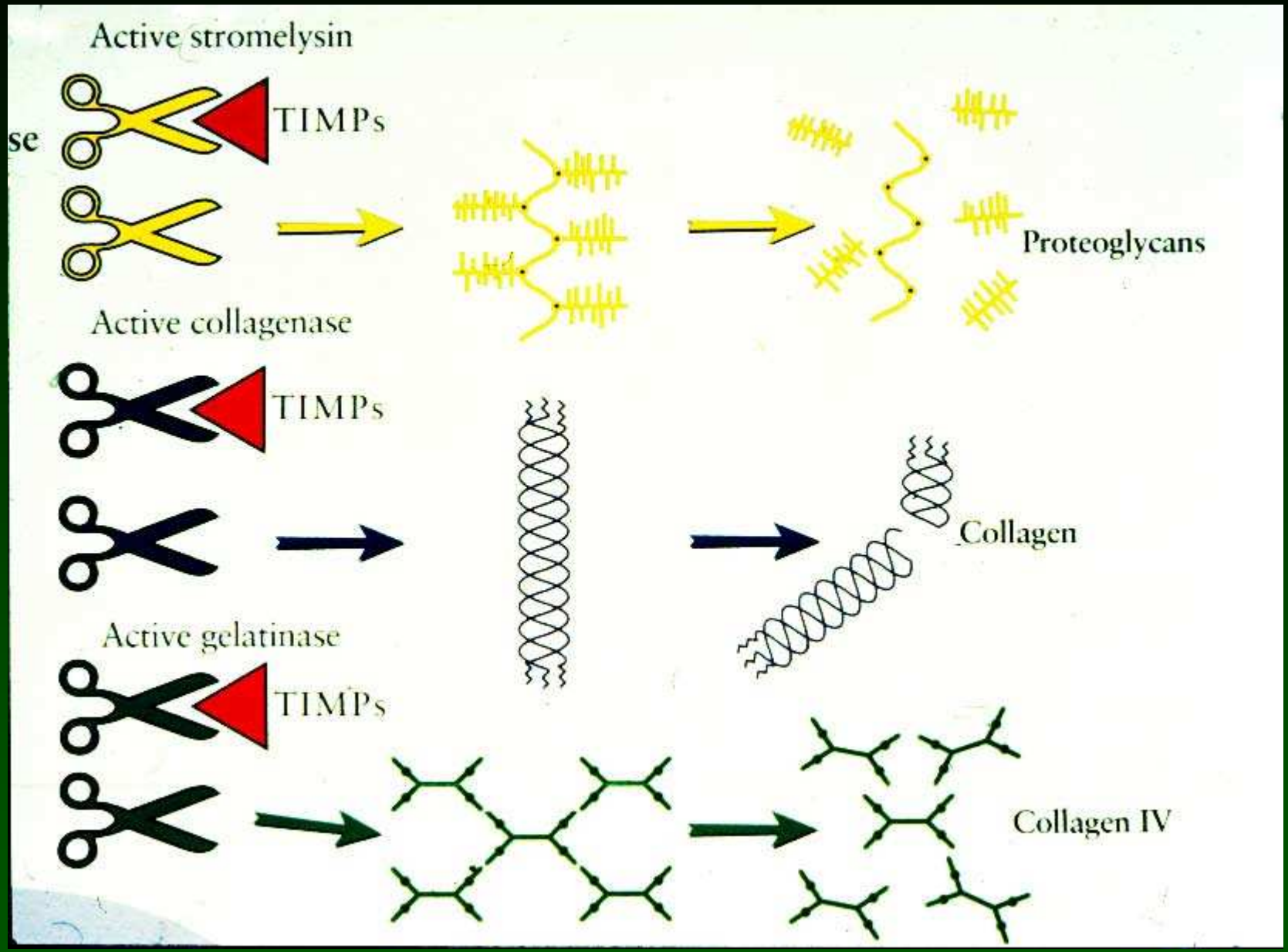


EVIDENCE THAT SMOKING CAUSES SKIN WRINKLING

We reviewed the English language literature published since 1960 and identified five studies that evaluated the association of cigarette smoking and skin wrinkling (table 1). Four of these five studies reported that white cigarette smokers were more wrinkled than nonsmokers (2–5). One study concluded


Active stromelysin
se
TIMPs
Proteoglycans
Active collagenase
TIMPs
Collagen
Active gelatinase
TIMPs
Collagen IV

British Journal of Obstetrics and Gynaecology
September 1997, Vol. 104, pp. 994–998

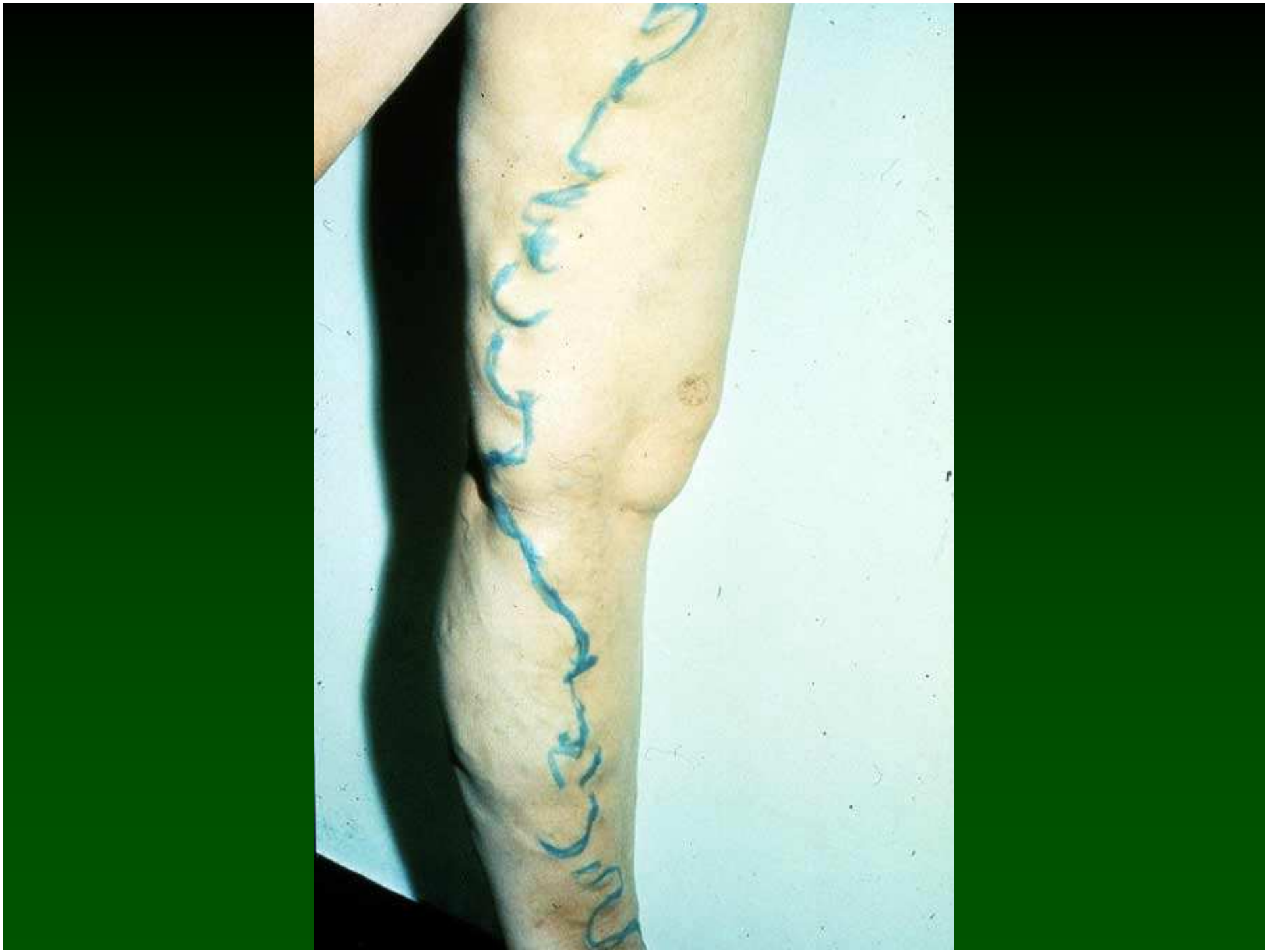
Analysis of collagen status in premenopausal nulliparous women with genuine stress incontinence

***Declan P. Keane** *Research Registrar*, **†Trevor J. Sims** *Chief Laboratory Technician*,
***Paul Abrams** *Consultant (Urology)*, **†Allen J. Bailey** *Professor*

**Bristol Urological Institute, Southmead Hospital, Bristol; †Muscle and Collagen Research Group, University of Bristol, Langford*

Objective To determine if differences exist in the collagen status of premenopausal nulliparous women with genuine stress incontinence compared with continent controls.

Design Thirty-six premenopausal nulliparous women with urodynamically-proven genuine stress incontinence were compared with 25 controls. All the women studied had a periurethral vaginal biopsy taken of approximately 30–50 mg in wet weight. This biopsy was then analysed to determine the collagen content, the type I:III collagen ratio and the collagen cross-link content.



Dermatologic Therapy, Vol. 21, 2008, 118–130
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DERMATOLOGIC THERAPY
ISSN 1396-0296

Esthetic and cosmetic dermatology

UWE WOLLINA*, ALBERTO GOLDMAN†, UWE BERGER‡ &
MOHAMMED BADAWY ABDEL-NASER§

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DERMATOLOGIC THERAPY
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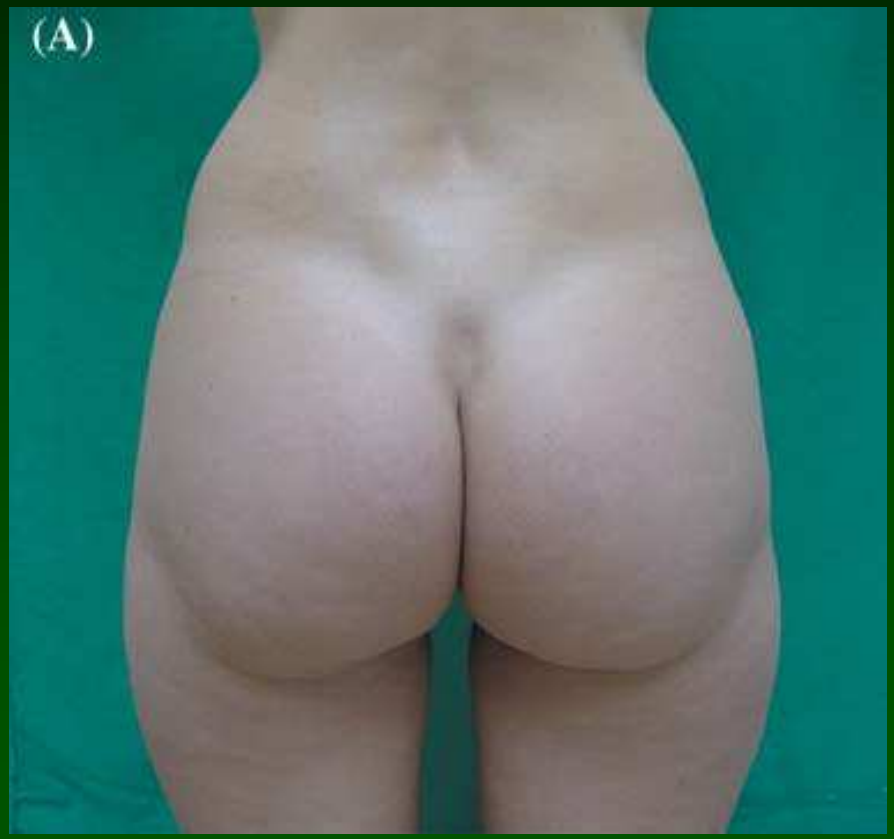
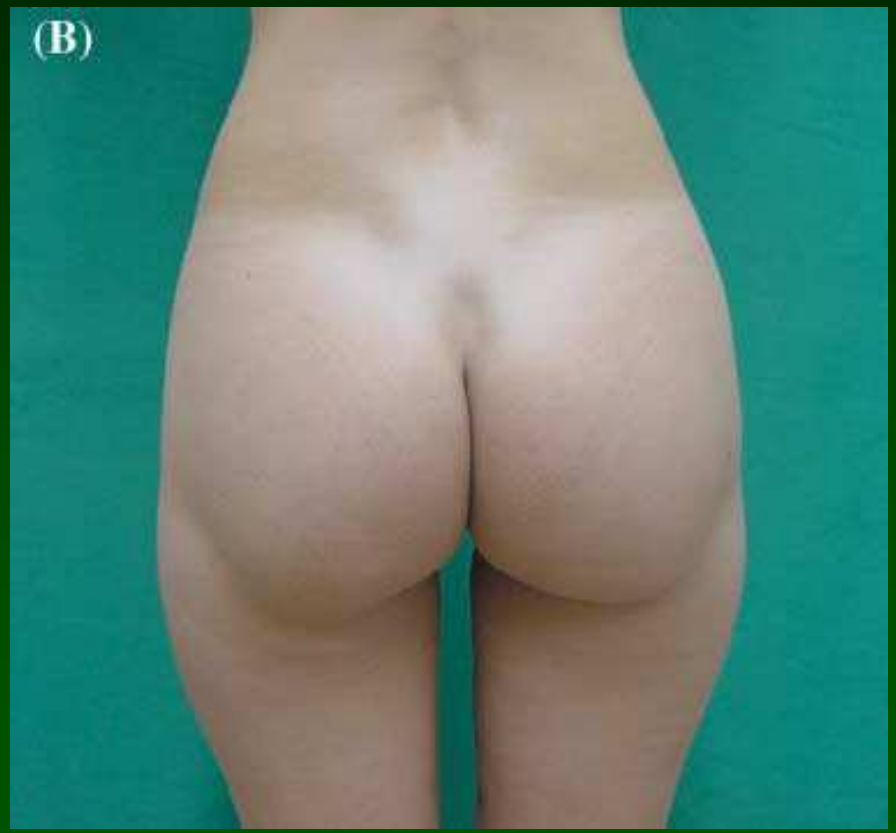




Rp./

Progesteron	**1,00 g**
Propylenglykol	**5,00 g**
Jojobaöl	**5,00 g**
Cremegrundlage	**ad 50,00 g**

D.S. Progesteron Jojoba creame 2%

L´application topique de la progestérone pour le traitement de la peau

PERGAMON

Journal of Steroid Biochemistry & Molecular Biology 80 (2002) 449–455

The Journal of
Steroid Biochemistry
&
Molecular Biology

www.elsevier.com/locate/jsbmb

Distribution and metabolism of topically applied progesterone in a rat model

Brendan J. Waddell [a,*], Peter C. O'Leary [b]

[a] *Department of Anatomy and Human Biology, The University of Western Australia, 35 Stirling Highway, Crawley, Perth, WA 6009, Australia*
[b] *Biochemistry Department, Royal Perth Hospital, Perth, WA, Australia*

Received 24 September 2001; accepted 6 December 2001

DEHYDROEPIANDROSTERONE IN THE TREATMENT OF ERECTILE DYSFUNCTION: A PROSPECTIVE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

WERNER J. REITER, ARMIN PYCHA, GEORG SCHATZL, ALEXEJ POKORNY, DORIS M. GRUBER, JOHANNES C. HUBER, AND MICHAEL MARBERGER

Urol Res. 2001 Aug;29(4):278-81

Modulation of Collagen Metabolism by the Topical Application of Dehydroepiandrosterone to Human Skin

Mi Hee Shin,[1] Gi-eun Rhie,[1] Chi-Hyun Park, Kyu Han Kim, Kwang Hyun Cho, Hee Chul Eun, and Jin Ho Chung

Department of Dermatology, Seoul National University College of Medicine and Laboratory of Cutaneous Aging Research, Clinical Research Institute, Seoul National University Hospital, Seoul, Korea

Dehydroepiandrosterone (DHEA) and its sulfate conjugate (DHEA-S) are the most abundantly produced human adrenal steroids to be reduced with age. DHEA may be related to the process of skin aging through the regulation and degradation of extracelluar matrix protein. In this study, we demonstrate that DHEA can increase procollagen synthesis and inhibit collagen degradation by decreasing matrix metalloproteinases (MMP)-1 synthesis and increasing tisuue inhibitor of matrix metalloprotease (TIMP-1) production in cultured dermal fibroblasts. DHEA was found to inhibit ultraviolet (UV)-induced MMP-1 production and the UV-induced decrease of procollagen synthesis, probably due to the inhibition of UV-induced AP-1 activity. DHEA (5%) in ethanol:olive oil (1:2) was topically applied to buttock skin of volunteers 12 times over 4 weeks, and was found to significantly increase the expression of procollagen α1(I) mRNA and protein in both aged and young skin. On the other hand, topical DHEA significantly decreased the basal expression of MMP-1 mRNA and protein, but increased the expression of TIMP-1 protein in aged skin. We also found that DHEA induced the expressions of transforming growth factor-β1 and connective tissue growth factor mRNA in cultured fibroblasts and aged skin, which may play a role in the DHEA-induced changes of procollagen and MMP-1 expression. Our results suggest the possibility of using DHEA as an anti-skin aging agent.

Key words: collagen/dermal fibroblast/DHEA/human skin/MMP-1/TIMP-1
J Invest Dermatol 124:315–323, 2005

Cell, Vol. 102, 451–461, August 18, 2000, Copyright ©2000 by Cell Press

Involvement of Follicular Stem Cells in Forming Not Only the Follicle but Also the Epidermis

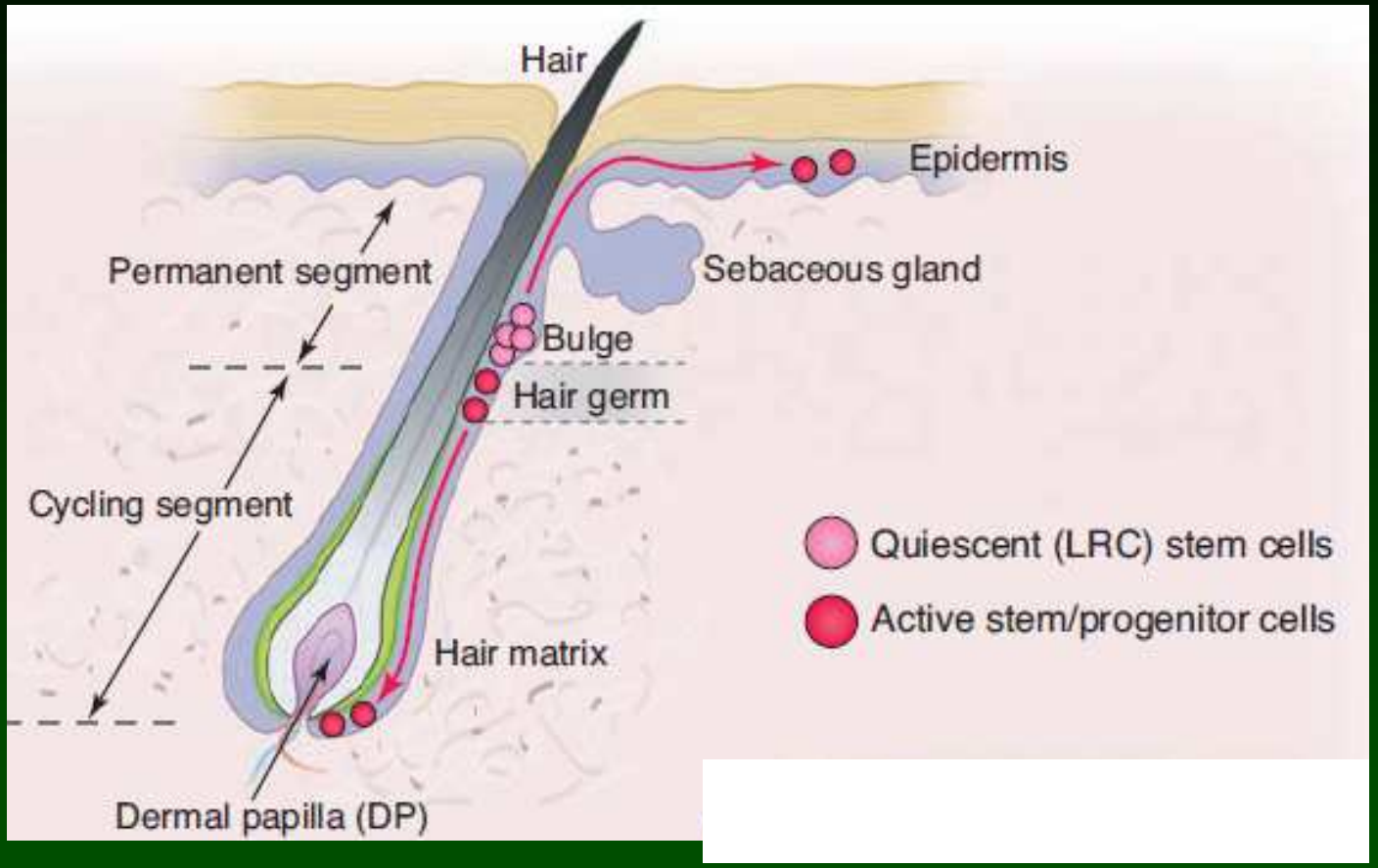
Gina Taylor,* Michael S. Lehrer,*
Pamela J. Jensen,* Tung-Tien Sun,†‡
and Robert M. Lavker*‡

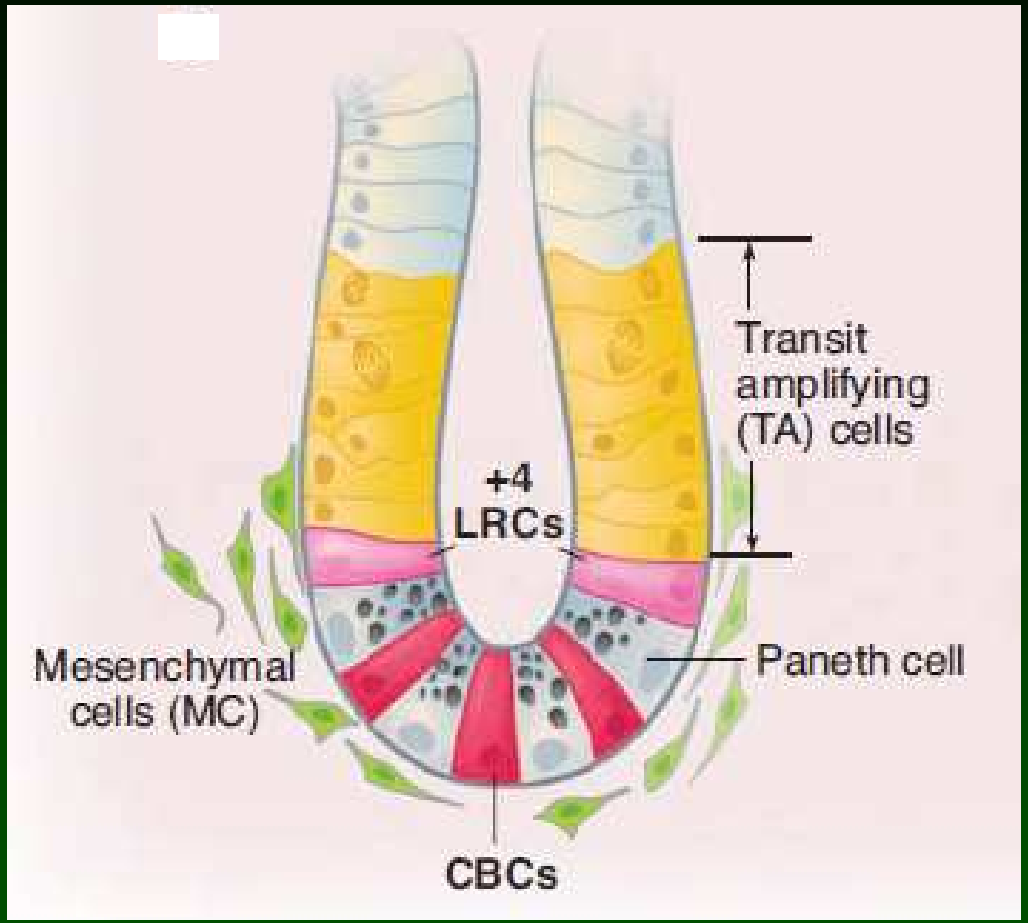
(LRCs) (Bickenbach, 1981; Cotsarelis et al., 1989, 1990; Morris and Potten, 1994, 1999; Wei et al., 1995; Bickenbach and Chism, 1998; Lehrer et al., 1998). In this approach, one labels all the cells in the epithelium by a

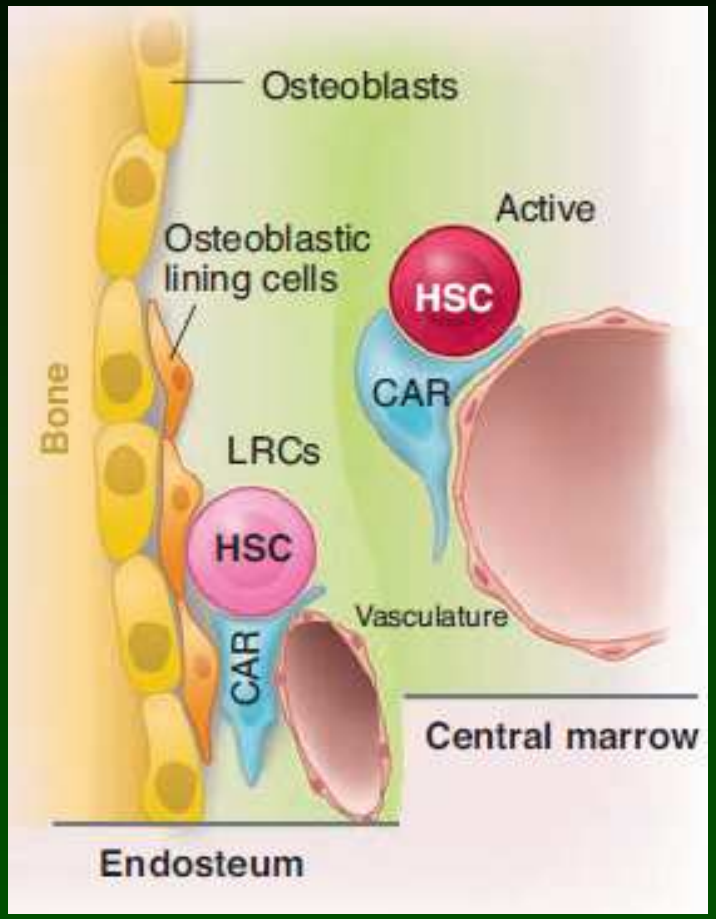
Coexistence of Quiescent and Active Adult Stem Cells in Mammals

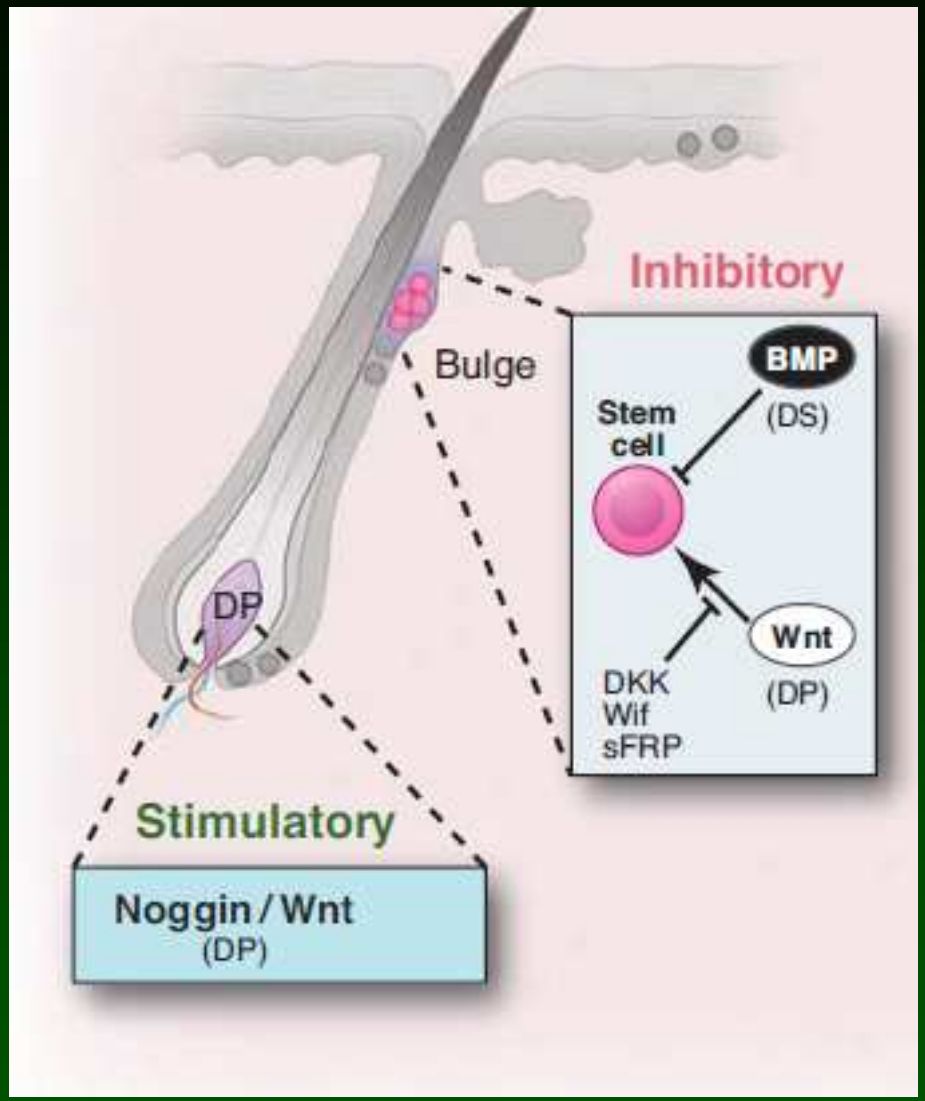
Linheng Li[1] and Hans Clevers[2]

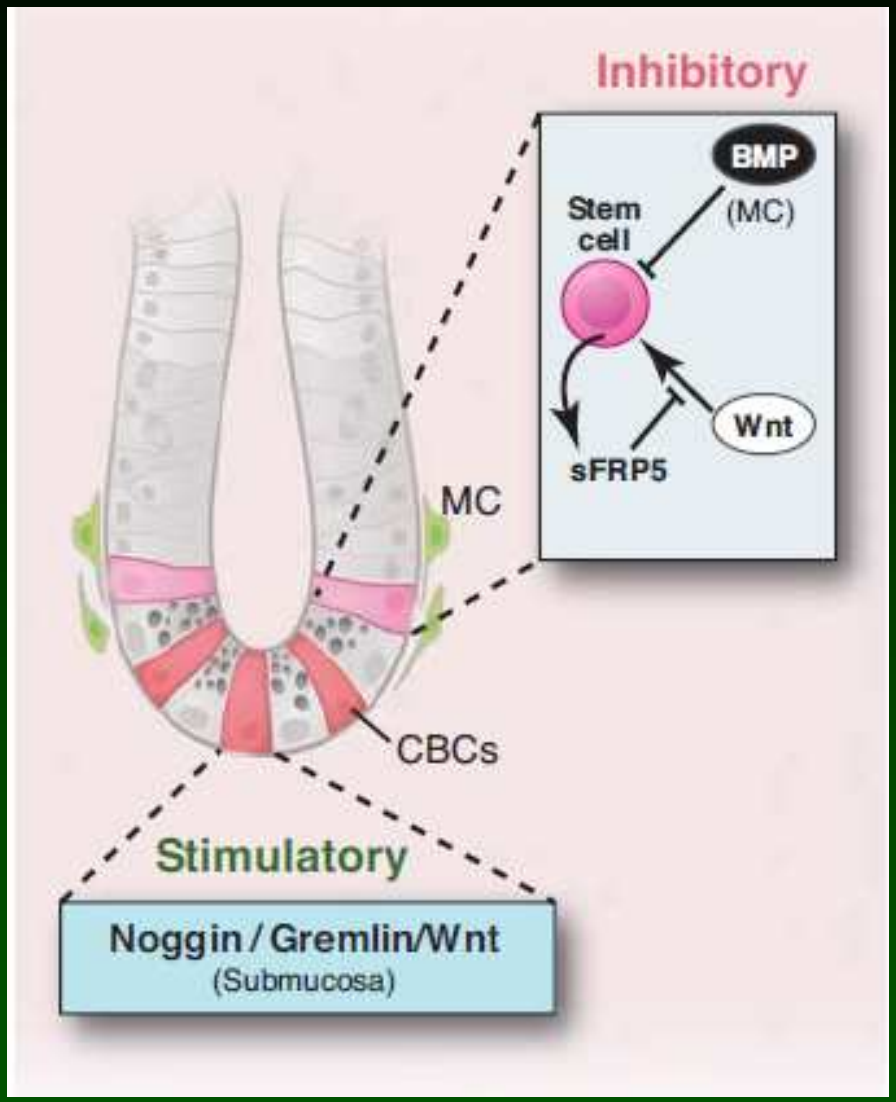
29 JANUARY 2010 VOL 327 SCIENCE www.sciencemag.org

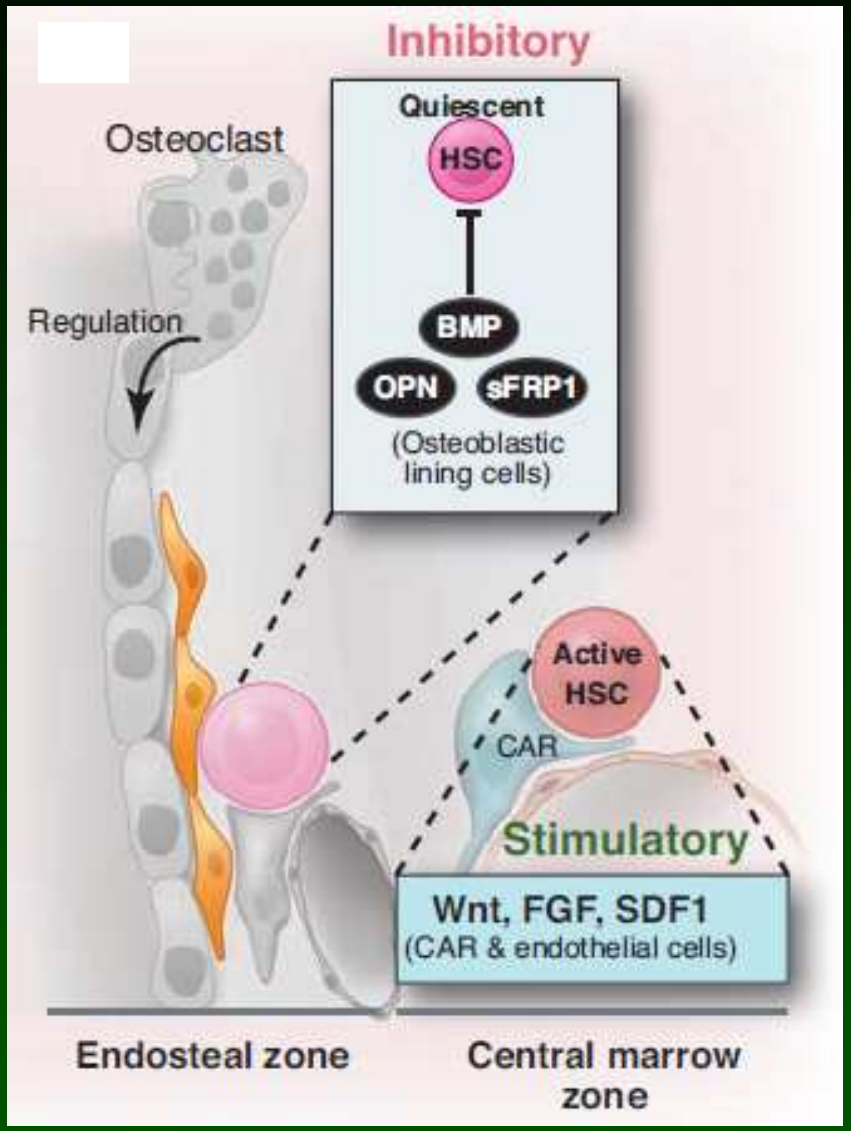

Hair
Epidermis
Permanent segment
Sebaceous gland
Bulge
Hair germ
Cycling segment
Quiescent (LRC) stem cells
Active stem/progenitor cells
Hair matrix
Dermal papilla (DP)

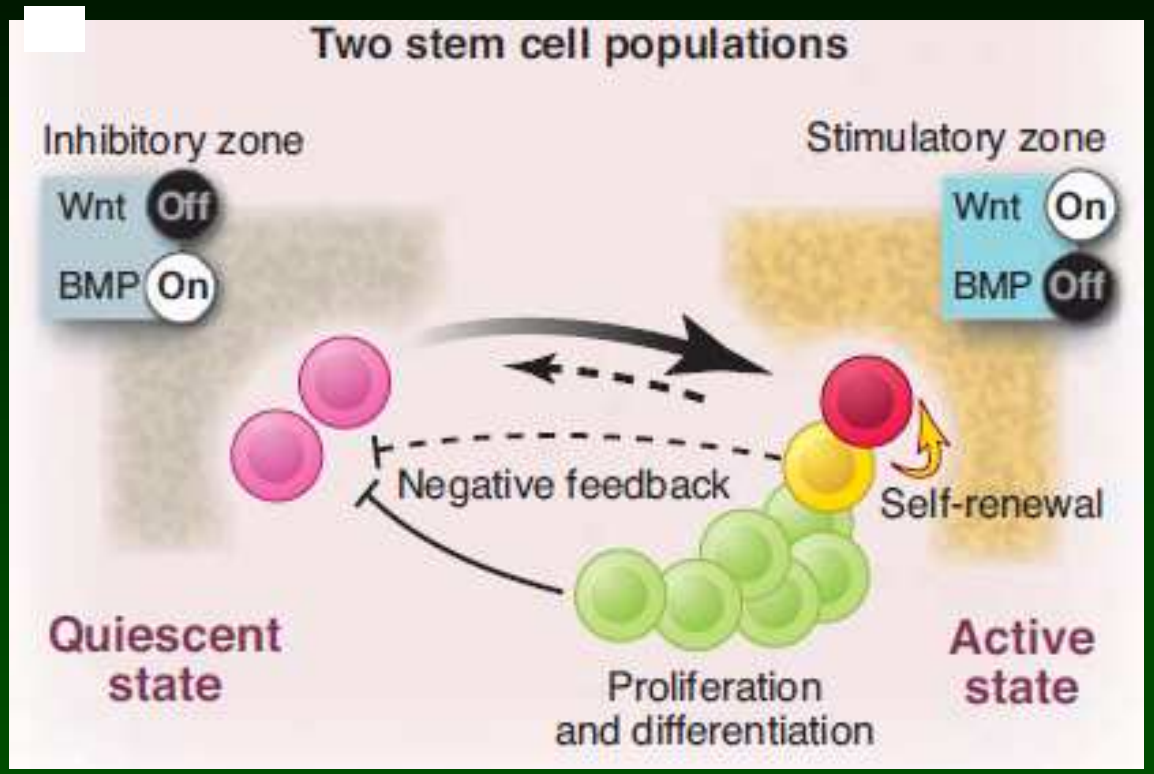

Transit
amplifying
(TA) cells
+4
LRCs
Mesenchymal
cells (MC)
Paneth cell
CBCs


Osteoblasts
Active
Osteoblastic lining cells
HSC
CAR
Bone
LRCs
HSC
Vasculature
CAR
Central marrow
Endosteum


Inhibitory
Bulge
BMP
Stem cell
(DS)
DP
Wnt
(DP)
DKK
Wif
sFRP
Stimulatory
Noggin / Wnt
(DP)


Inhibitory
BMP
Stem cell
(MC)
Wnt
sFRP5
MC
CBCs
Stimulatory
Noggin / Gremlin/Wnt
(Submucosa)


Inhibitory
Quiescent
HSC
Osteoclast
Regulation
BMP
OPN
sFRP1
(Osteoblastic lining cells)
Active HSC
CAR
Stimulatory
Wnt, FGF, SDF1
(CAR & endothelial cells)
Endosteal zone
Central marrow zone


Two stem cell populations
Inhibitory zone
Wnt Off
BMP On
Stimulatory zone
Wnt On
BMP Off
Negative feedback
Self-renewal
Quiescent state
Proliferation and differentiation
Active state

Sex hormones, acting on the *TERT* gene, increase telomerase activity in human primary hematopoietic cells

Rodrigo T. Calado,[1] William T. Yewdell,[1] Keisha L. Wilkerson,[1] Joshua A. Regal,[1] Sachiko Kajigaya,[1] Constantine A. Stratakis,[2] and Neal S. Young[1]

[1]Hematology Branch, National Heart, Lung, and Blood Institute, and [2]Section on Endocrinology and Genetics, Program on Developmental Endocrinology and Genetics, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

Androgens have been used in the treatment of bone marrow failure syndromes without a clear understanding of their mechanism of action. Blood counts of patients with dyskeratosis congenita or aplastic anemia with mutations in telomerase genes can improve with androgen therapy. Here we observed that exposure in vitro of normal peripheral blood lymphocytes and human bone marrow–derived CD34+ cells to androgens increased telomerase activity, coincident with higher *TERT* mRNA levels. Cells from patients who were heterozygous for telomerase mutations had low baseline telomerase activity, which was restored to normal levels by exposure to androgens. Estradiol had an effect similar to androgens on *TERT* gene expression and telomerase enzymatic activity. Tamoxifen abolished the effects of both estradiol and androgens on telomerase function, and letrozole, an aromatase inhibitor, blocked androgen effects on telomerase activity. Conversely, flutamide, an androgen receptor antagonist, did not affect androgen stimulation of telomerase. Down-regulation by siRNA of estrogen receptor-α (ERα), but not ERβ, inhibited estrogen-stimulated telomerase function. Our results provide a mechanism for androgen therapy in bone marrow failure: androgens appear to regulate telomerase expression and activity mainly by aromatization and through ERα. These findings have potential implications for the choice of current androgenic compounds and the development of future agents for clinical use. (Blood. 2009;114: 2236-2243)

VOLUME 23 · NUMBER 13 · MAY 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Neoadjuvant Percutaneous 4-Hydroxytamoxifen Decreases Breast Tumoral Cell Proliferation: A Prospective Controlled Randomized Study Comparing Three Doses of 4-Hydroxytamoxifen Gel to Oral Tamoxifen

Philippe Rouanet, Gustavo Linares-Cruz, François Dravet, Sylvain Poujol, Sophie Gourgou, Joelle Simony-Lafontaine, Jean Grenier, Andrew Kramar, Jean Girault, Elisabeth Le Nestour, and Thierry Maudelonde

Table 3. Percentage of Patients Exhibiting a Decrease in Ki-67/MIB1 Index or in PCNA Index According to the Treatment

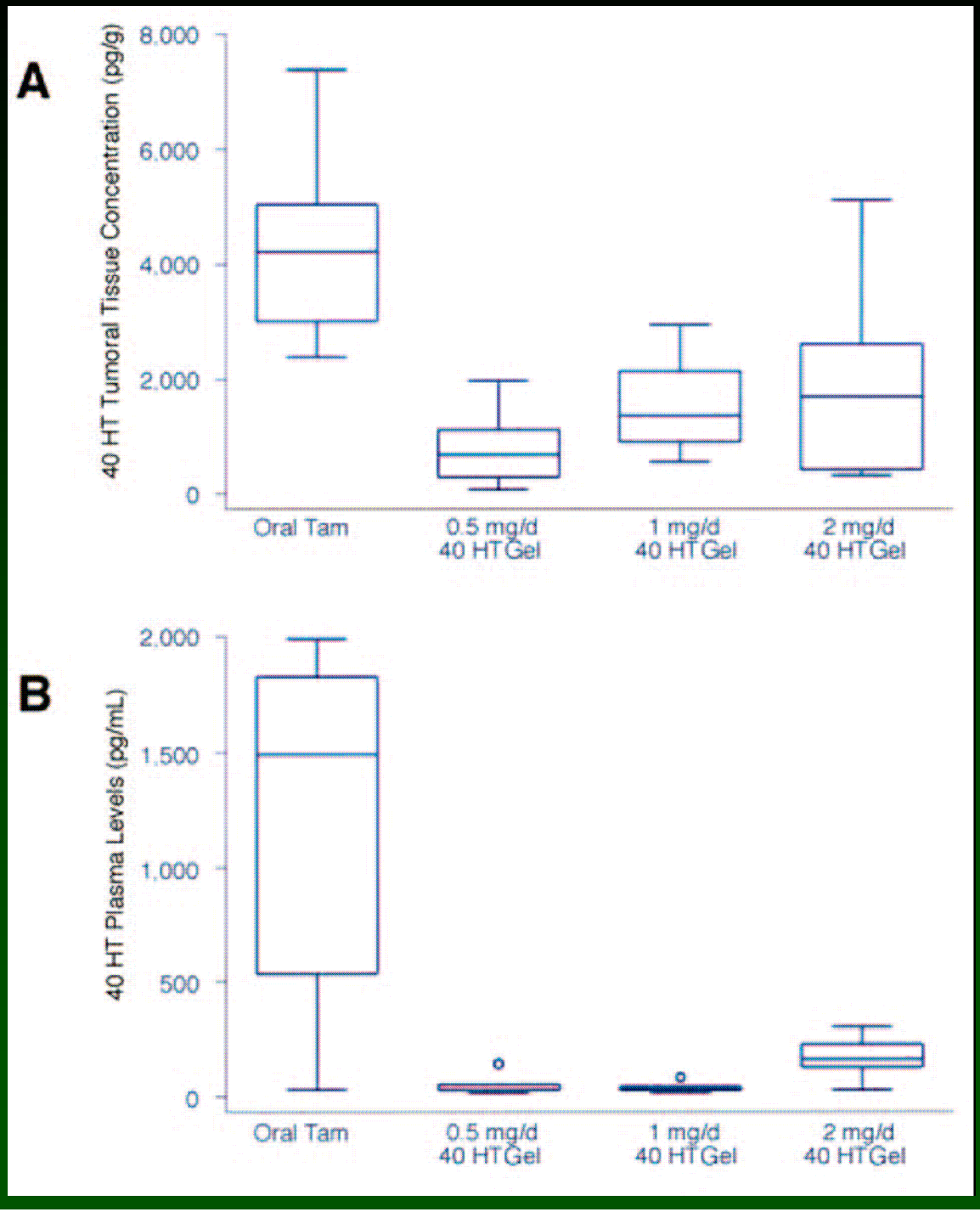
	%				
	Control (n = 11)	Oral Tamoxifen (20 mg/d) (n = 11)	4-OHT Gel (0.5 mg/d) (n = 8)	4-OHT Gel (1 mg/d) (n = 9)	4-OHT Gel (2 mg/d) (n = 10)
Ki-67/MIB1 index					
≥ 1.0 unit decrease	40	90	50	89	87
≥ 2.0 unit decrease	20	70	25	78	62
≥ 3.0 unit decrease	0	60	25	56	62
PCNA index					
≥ 1.0 unit decrease	0	73	75	87	78
≥ 2.0 unit decrease	0	73	50	87	78
≥ 3.0 unit decrease	0	45	37	75	67

Abbreviations: 4-OHT, 4-hydroxytamoxifen; PCNA, proliferating cell nuclear antigen.

Table 4. 4-OHT Concentration in Tumor, Normal Breast Tissue, and Plasma

4-OHT	Control (n = 11)	Oral Tamoxifen (20 mg/d) (n = 11)	4-OHT Gel (0.5 mg/d) (n = 8)	4-OHT Gel (1.0 mg/d) (n = 9)	4-OHT Gel (2.0 mg/d) (n = 10)	*P**	*P*†	*P*‡
Tumor, pg/g	—							
Median		4,237	687	1,377	1,698	—	.0003	.13
Range		2,388-7,386	83-1,978	556-2,955	327-5,123			
Nontumor tissue, pg/g	—							
Median		2,038	528	278	762	—	.0024	.36
Range		1,058-4,461	83-3,126	73-777	141-2,080			
Plasma, pg/mL	—							
Median		1,495	31	35	164	—	.0015	.035
Range		32-1,995	18-144	20-84	31-306			

Abbreviation: 4-OHT, 4-hydroxytamoxifen.
*Kruskal-Wallis test among the five groups.
†Kruskal-Wallis test among the four groups with oral tamoxifen.
‡Kruskal-Wallis test among the three groups with 4-OHT gel.


A
40 HT Tumoral Tissue Concentration (pg/g)
8.000
6.000
4.000
2.000
0
Oral Tam
0.5 mg/d 40 HT Gel
1 mg/d 40 HT Gel
2 mg/d 40 HT Gel
B
40 HT Plasma Levels (pg/mL)
2,000
1,500
1,000
500
0
Oral Tam
0.5 mg/d 40 HT Gel
1 mg/d 40 HT Gel
2 mg/d 40 HT Gel

Cancer Chemother Pharmacol (1995) 36: 493–498

ORIGINAL ARTICLE

Henri Pujol · Jacques Girault · Philippe Rouanet
Sabine Fournier · Jean Grenier · Joëlle Simony
Jean-Bernard Fourtillan · Jean-Louis Pujol

Phase I Study of percutaneous 4-hydroxy-tamoxifen with analyses of 4-hydroxy-tamoxifen concentrations in breast cancer and normal breast tissue

HUMAN GENE THERAPY 13:1075–1080 (June 10, 2002)

The Epidermis as a Bioreactor: Topically Regulated Cutaneous Delivery into the Circulation

TONGYU CAO,[1,2] SOPHIA Y. TSAI,[1] BERT W. O'MALLEY,[1] XIAO-JING WANG,[1,3] and DENNIS R. ROOP[1,3]

International Research Conference on Food, Nutrition, and Cancer

Isoflavone Genistein: Photoprotection and Clinical Implications in Dermatology[1,2]

Huachen Wei,*†**[3] Rao Saladi,*‡ Yuhun Lu,* Yan Wang,* Sapna R. Palep,* Julian Moore,* Robert Phelps,*‡ Eileen Shyong,* and Mark G. Lebwohl*

*Departments of *Dermatology, †Community Medicine, **Herald Ruttenberg Cancer Center, and ‡Pathology, Mount Sinai School of Medicine, New York, NY 10029*

Experimental Dermatology 2003: 12: 181–190
Blackwell Munksgaard . Printed in Denmark

EXPERIMENTAL DERMATOLOGY
ISSN 0906-6705

Oestrogen receptor beta is the predominant oestrogen receptor in human scalp skin

Thornton MJ, Taylor AH, Mulligan K, Al-Azzawi F, Lyon CC, O'Driscoll J, Messenger AG. Oestrogen receptor beta is the predominant oestrogen receptor in human scalp skin.
Exp Dermatol 2003: 12: 181–190. © Blackwell Munksgaard, 2003

M. J. Thornton[1], A. H. Taylor[2], K. Mulligan[2], F. Al-Azzawi[2], C. C. Lyon[3], J. O'Driscoll[3] and A. G. Messenger[4]

CLINICAL AND LABORATORY INVESTIGATIONS

BJD British Journal of Dermatology

Gene-wide association study between the aromatase gene (*CYP19A1*) and female pattern hair loss

L. Yip,*† S. Zaloumis,† D. Irwin,‡ G. Severi,§ J. Hopper,¶ G. Giles,§ S. Harrap,† R. Sinclair* and J. Ellis†**

Experimental Dermatology 2003: 12: 30–36
Blackwell Munksgaard . Printed in Denmark

EXPERIMENTAL DERMATOLOGY
ISSN 0906-6705

Dietary soy oil content and soy-derived phytoestrogen genistein increase resistance to alopecia areata onset in C3H/HeJ mice

McElwee KJ, Niiyama S, Freyschmidt-Paul P, Wenzel E, Kissling S, Sundberg JP, Hoffmann R. Dietary soy oil content and soy-derived phytoestrogen genistein increase resistance to alopecia areata onset in C3H/HeJ mice.
Exp Dermatol 2003: 12: 30–36. © Blackwell Munksgaard, 2003

K. J. McElwee[1], S. Niiyama[1]*, P. Freyschmidt-Paul[1], E. Wenzel[1], S. Kissling[1], J. P. Sundberg[2] and R. Hoffmann[1]

ORIGINAL ARTICLE
See related Commentary on page iv and v

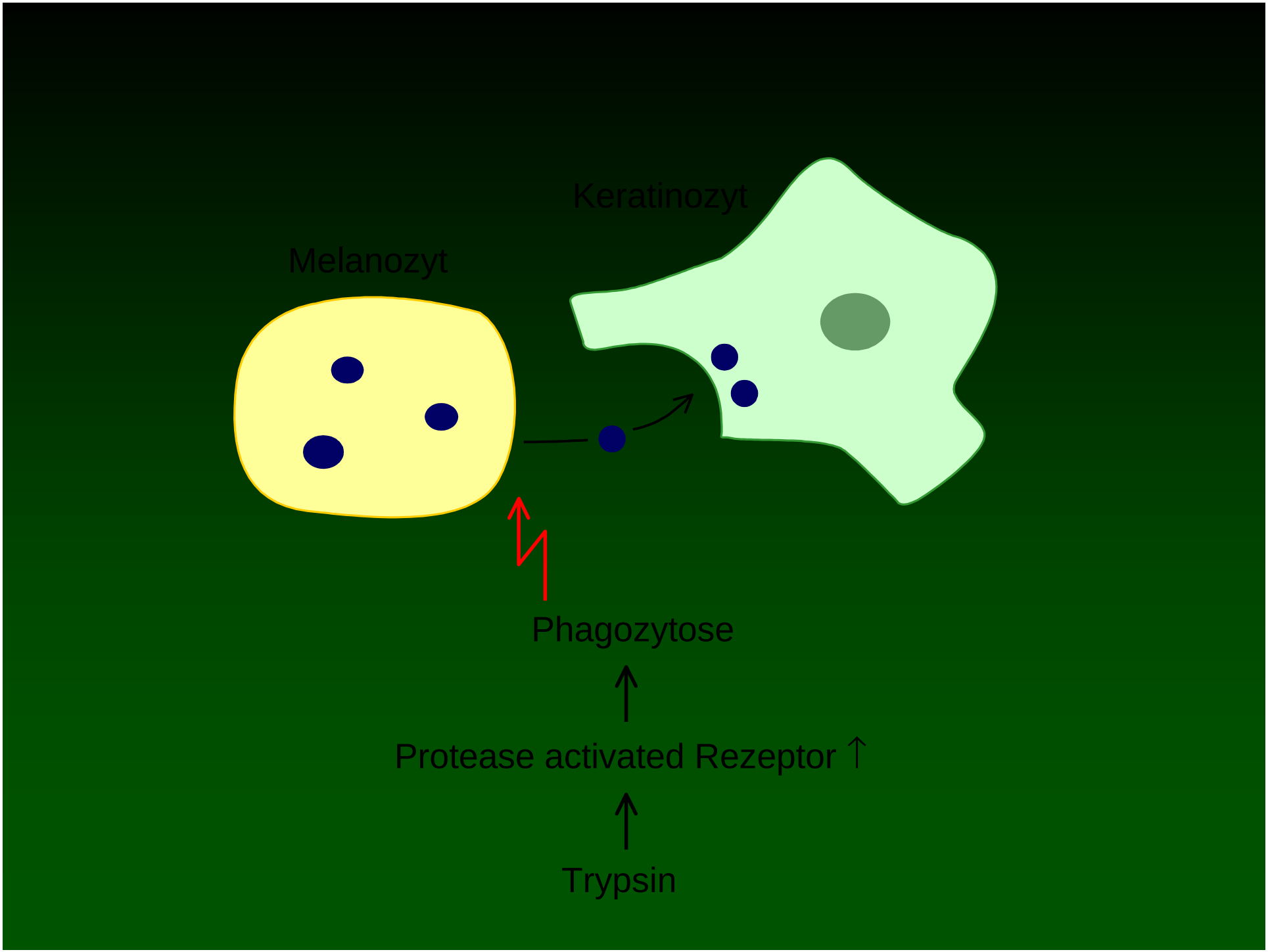
Topical N-Acetyl Cysteine and Genistein Prevent Ultraviolet-Light-Induced Signaling That Leads to Photoaging in Human Skin *in vivo*

Sewon Kang, Jin Ho Chung,[1] Joo Heung Lee,[2] Gary J. Fisher, Yian Sheng Wan, Elizabeth A. Duell, and John J. Voorhees

J Invest Dermatol 120:835-841, 2003

Inhibition of the PAR-2 pathway by soymilk leads to skin depigmentation, suggesting that soymilk could be used as a natural alternative to skin lightening.

Paine C et al. J Invest Dermatol. 2001 Apr;116(4):587-95.


Keratinozyt
Melanozyt
Phagozytose
Protease activated Rezeptor ↑
Trypsin

Mechanisms of Hair Graying: Incomplete Melanocyte Stem Cell Maintenance in the Niche

Emi K. Nishimura,[1*†] Scott R. Granter,[2] David E. Fisher[1*]

Hair graying is the most obvious sign of aging in humans, yet its mechanism is largely unknown. Here, we used melanocyte-tagged transgenic mice and aging human hair follicles to demonstrate that hair graying is caused by defective self-maintenance of melanocyte stem cells. This process is accelerated dramatically with *Bcl2* deficiency, which causes selective apoptosis of melanocyte stem cells, but not of differentiated melanocytes, within the niche at their entry into the dormant state. Furthermore, physiologic aging of melanocyte stem cells was associated with ectopic pigmentation or differentiation within the niche, a process accelerated by mutation of the melanocyte master transcriptional regulator *Mitf*.

Thyroid Hormones Directly Alter Human Hair Follicle Functions: Anagen Prolongation and Stimulation of Both Hair Matrix Keratinocyte Proliferation and Hair Pigmentation

Nina van Beek,* Enikő Bodó,* Arno Kromminga, Erzsébet Gáspár, Katja Meyer, Michal A. Zmijewski, Andrzej Slominski, Björn E. Wenzel, and Ralf Paus

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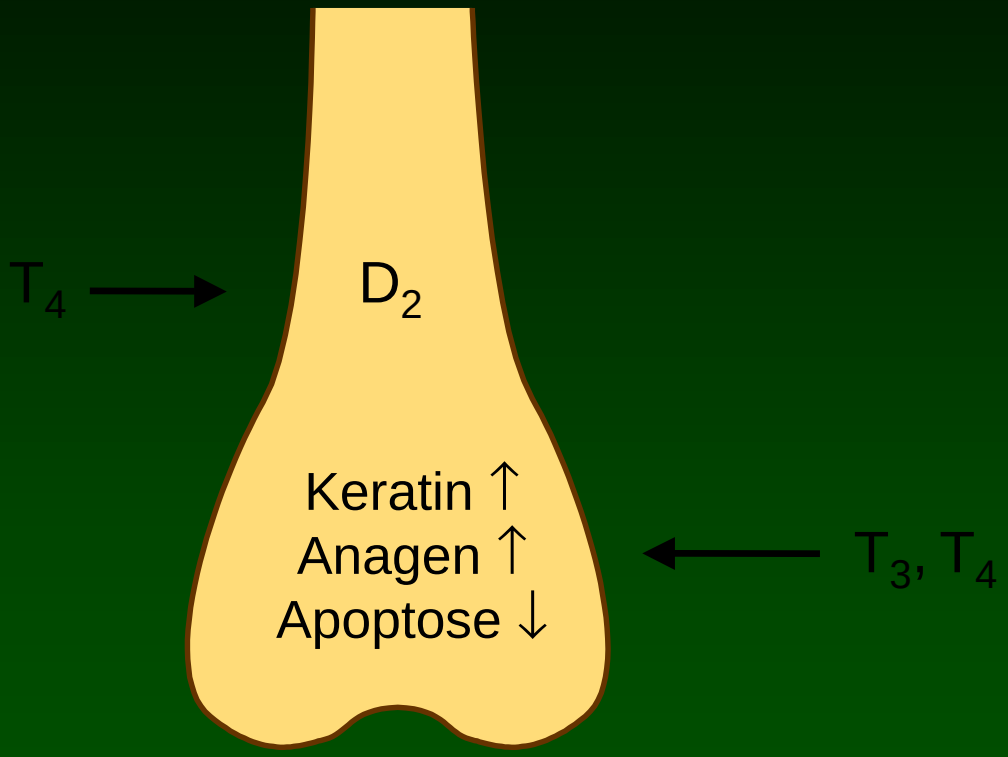
J Clin Endocrinol Metab. 2008 Nov;93(11):4381-8. Epub 2008 Aug 26.



van Beek N et al. J Clin Endocrinol Metab. 2008 Nov;93(11):4381-8. Epub 2008 Aug 26.

Hypothyroidism causes disturbances of skin quality and hair character and growth with an increased telogen rate and diffuse alopecia Replacement reestablishes the normal anagen/telogen ratio. L-Triiodothyronine was shown to stimulate proliferation of outer root sheath keratinocytes and dermal papilla cells

Actas Dermosifiliogr. 2007;98:603-10

ORIGINAL ARTICLES

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Maksim V. Plikus[1], Julie Ann Mayer[1], Damon de la Cruz[1], Ruth E. Baker[2], Philip K. Maini[2,3], Robert Maxson[4] & Cheng-Ming Chuong[1]

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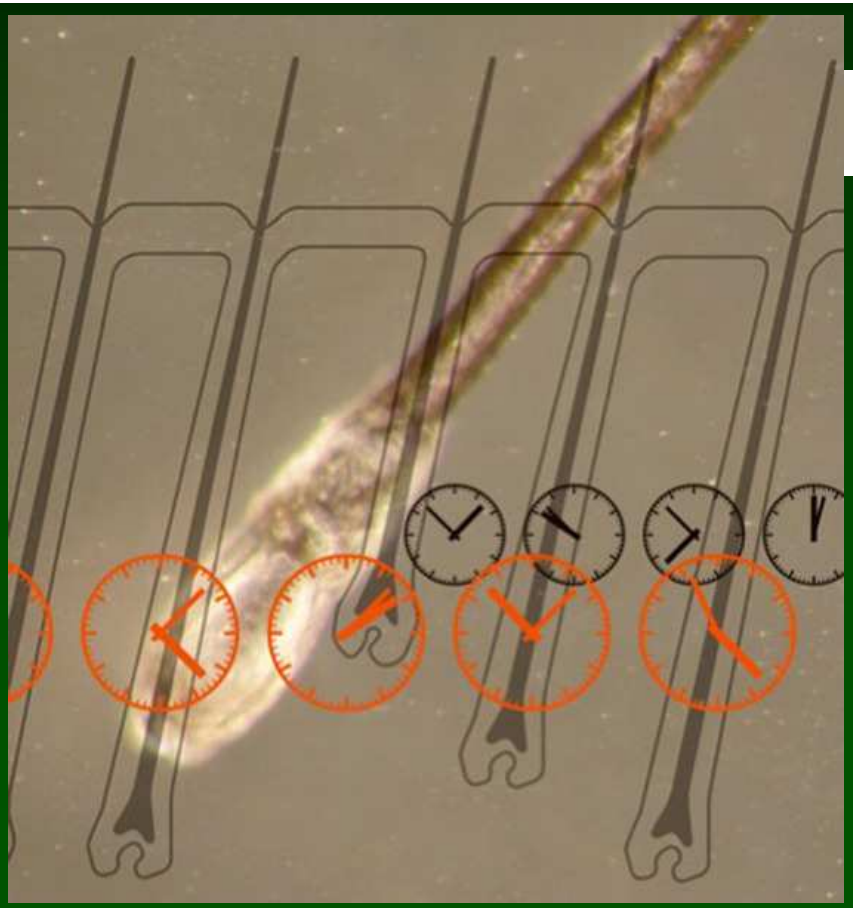

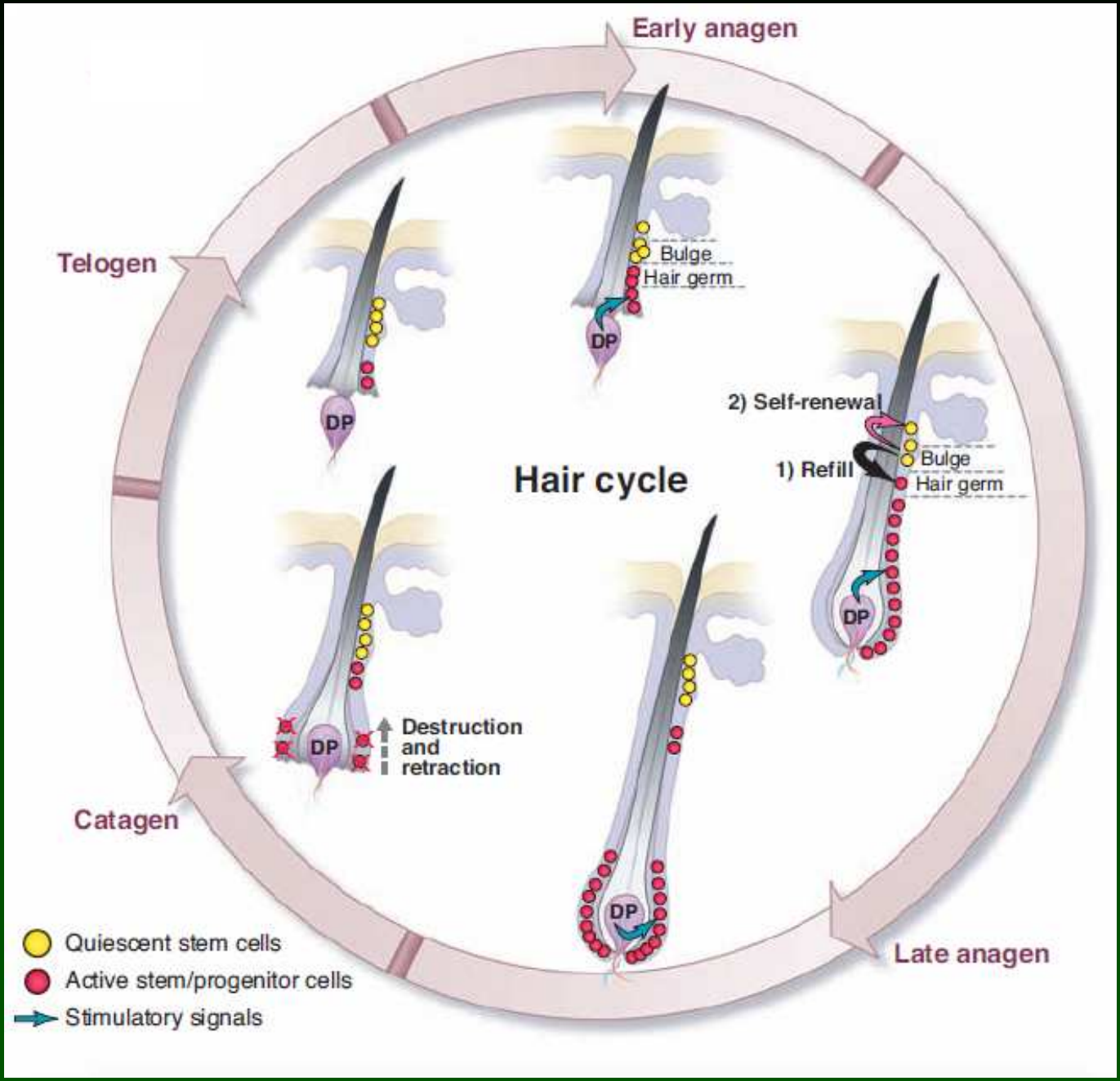
Early anagen
Telogen
Bulge
Hair germ
DP
2) Self-renewal
1) Refill
Hair cycle
Destruction
and
retraction
Catagen
Late anagen
Quiescent stem cells
Active stem/progenitor cells
Stimulatory signals