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Journal ABSTRACTS

Progesterone

PROGESTINS AND PROGESTERONE IN HORMONE REPLACEMENT THERAPY AND THE RISK OF BREAST CANCER.

Controlled studies and most observational studies published over the last 5 years suggest that the addition of synthetic progestins to estrogen in hormone replacement therapy (HRT), particularly in continuous-combined regimen, increases the breast cancer (BC) risk compared to estrogen alone. By contrast, a recent study suggests that the addition of natural progesterone in cyclic regimens does not affect BC risk. This finding is consistent with in vivo data suggesting that progesterone does not have a detrimental effect on breast tissue. The increased BC risk found with the addition of synthetic progestins to estrogen could be due to the regimen and/or the kind of progestin used. Continuous-combined regimen inhibits the sloughing of mammary epithelium that occurs after progesterone withdrawal in a cyclic regimen. More importantly, the progestins used (medroxyprogesterone acetate and 19-Nortestosterone-derivatives) are endowed with some non-progesterone-like effects, which can potentiate the proliferative action of estrogens. Particularly relevant seem to be the metabolic and hepatocellular effects (decreased insulin sensitivity, increased levels and activity of insulin-like growth factor-I, and decreased levels of SHBG), which contrast the opposite effects induced by oral estrogen.

J Steroid Biochem Mol Biol. 2005 Jul;96(2):95-108

THE CASE FOR PROGESTERONE.

Recent clinical trials in hormone therapy (HT) for women approaching or past menopause have been disappointing. Most women who have been taking conjugated equine estrogens combined with synthetic progestins have been encouraged to stop these supplements because of increased health risks. The results of the clinical trials may be accurate about the risks associated with the synthetic compounds and combinations, but the data do not reflect what might have been the case if 17beta-estradiol had been tested with natural progesterone instead of synthetic medroxyprogesterone acetate. For the most part, in almost all work on HT, estrogens have been given the primary focus despite the fact that progesterone has important properties that can enhance the repair of neurodegenerative and traumatic injuries to the central nervous system. This article reviews some of those properties and discusses the evidence suggesting that, if HT is to be reconsidered, progesterone should be given more attention as a potent neurotrophic agent that may play an important role in reducing or preventing motor, cognitive, and sensory impairments that can accompany senescence in both males and females.

Ann N Y Acad Sci. 2005 Jun;1052:152-69

NEUROACTIVE STEROIDS: MECHANISMS OF ACTION AND NEUROPSYCHOPHARMACOLOGICAL PROPERTIES.

Steroids influence neuronal function through binding to cognate intracellular receptors which may act as transcription factors in the regulation of gene expression. In addition, certain so-called neuroactive steroids modulate ligand-gated ion channels via non-genomic mechanisms. Especially distinct 3alpha-reduced metabolites of progesterone and deoxycorticosterone are potent positive allosteric modulators of gamma-aminobutyric acid type A (GABA(A)) receptors. However, also classical steroid hormones such as 17beta-estradiol, testosterone and progesterone are neuroactive steroids because they may act as functional antagonists at the 5-hydroxytryptamine type 3 (5-HT(3)) receptor, a ligand-gated ion channel or distinct glutamate receptors. A structure-activity relationship for the actions of a variety of steroids at the 5-HT(3) receptor was elaborated that differed considerably from that known for GABA(A) receptors. Although a binding site for steroids at GABA(A) receptors is still a matter of debate, meanwhile there is also evidence that steroids interact allosterically with ligand-gated ion channels at the receptor membrane interface. On the other hand, also 3alpha-reduced neuroactive steroids may regulate gene expression via the progesterone receptor after intracellular oxidation into 5alpha-pregnane steroids. Animal studies showed that progesterone is converted rapidly into GABAergic neuroactive steroids in vivo. Progesterone reduces locomotor activity in a dose-dependent fashion in male Wistar rats. Moreover, progesterone and 3alpha-reduced neuroactive steroids produce a benzodiazepine-like sleep EEG profile in rats and humans. During major depression, there is a disequilibrium of such 3alpha-reduced neuroactive steroids which is corrected by successful treatment with antidepressant drugs. Neuroactive steroids may further be involved in

the treatment of depression and anxiety with antidepressants during ethanol withdrawal. Studies in patients with panic disorder suggest that neuroactive steroids may also play a role in modulating human anxiety. Both the genomic and non-genomic effects of steroids in the brain may contribute to the pathophysiology of psychiatric disorders and the mechanisms of action of antidepressants. Neuroactive steroids affect a broad spectrum of behavioral functions through their unique molecular properties and may represent a new treatment strategy for neuropsychiatric disorders.

Psychoneuroendocrinology. 2003 Feb; 28(2):139-68

ROLE OF PROGESTERONE AND OTHER NEUROACTIVE STEROIDS IN ANXIETY DISORDERS.

It remains unexplained why a greater prevalence of anxiety disorders exists in women than in men, and how female hormone-related events (i.e., menstrual cycle and postpartum) can influence the course of anxiety disorders. It would appear logical that female hormones and their derivatives play a major role in these observations. The abundance of preclinical data demonstrating a role for sex hormones and their derivatives in anxiety-like behavior is in contrast to the relative paucity of experimental clinical data on the role of female hormones and neuroactive steroids in anxiety disorders. There is a dramatic potential for therapeutic anxiolytic activity of pharmacological compounds derived from powerful anxiolytic agents, such as the progesterone derivative, allopregnanolone. As a result, there is currently tremendous interest from the pharmaceutical industry in developing and testing such agents in anxiety disorders.

Expert Rev Neurother. 2004 Sep;4(5):851-60

DIFFERENTIAL REGULATION OF GLUCOSE TRANSPORTER EXPRESSION BY ESTROGEN AND PROGESTERONE IN ISHIKAWA ENDOMETRIAL CANCER CELLS.

Estrogen replacement therapy and other unopposed estrogen treatments increase the incidence of endometrial abnormalities, including cancer. However, this effect is counteracted by the co-administration of progesterone. In the endometrium, glucose transporter (GLUT) expression and glucose transport are known to fluctuate throughout the menstrual cycle. Here, we determined the effect of estrogen and progesterone on the expression of GLUT1-4 and on the transport of deoxyglucose in Ishikawa endometrial cancer cells. Cells were incubated with estrogen, progesterone or combined estrogen and progesterone for 24 h and the effect on the expression of GLUT1-4 and on deoxyglucose transport was determined. We show that GLUT1 expression is upregulated by estrogen and progesterone individually, but that combined estrogen and progesterone treatment reverses this increase. Hormonal treatments do not affect GLUT2, GLUT3 or GLUT4 expression. Transport studies demonstrate that estrogen increases deoxyglucose transport at Michaelis-Menten constants (Kms) corresponding to GLUT1/4, an effect which disappears when progesterone is added concomitantly. These data demonstrate that different hormonal treatments differentially regulate GLUT expression and glucose transport in this endometrial cancer cell line. This regulation mirrors the role played by estrogen and progesterone on the incidence of cancer in this tissue and suggests that GLUT1 may be utilized by endometrial cancer cells to fuel their demand for increased energy requirement.

J Endocrinol. 2004 Sep;182(3):467-78

TESTOSTERONE REPLACEMENT-INDUCED HYPERPROLACTINAEMIA: CASE REPORT AND REVIEW OF THE LITERATURE.

Half of all men with prolactin (PRL)-producing macroadenomas present with hypogonadism, decreased libido and impotence, and therefore require testosterone replacement. However, very little is known about the effect of testosterone on prolactinomas. We report a case of an 18-year-old obese man who presented with hypogonadism and hyperprolactinaemia and underwent a transphenoidal hypophysectomy after a computer tomography scan showed the presence of a suprasellar macroadenoma. On separate occasions, we documented a rise in PRL when testosterone replacement was started and a fall in PRL when testosterone replacement was stopped ($r = 0.6090$, $P = 0.0095$). Furthermore, imaging studies suggested the possibility of tumour re-growth after testosterone therapy. We hypothesize that the exogenous testosterone was aromatized to oestradiol, which stimulated the release of PRL by the anterior pituitary. This was supported by the increase in oestradiol levels after testosterone replacement, although statistical significance was not achieved due to the availability of only a few data points. This case highlights the need to be aware of testosterone-replacement-induced hyperprolactinaemia, an under-recognized complication of androgen replacement in this setting. The use of aromatase inhibitors together with testosterone-replacement therapy or the use of non-aromatizable androgens might be indicated in such patients. Taken together, this report and previous studies show that dopamine agonists apparently do not suppress the hyperprolactinaemia induced by testosterone replacement.

Ann Clin Biochem. 2005 Mar;42(Pt 2):153-9

PREVENTING DISEASES OF THE PROSTATE IN THE ELDERLY USING HORMONES AND NUTRICEUTICALS.

The prostate has only one function, namely to secrete fluid containing substances that are needed for reproduction. This requires

an extremely high concentration of androgens in the tissues. Benign prostatic hypertrophy (BPH) seems to be related to the long-term exposure of the prostate to the strong androgen 5alpha-dihydrotestosterone (DHT) and, possibly, to estrogens. The relation between prostate cancer and androgens is suggested to be U-shaped, with both extremes of androgen concentrations being associated with increased risk of invasive cancer. In the treatment of patients with BPH, the lipidic liposterolic extracts of *Serenoa repens* were as effective as the pharmaceutical inhibitors of the 5alpha-reductase enzyme or alpha1-adrenergic blockers in relieving urinary symptoms. In addition to moderately inhibiting the 5alpha-reductase activity, *Serenoa* seems to exert antiinflammatory and complementary cellular actions with beneficial effects on the prostate. Unlike the pharmaceutical 5alpha-reductase inhibitors, finasteride and dutasteride, *Serenoa* does not suppress serum PSA, facilitating the followup and the early detection of prostate cancer. We suggest a strategy to prevent prostate cancer that aims at providing men with partial androgen deficiency correct testosterone substitution with a sustained release buccal bio-adhesive tablet. In addition, food supplementation with extracts of *Serenoa repens* and a combination of the antioxidants selenium, (cis)-lycopene and natural vitamin E, together with fish oil rich in long-chain polyunsaturated essential fatty acids of the omega-3 group seems warranted. Clearly, a holistic approach including careful clinical and biological monitoring of the aging man and his prostate remains mandatory.

Aging Male. 2004 Jun;7(2):155-69

GAMMA-TOCOPHEROL—AN UNDERESTIMATED VITAMIN?

The main research activities of the last decades on tocopherols were mainly focused on alpha-tocopherol, in particular when considering the biological activities. However, recent studies have increased the knowledge on gamma-tocopherol, which is the major form of vitamin E in the diet in the USA, but not in Europe. gamma-Tocopherol provides different antioxidant activities in food and in-vitro studies and showed higher activity in trapping lipophilic electrophiles and reactive nitrogen and oxygen species. The lower plasma levels of gamma- compared to alpha-tocopherol might be discussed in the light of different bioavailability, but also in a potential transformation from gamma- to alpha-tocopherol. From the metabolism end product, only that of gamma-tocopherol (2,7,8-trimethyl-2-(beta-carboxyethyl)-6-hydroxychroman), but not that of alpha-tocopherol, was identified to provide natriuretic activity. Studies also indicate that only the gamma-tocopherol plasma level served as biomarker for cancer and cardiovascular risk. Therefore, this paper provides a comprehensive review on gamma-tocopherol with emphasis on its chemistry, biosynthesis, occurrence in food, different intake linking to different plasma levels in USA and Europe, absorption and metabolism, biological activities, and possible role in human health.

Ann Nutr Metab. 2004;48(3):169-88

TOCOPHEROLS AND THE TREATMENT OF COLON CANCER.

Colorectal cancer is the second most common cause of cancer deaths in the United States. Vitamin E (VE) and other antioxidants may help prevent colon cancer by decreasing the formation of mutagens arising from the free radical oxidation of fecal lipids or by "non-antioxidant" mechanisms. VE is not a single molecule, but refers to at least eight different molecules, that is, four tocopherols and four tocotrienols. Methods: Both animal models and human colon cancer cell lines were used to evaluate the chemopreventive potential of different forms of VE. Rats were fed diets deficient in tocopherols or supplemented with either alpha-tocopherol or gamma-tocopherol. Half the rats in each of these groups received normal levels of dietary Fe and the other half Fe at eight times the normal level. In our cell experiments, we looked at the role of gamma-tocopherol in upregulating peroxisome proliferator-activated receptor-gamma (PPAR-gamma) in the SW 480 human cell line. Results: Rats fed the diets supplemented with alpha-tocopherol had higher levels of VE in feces, colonocytes, plasma, and liver than did rats fed diets supplemented with gamma-tocopherol. Dietary Fe levels did not influence tocopherol levels in plasma, liver, or feces. For colonocytes, high dietary Fe decreased tocopherol levels. Rats fed the gamma-tocopherol-supplemented diets had lower levels of fecal lipid hydroperoxides than rats fed the alpha-tocopherol-supplemented diets. Ras-p21 levels were significantly lower in rats fed the gamma-tocopherol-supplemented diets compared with rats fed the alpha-tocopherol-supplemented diets. High levels of dietary Fe were found to promote oxidative stress in feces and colonocytes. Our data with the SW480 cells suggest that both alpha- and gamma-tocopherol upregulate PPAR-gamma mRNA and protein expression. gamma-tocopherol was, however, found to be a better enhancer of PPAR-gamma expression than alpha-tocopherol at the concentrations tested.

Ann N Y Acad Sci. 2004 Dec;1031:223-33

SERUM ALPHA-TOCOPHEROL AND GAMMA-TOCOPHEROL IN RELATION TO PROSTATE CANCER RISK IN A PROSPECTIVE STUDY.

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study demonstrated a 32% reduction in prostate cancer incidence in response to daily alpha-tocopherol supplementation. We examined baseline serum concentrations of alpha-tocopherol and gamma-tocopherol to compare their respective associations with prostate cancer risk. From the ATBC Study cohort of 29 133 Finnish men, 50-69 years old, we randomly selected 100 incident prostate cancer case patients and matched 200 control subjects. Odds ratios and 95% confidence intervals (CIs) were estimated for the serum tocopherols (measured by high-performance liquid chromatography) using logistic regression models. All P values were two-sided. Odds ratios for the highest versus the lowest tertiles were 0.49 (95% CI = 0.24 to 1.01, P(trend) = .05) for alpha-tocopherol and 0.57 (95% CI = 0.31 to 1.06, P(trend) = .08) for gamma-tocopherol. Further analyses indicated that the association of high serum tocopherols with low prostate cancer risk was stronger in the alpha-tocopherol-supplemented group than in those not receiving alpha-tocopherol. Participants with higher circulating concentrations of the major vitamin E fractions, alpha-tocopherol and gamma-tocopherol, had similarly lower prostate cancer risk.

J Natl Cancer Inst. 2005 Mar 2;97(5):396-9

RELATION OF THE TOCOPHEROL FORMS TO INCIDENT ALZHEIMER DISEASE AND TO COGNITIVE CHANGE.

BACKGROUND: High intake of vitamin E from food (tocopherol), but not from supplements (which usually contain alpha-tocopherol), is inversely associated with Alzheimer disease. **OBJECTIVE:** We examined whether food intakes of vitamin E, alpha-tocopherol equivalents (a measure of the relative biologic activity of tocopherols and tocotrienols), or individual tocopherols would protect against incident Alzheimer disease and cognitive decline over 6 y in participants of the Chicago Health and Aging Project. **DESIGN:** The 1993-2002 study of community residents aged ≥ 65 y included the administration of 4 cognitive tests and clinical evaluations for Alzheimer disease. Dietary assessment was by food-frequency questionnaire. **RESULTS:** Tocopherol intake from food was related to the 4-y incidence of Alzheimer disease determined by logistic regression in 1041 participants who were clinically evaluated (n=162 incident cases) and to change in a global cognitive score determined by mixed models in 3718 participants. Higher intakes of vitamin E (relative risk: 0.74 per 5 mg/d increase; 95% CI: 0.62, 0.88) and alpha-tocopherol equivalents (relative risk: 0.56 per 5 mg/d increase; 95% CI: 0.32, 0.98) were associated with a reduced incidence of Alzheimer disease in separate multiple-adjusted models that included intakes of saturated and trans fats and docosahexaenoic acid. alpha- and gamma-Tocopherol had independent associations. In separate mixed models, a slower rate of cognitive decline was associated with intakes of vitamin E, alpha-tocopherol equivalents, and alpha- and gamma-tocopherols. **CONCLUSION:** The results suggest that various tocopherol forms rather than alpha-tocopherol alone may be important in the vitamin E protective association with Alzheimer disease.

Am J Clin Nutr. 2005 Feb;81(2):508-14

DIETARY VITAMIN E MODULATES DIFFERENTIAL GENE EXPRESSION IN THE RAT HIPPOCAMPUS: POTENTIAL IMPLICATIONS FOR ITS NEUROPROTECTIVE PROPERTIES.

A wide range of cell culture, animal and human epidemiological studies are suggestive of a role of vitamin E (VE) in brain function and in the prevention of neurodegeneration. However, the underlying molecular mechanisms remain largely unknown. In the current investigation Affymetrix gene chip technology was utilized to establish the impact of chronic VE deficiency on hippocampal genes expression. Male albino rats were fed either a VE deficient or standard diet (60 mg/kg feed) for a period of 9 months. Rats were sacrificed, the hippocampus removed and genes expression established in individual animals. VE deficiency showed to have a strong impact on genes expression in the hippocampus. An important number of genes found to be regulated by VE was associated with hormones and hormone metabolism, nerve growth factor, apoptosis, dopaminergic neurotransmission, and clearance of amyloid-beta and advanced glycated endproducts. In particular, VE strongly affected the expression of an array of genes encoding for proteins directly or indirectly involved in the clearance of amyloid beta, changes which are consistent with a protective effect of VE on Alzheimer's disease progression.

Nutr Neurosci. 2005 Feb;8(1):21-9

PERSONAL EXPOSURE TO ULTRAFINE PARTICLES AND OXIDATIVE DNA DAMAGE.

Exposure to ultrafine particles (UFPs) from vehicle exhaust has been related to risk of cardiovascular and pulmonary disease and cancer, even though exposure assessment is difficult. We studied personal exposure in terms of number concentrations of UFPs in the breathing zone, using portable instruments in six 18-hr periods in 15 healthy nonsmoking subjects. Exposure contrasts of outdoor pollution were achieved by bicycling in traffic for 5 days and in the laboratory for 1 day. Oxidative DNA damage was assessed as strand breaks and oxidized purines in mononuclear cells isolated from venous blood the morning after exposure measurement. Cumulated outdoor and cumulated indoor exposures to UFPs each were independent significant predictors of the level of purine oxidation in DNA but not of strand breaks. Ambient air concentrations of particulate matter with an aerodynamic diameter of ≤ 10 microm (PM₁₀), nitrous oxide, nitrogen dioxide, carbon monoxide, and/or number concentration of UFPs at urban background or busy street monitoring stations was not a significant predictor of DNA damage, although personal UFP exposure was correlated with urban background concentrations of CO and NO₂, particularly during bicycling in traffic. The results indicate that biologic effects of UFPs occur at modest exposure, such as that occurring in traffic, which supports the relationship of UFPs and the adverse health effects of air pollution.

Environ Health Perspect. 200 Nov;113(11):1485-90

ALPHA-TOCOPHEROL: ROLES IN PREVENTION AND THERAPY OF HUMAN DISEASE.

Alpha-tocopherol, one of the eight isoforms of vitamin E, is the most potent fat-soluble antioxidant known in nature. For years, it was thought that alpha-tocopherol only functioned as a scavenger of lipid peroxyl radicals, specifically, oxidized low-density lipoprotein (oxLDL), thereby serving as a chief antioxidant for the prevention of atherosclerosis. In recent years, the many roles of alpha-tocopherol have been uncovered, and include not only antioxidant functions, but also pro-oxidant, cell signaling and gene regulatory functions. Decades of clinical and preclinical studies have broadened our understanding of the antioxidant vitamin E and its utility in a number of chronic, oxidative stress-induced pathologies. The results of these studies have shown promising,

albeit mixed reviews on the efficacy of alpha-tocopherol in the prevention and treatment of heart disease, cancer and Alzheimer's disease. Future studies to uncover cellular and systemic mechanisms may help guide appropriate clinical treatment strategies using vitamin E across a diverse population of aging individuals.

Biomed Pharmacother. 2005 Aug;59(7):380-7

VITAMIN E IN NEURODEGENERATIVE DISORDERS: ALZHEIMER'S DISEASE.

Oxidative stress is important in the pathogenesis of Alzheimer's disease (AD). The brain contains high levels of oxidizable lipids that must be protected by antioxidants. Low concentrations of vitamin E, quantitatively the major lipophilic antioxidant in the brain, are frequently observed in cerebrospinal fluid (CSF) of AD patients, suggesting that supplementation with vitamin E might delay the development of AD. In a placebo-controlled trial, vitamin E (2000 IU/day, 2 years) slowed (-53%) functional deterioration in patients with moderate AD. Recently, use of vitamin E and vitamin C supplements in combination was found to be associated with reduced prevalence (-78%) and incidence (-64%) of AD in elderly population. These results are consistent with the ability of the supplementation with vitamin E (400 IU/day, 1 month) to increase its levels in CSF (123%) and plasma (145%) of AD patients and, in combination with vitamin C (1000 g/ day), to decrease the susceptibility of CSF lipoproteins (up to -32%) to in vitro oxidation. In addition, vitamin E reduced lipid peroxidation and amyloid deposition in a transgenic mice model of AD. Computer modeling of the influence of vitamin E on lipoprotein oxidation reveals that the vitamin develops antioxidative activity in CSF lipoproteins in the presence of physiologically relevant, low amounts of oxidants. By contrast, under similar conditions, vitamin E behaves as a pro-oxidant in plasma lipoproteins, consistent with the model of tocopherol-mediated peroxidation. This distinction is related to major differences in the levels of vitamin E (50 nM vs. 30 microM) and oxidizable lipids (4 microM vs. 2.5 mM) between CSF and plasma, which result in major differences in oxidative conditions (per unit of vitamin E) between CSF and plasma in the presence of similar amounts of oxidants. Altogether, these data suggest that vitamin E may be effective against in vivo oxidation of CSF lipoproteins and brain lipids, and offer new perspectives in the treatment of AD and other neurodegenerative disorders.

Ann N Y Acad Sci. 2004 Dec;1031:249-62

NEW PERSPECTIVES ON VITAMIN E: GAMMA-TOCOPHEROL AND CARBOXYETHYLHYDROXYCHROMAN METABOLITES IN BIOLOGY AND MEDICINE.

Vitamin E (alpha-tocopherol or alphaT) has long been recognized as a classic free radical scavenging antioxidant whose deficiency impairs mammalian fertility. In actuality, alpha-tocopherol is one member of a class of phytochemicals that are distinguished by varying methylation of a chroman head group. Early studies conducted between 1922 and 1950 indicated that alpha-tocopherol was specific among the tocopherols in allowing fertility of laboratory animals. The unique vitamin action of alphaT, combined with its prevalence in the human body and the similar efficiency of tocopherols as chainbreaking antioxidants, led biologists to almost completely discount the "minor" tocopherols as topics for basic and clinical research. Recent discoveries have forced a serious reconsideration of this conventional wisdom. New and unexpected biological activities have been reported for the desmethyl tocopherols, such as gamma-tocopherol, and for specific tocopherol metabolites, most notably the carboxyethyl-hydroxychroman (CEHC) products. The activities of these other tocopherols do not map directly to their chemical antioxidant behavior but rather reflect anti-inflammatory, antineoplastic, and natriuretic functions possibly mediated through specific binding interactions. Moreover, a nascent body of epidemiological data suggests that gamma-tocopherol is a better negative risk factor for certain types of cancer and myocardial infarction than is an alphatocopherol. The potential public health implications are immense, given the extreme popularity of alphaT supplementation which can unintentionally deplete the body of gamma-tocopherol. These findings may or may not signal a major paradigm shift in free radical biology and medicine. The data argue for thorough experimental and epidemiological reappraisal of desmethyl tocopherols, especially within the contexts of cardiovascular disease and cancer biology.

Free Radic Biol Med. 2004 Jan 1;36(1):1-15.

RELATIONSHIP BETWEEN DEMENTIA AND NUTRITION-RELATED FACTORS AND DISORDERS: AN OVERVIEW.

This review gives a brief overview of the main types of dementia and summarizes current thinking on the relationship between nutritional related factors and disorders, and dementia. Dementia is a multi-factor pathological condition, and nutrition is one factor that may play a role on its onset and progression. An optimal intake of nutrients doesn't protect people from dementia. However, studies in this area show that inadequate dietary habits, which are of particular concern in elderly populations, may increase the risk of developing a number of age-related diseases, including disorders of impaired cognitive function. They show that a deficiency in essential nutrients, such as certain B complex vitamins, can result in hyperhomocysteinemia, a well-known risk factor for atherosclerosis and recently associated with cognitive impairment in old age. A deficiency of antioxidants such as vitamins C and E, and beta-carotene, as well as nutrition-related disorders like hypercholesterolemia, hypertension, and diabetes, may also have some role in cognitive impairment. These factors can be present for a long time before cognitive impairment becomes evident, therefore they could be potentially detected and corrected in a timely manner.

PREVALENCE OF VITAMIN K DEFICIENCY IN CHILDREN WITH MILD TO MODERATE CHRONIC LIVER DISEASE.

OBJECTIVES: Children with chronic liver disease are at risk for vitamin K deficiency because of fat malabsorption and inadequate dietary intake. The objective of this study was to determine the prevalence of vitamin K deficiency in children with mild to moderate chronic cholestatic and noncholestatic liver disease. **METHODS:** Vitamin K status was examined in 43 children (0.25-15.9 years) with mild to moderate chronic cholestatic liver disease, 29 children (0.9-16.9 years) with chronic mild to moderate noncholestatic liver disease, and in 44 healthy children (1-18 years). Vitamin K status was assessed by the plasma PIVKA-II (protein induced in vitamin K absence) assay (enzymelinked immunosorbent assay). Plasma PIVKA-II values greater than 3 ng/mL are indicative of vitamin K deficiency. **RESULTS:** The mean plasma PIVKA-II (+/-SD) in cholestatic, noncholestatic, and healthy children was 61.9 +/-144, 1.2 +/- 3, and 2.1 +/- ng/mL, respectively ($P < 0.002$). Fifty-four percent of the children supplemented with vitamin K had plasma PIVKA-II greater than 3 ng/mL. Plasma conjugated bilirubin, total bile acids, and severity of liver disease were positively correlated with plasma PIVKA-II levels ($P < 0.05$). **CONCLUSIONS:** Vitamin K deficiency is prevalent in children with mild to moderate chronic cholestatic liver disease, even with vitamin K supplementation. Elevated PIVKA-II levels occurred in children with a normal prothrombin, indicating that more sensitive markers of vitamin K status should be used in children with chronic liver disease. Vitamin K deficiency was related to degree of cholestasis and severity of liver disease in children. Children without cholestasis did not exhibit vitamin K deficiency.

J Pediatr Gastroenterol Nutr. 2006 Jan;42(1):71-76

POSITIVE FEEDBACKS OF COAGULATION: THEIR ROLE IN THRESHOLD REGULATION.

Tissue factor (TF), the initiator of coagulation, continuously circulates in the plasma, and the clotting system "idles," generating very low levels of active clotting enzymes, clotting products, and by-products. Given the enormous amplification potential of the clotting cascade, rigorous control is required to ensure that such low-level stimulation does not cause massive system amplification and response. We propose that among the various mechanisms of regulation, activation thresholds may play a major role. These arise when positive-feedback reactions, of which there are several in the clotting system, are regulated by inhibitors. Such thresholds act like switches, so that small stimuli and/ or nonproductive local conditions will generate no response, whereas larger stimuli or the existence of local prothrombotic conditions will produce a full, explosive response. We review here the evidence for system idling, the structures of the various feedback mechanisms of clotting, the mechanisms by which they can produce threshold behavior, and the possible role of thresholds in system regulation.

Arterioscler Thromb Vasc Biol. 2005 Dec;25(12):2463-9

THE MULTIFUNCTIONAL PROTEIN C SYSTEM.

The protein C pathway is a major regulator of blood coagulation, since it controls the conversion of prothrombin to thrombin through a feedback inhibition mechanism. Protein C circulates in plasma as an inactive zymogen and is activated on the surface of endothelial cells by the thrombin-thrombomodulin complex, a process that can be further enhanced when protein C binds to its membrane receptor, the endothelial-cell protein C receptor. Activated protein C (APC) is then released from the complex, binds protein S and inhibits thrombin formation by inactivating coagulation factors Va and VIIIa. The importance of the protein C anticoagulant pathway is emphasized by the increased risk of venous thromboembolism (VTE) associated with protein C and protein S deficiencies, the factor V Leiden mutation, and reduced circulating APC levels. The protein C pathway also plays a significant role in inflammatory processes, since it prevents the lethal effects of E. coli-associated sepsis in animal models and improves the outcome of patients with severe sepsis. APC seems to display anti-apoptotic and neuroprotective activities. Thus, it reduces organ damage in animal models of sepsis, ischemic injury, endothelial cell injury, or stroke. Further research will hopefully widen the current therapeutic perspectives in all these illnesses, where these effects might play a crucial role in their treatment. This review will summarize the mechanisms that contribute to these biological activities of the protein C pathway.

Curr Med Chem Cardiovasc Hematol Agents. 2005 Apr;3(2):119-31

THE ANTICOAGULANT PROTEIN C PATHWAY.

The anticoagulant protein C system regulates the activity of coagulation factors VIIIa and Va, cofactors in the activation of factor

X and prothrombin, respectively. Protein C is activated on endothelium by the thrombin-thrombomodulin-EPCR (endothelial protein C receptor) complex. Activated protein C (APC)- mediated cleavages of factors VIIIa and Va occur on negatively charged phospholipid membranes and involve protein cofactors, protein S and factor V. APC also has antiinflammatory and anti-apoptotic activities that involve binding of APC to EPCR and cleavage of PAR- 1 (protease-activated receptor-1). Genetic defects affecting the protein C system are the most common risk factors of venous thrombosis. The protein C system contains multidomain proteins, the molecular recognition of which will be reviewed.

FEBS Lett. 2005 Jun 13;579(15):3310-6

COAGULATION INHIBITORS IN INFLAMMATION.

Coagulation is triggered by inflammatory mediators in a number of ways. However, to prevent unwanted clot formation, several natural anticoagulant mechanisms exist, such as the antithrombin-heparin mechanism, the tissue factor pathway inhibitor mechanism and the protein C anticoagulant pathway. This review examines the ways in which these pathways are down-regulated by inflammation, thus limiting clot formation and decreasing the natural anti-inflammatory mechanisms that these pathways possess.

Biochem Soc Trans. 2005 Apr;33(Pt 2):401-5

VITAMIN D, K, AND BONE MINERAL DENSITY.

Both vitamin D and vitamin K are essential nutrients for bone health. It is believed that vitamin D deficiency is responsible for rickets in infants and osteomalacia in adults, and chronic vitamin D insufficiency induces hyperparathyroidism and reduces bone mineral density, resulting in an increased risk of osteoporosis. Vitamin K deficiency is thought to cause impaired activation of bone matrix protein osteocalcin, and reduction of osteoblast function, resulting in impaired bone formation. Recently, we reported that a high prevalence of low vitamin D status (low serum 25-hydroxyvitamin D concentration), low bone mineral density, and a high prevalence of low vitamin K status (high serum undercarboxylated osteocalcin concentration), high frequency of bone fracture in elderly women in Japan. However, no correlation between low vitamin K status and low bone mineral density was observed in this subjects.

Clin Calcium. 2005 Sep;15(9):1489-94

VITAMIN K2 AS A PROTECTOR OF BONE HEALTH AND BEYOND.

Several lines of evidence indicate a protective effect of vitamin K against osteoporosis. Epidemiological studies showed that low vitamin K intake is associated with the increased risk of osteoporosis. Vitamin K2 (menatetrenone, MK-4) has been clinically used in the treatment of patients with osteoporosis in Japan, Korea, and Thailand. Previous studies demonstrated the efficacy of vitamin K2 (45 mg/day) to prevent bone loss and reduce the rate of vertebral fractures, although a large, randomized intervention study is anticipated to provide more detailed evidence. Recently, vitamin K2 has been shown to reduce the progression of hepatocarcinoma. Moreover, it has been proposed that vitamin K may also have beneficial effects to prevent atherosclerosis. The clarification of molecular mechanisms by which vitamin K2 exerts these salutary effects deserve further investigations.

Clin Calcium. 2005 Apr;15(4):605-10

ATHEROSCLEROSIS AND MATRIX DYSTROPHY.

Atherosclerosis is characterized by inflammatory metabolic change with lipid accumulation in the artery. Atherosclerotic plaque occurs at discrete locations in the arterial system and involves the proliferation of smooth muscle cells (SMCs) together with imbalance of the extracellular matrix elements, elastic fiber in particular. The role of elastin in arterial development and disease was confirmed by generating mice that lack elastin. Thus, elastin is a critical regulatory molecule that regulates the phenotypic modulation, proliferation and migration of SMCs. We estimated that elastin expression and SMC proliferation are coupled inversely: potent stimulators of cell proliferation may potentially inhibit elastin expression and potent inhibitors of cell proliferation can stimulate elastin expression. Moreover, elastin was found to be expressed maximally at the G(0) and minimally at the G(2)/M phase during the cell cycle, suggesting that its expression is regulated by the cell growth state. The elastin peptide VPGVG enhanced SMC proliferation, resulting in the reduction of elastin expression. The inhibition of elastin expression by elastin fragments may be reflected in the negative feedback regulatory mechanism. The relationship between cell proliferation and elastin expression may be changed in atherosclerosis. Areas of atherosclerotic plaque show abnormality of elasticity and permeability from the viewpoint of the physiological function of the arterial wall. The etiology was estimated to be that cholesterol and calcium are deposited on the elastic fiber, resulting in decreased elastin synthesis and cross-linking formation. In addition, these dysfunctions of elastin fiber are also associated, in that the down-regulation of elastin and its related components (fibrillin-1 and lysyl oxidase) are directly related to calcification in SMCs. The denatured arterial elastin by cholesterol and calcium accumulation was also susceptible to proteolytic enzymes such as elastase and matrix metalloproteinase (MMP). Therefore,

metabolic change in elastic fiber induces decreased elasticity and is associated with essential hypertension. Vitamin K(2) is used in drug therapy against atherosclerosis, or calcification in diabetes mellitus or dialysis, due to its promotion of the carboxylation of the matrix Gla protein.

J Atheroscler Thromb. 2004;11(5):236-45

PYGEUM AFRICANUM FOR THE TREATMENT OF PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA: A SYSTEMATIC REVIEW AND QUANTITATIVE META-ANALYSIS.

PURPOSE: To conduct a systematic review and quantitative meta-analysis of the therapeutic efficacy and tolerability of *Pygeum africanum* in men with symptomatic benign prostatic hyperplasia. **METHODS:** Studies were identified through the search of Medline (1966 to 2000), Embase, Phytodok, the Cochrane Library, bibliographies of identified trials and review articles, and contact with relevant authors and drug companies. Randomized trials were included if participants had symptomatic benign prostatic hyperplasia, the intervention was a preparation of *P. africanum* alone or in combination with other phytotherapeutic agents, a control group received placebo or other pharmacologic therapies for benign prostatic hyperplasia, and treatment duration was at least 30 days. Two investigators independently extracted key data on design features, subject characteristics, and therapy allocation. **RESULTS:** A total of 18 randomized controlled trials involving 1,562 men met the inclusion criteria and were analyzed. Many studies did not report results in a method that permitted meta-analysis. Only 1 of the studies reported a method of treatment allocation concealment, although 17 were double-blinded. The mean study duration was 64 days (range 30 to 122). Compared with placebo in 6 studies, *P. africanum* provided a moderately large improvement in the combined outcome of urologic symptoms and flow measures as assessed by an effect size defined by the difference of the mean change for each outcome divided by the pooled standard deviation for each outcome (-0.8 SD [95% confidence interval (CI): -1.4 to -0.3]). Summary estimates of individual outcomes were also improved by *P. africanum*. Men were more than twice as likely to report an improvement in overall symptoms (risk ratio = 2.1, 95% CI: 1.40 to 3.1). Nocturia was reduced by 19% and residual urine volume by 24%; peak urine flow was increased by 23%. Adverse effects due to *P. africanum* were mild and similar to placebo. The overall dropout rate was 12% and was similar for *P. africanum* (13%), placebo (11%), and other controls (8%; $P = 0.4$ versus placebo and $P = 0.5$ versus other controls). **CONCLUSIONS:** The literature on *P. africanum* for the treatment of benign prostatic hyperplasia is limited by the short duration of studies and the variability in study design, the use of phytotherapeutic preparations, and the types of reported outcomes. However, the evidence suggests that *P. africanum* modestly, but significantly, improves urologic symptoms and flow measures. Further research is needed using standardized preparations of *P. africanum* to determine its longterm effectiveness and ability to prevent complications associated with benign prostatic hyperplasia.

Am J Med. 2000 Dec 1;109(8):654-64

LOW-DOSE TADENAN PROTECTS THE RABBIT BLADDER FROM BILATERAL ISCHEMIA/ REPERFUSION-INDUCED CONTRACTILE DYSFUNCTION.

Recent studies indicate that focal ischemia/reperfusion (I/R) can cause the contractile dysfunctions induced in animal models of partial bladder outlet obstruction. Tadenan (*Pygeum africanum*) pretreatment can prevent the rabbit bladder from developing the contractile and biochemical dysfunctions induced by partial outlet obstruction, possibly by protecting the bladder from ischemic injury. The current study was designed to determine whether pre-treating rabbits with a clinically relevant dose of Tadenan could prevent the bladder from developing the contractile dysfunctions that are induced by bilateral ischemia followed by reperfusion. New Zealand White rabbits were separated into two groups. One group was pretreated by oral gavage for 3 weeks with Tadenan (3.0 mg/kg body wt./ day). The second group was treated with vehicle (peanut oil). Five rabbits from each group were subjected to either bilateral ischemia for 1 or 3 h and then reperfused for either 1 h or 1 week. Five rabbits from each group were subjected to sham surgery and run with each of the experimental groups. The results of the current study show that Tadenan pretreatment at the clinically relevant dose of 3.0 mg/kg body wt./day protected the bladder from the contractile dysfunctions induced by bilateral ischemia followed by reperfusion. These data are consistent with the assertion that Tadenan therapy in both rabbits and humans acts by protecting the bladder smooth muscle against cellular damage caused by ischemia and reperfusion.

Phytomedicine. 2005 Jan;12(1-2):17-24

DIHYDROTESTOSTERONE AND THE ROLE OF 5 ALPHA-REDUCTASE INHIBITORS IN BENIGN PROSTATIC HYPERPLASIA.

The genesis of benign prostate hyperplasia (BPH) depends on two factors: testicular androgen and the aging process. The most important androgen in the prostate is dihydrotestosterone (DHT). In the aging male the level of DHT in the prostate remains largely constant although the plasma level of testosterone decreases. DHT is formed by the reduction of testosterone by the enzyme 5-alpha-reductase, which has two isoenzymes. The 5-alpha-reductase type 2 is the predominant isoenzyme in genital

tissue and thus also in the prostate. Finasteride is a 5-alpha-reductase inhibitor, which is applied in the treatment of BPH and male baldness. In the doses used finasteride acts mainly by inhibiting the 5-alpha-reductase type 2, thereby reducing the serum level of DHT by approximately 70% and by about 85-90% in the prostate. Indeed the effect of finasteride in BPH was proven in clinical studies. However, the circulating and intraprostatic DHT could be further reduced by a more effective dual 5-alpha-reductase inhibitor, which would be efficacious in the treatment of benign prostate hyperplasia and other DHT-related disorders.

Urologe A. 2002 Sep;41(5):412-24

IMPORTANCE OF THE NATURAL HISTORY OF BENIGN PROSTATIC HYPERPLASIA IN THE EVALUATION OF PHARMACOLOGIC INTERVENTION.

The variable natural history of untreated symptomatic benign prostatic hyperplasia (BPH) and the fact that therapeutic intervention is based more on subjective than objective criteria of progressive disease have important consequences for appropriately evaluating the effects of pharmacologic intervention on clinical BPH. To evaluate accurately the success of drug therapy for symptomatic BPH, any trial must include a placebo treatment arm for comparison. However, for such a placebo control to be legitimate, it must not affect the natural history of BPH. To evaluate the effect of placebo treatment on BPH, a large body of data following the natural history of untreated clinical BPH from a variety of independent studies was combined and compared to those from a large variety of independent studies in which a April 2006 LIFE EXTENSION 107 Journal ABSTRACTS placebo-treated group of patients with clinical BPH also followed. These comparisons demonstrate that 1) placebo treatment does not affect the natural history of the disease; 2) spontaneous improvement usually occurs within the first 6 months of initial presentation of symptoms, if it is to occur at all; and 3) 3-6 months of followup are needed to determine if a patient is going to get worse. Thus, to evaluate accurately the potential benefit of any medical intervention for symptomatic BPH, placebocontrolled clinical trials will be required and should be of at least 6 month's duration.

Prostate Suppl. 1990;3:1-7

ANTIPROLIFERATIVE EFFECT OF PYGEUM AFRICANUM EXTRACT ON RAT PROSTATIC FIBROBLASTS.

The effect of a Pygeum africanum extract (Tadenan) (Pa), used in the treatment of micturition disorders associated with BPH, has been examined on the proliferation of rat prostatic stromal cells stimulated by different growth factors. EGF, bFGF, and IGF-I but not KGF are mitogenic for prostatic fibroblasts in culture. Pygeum africanum inhibits both basal and stimulated growth with IC50 values of 4.5, 7.7, and 12.6 micrograms./ml. for EGF, IGF-I and bFGF, respectively, compared to 14.4 micrograms./ml. for untreated cells, the inhibition being stronger towards EGF. Pygeum africanum inhibited the proliferation induced by TPA or PDBu in a concentration-dependent manner with IC50 values of 12.4 and 8.1 micrograms./ ml. respectively. The antiproliferative effects of Pa were not ascribed to cytotoxicity. These results show that Pygeum africanum is a potent inhibitor of rat prostatic fibroblast proliferation in response to direct activators of protein kinase C, the defined growth factors bFGF, EGF and IGF-I, and the complex mixture of mitogens in serum depending on the concentration used. PKC activation appears to be an important growth factor-mediated signal transduction for this agent. These data suggest that therapeutic effect of Pygeum africanum may be due at least in part to the inhibition of growth factors responsible for the prostatic overgrowth in man.

J Urol. 1997 Jun;157(6):2381-7

COMPARISON OF ONCE AND TWICE DAILY DOSAGE FORMS OF PYGEUM AFRICANUM EXTRACT IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA: A RANDOMIZED, DOUBLE-BLIND STUDY, WITH LONG-TERM OPEN LABEL EXTENSION.

OBJECTIVES: To compare the efficacy and safety of Pygeum africanum extract, 50 mg twice daily and 100 mg once daily. **METHODS:** Patients with symptomatic benign prostatic hyperplasia (BPH) entered a 2-month randomized, parallelgroup, double-blind, comparative phase (group A, 50 mg twice daily; group B, 100 mg once daily), followed by a 10-month, open phase (100 mg once daily). Main efficacy assessment parameters included International Prostate Symptom Score (IPSS), quality of life (QOL), and maximum urinary flow rate (Qmax). **RESULTS:** Two hundred nine patients completed the comparative phase in compliance with the protocol; 174 were included in the open phase. Both treatments had similar efficacy. IPSS (baseline 17 in both groups) improved by 38% in group A and 35% in group B. QOL improved by 28% in both groups. Qmax increased by 1.63 mL/s (16%) in group A and 2.02 mL/s (19%) in group B. After 12 months, the IPSS fell from 16 (baseline) to 9 (-46%). Half of the patients had an IPSS below 8. Mean Qmax increased by 1.65 Journal ABSTRACTS 108 LIFE EXTENSION April 2006 mL/s (15%). The safety profile was similar between groups and study phases. **CONCLUSIONS:** P. africanum extract at 50 mg twice daily and 100 mg once daily proved equally effective and safe at 2 months. Further improvements in efficacy with a satisfactory safety profile were documented after 12 months.

Urology. 1999 Sep;54(3):473-8

UROLOGICAL AND SEXUAL EVALUATION OF TREATMENT OF BENIGN PROSTATIC DISEASE USING PYGEUM

This clinical study has been designed to evaluate the efficacy of an extract of *Pygeum Africanum* (Tadenan) (Roussel-Pharma) in patients suffering from prostatic hypertrophy or chronic prostatitis. The drug has been administered to 18 patients, for 60 days, as double of standard dosage (200 mg/die per os, instead of 100 mg/die). Because of the high frequency of association of sexual disorders with those two pathologies, we have extended the study also to sexual disorders selecting patients suffering from prostatic hypertrophy or chronic prostatitis and, simultaneously, from sexual disturbances. No side effects have been observed during the treatment. The urinary disturbances have been evaluated by anamnesis and prostatic transrectal echography; sexual disorders have been evaluated by anamnesis and nocturnal penile tumescence and rigidity (NPTR) monitoring. Furthermore, dosage of serum levels of the hormones LH, FSH, Prolactin, 17 beta-Estradiol and Testosterone has been performed before and after therapy. *Pygeum Africanum* extract administration improved all the urinary parameters we investigated; prostatic echography relieved reduction of peri-urethral edema. Also an improvement of sexual behaviour has been obtained; but we have not found significant differences between serum hormonal levels before and after therapy, as well as for NPTR.

Arch Ital Urol Nefrol Androl. 1991 Sep;63(3):341-5

EFFICACY AND ACCEPTABILITY OF TADENAN (PYGEUM AFRICANUM EXTRACT) IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA (BPH): A MULTICENTRE TRIAL IN CENTRAL EUROPE.

Pygeum africanum extract is available as Tadenan in many countries, including those in central and eastern Europe, for the treatment of mild to moderate BPH. Its efficacy and acceptability have been demonstrated in numerous open and placebo-controlled studies in large populations. The present open three-centre efficacy and safety study was conducted according to common protocol at urology clinics in the Czech and Slovak Republics and in Poland, in order to confirm the therapeutic profile of *Pygeum africanum* in conditions of daily practice, using International Prostate Symptom Score (IPSS) and flowmetry assessments. Men aged 50-75 years and in compliance with the selection criteria (including IPSS \geq 12, quality of life (QoL) score \geq 3, and maximum urinary flow \leq 15 ml/s) were first examined then recalled after two weeks during which no treatment was provided (washout and check of stability). If still compliant, they were entered at this point into a two-month period of treatment with *Pygeum africanum* extract 50 mg twice daily. There followed a further one-month period without treatment, the objective being to evaluate the persistence of any effects observed during the previous two months of *Pygeum africanum* administration. The primary efficacy parameter investigated was IPSS; the other efficacy parameters were QoL, nocturnal frequency, maximum urinary flow, average urinary flow, post-voiding residual volume and prostatic volume, after one and two months of *Pygeum africanum* treatment and one month after stopping treatment. A total of 85 patients were evenly distributed between the three centres and completed the entire study. At inclusion their mean IPSS was 16.17, QoL was 3.60 and nocturia was 2.6 times per night. The changes in subjective scores, IPSS and QoL after the two-month treatment period were highly statistically significant with mean improvements of 40% and 31%, respectively. Nocturnal frequency was reduced by 32% and the mean reduction was again highly statistically significant. Mean maximum urinary flow, average urinary flow and urine volume were also statistically significantly improved, but the modest improvement in post-voiding volume did not reach statistical significance. The improvements, which exceeded those observed with placebo in earlier studies, were maintained after one month without treatment indicating an interesting persistence of clinically useful activity. Prostatic volume and quality of sexual life remained unchanged throughout. No treatment-related adverse effects were observed. In conclusion, under conditions of daily practice, *Pygeum africanum* extract induces significant improvement in IPSS and uroflowmetry parameters. These positive effects are accompanied by a very satisfactory safety profile with the overall result of a substantial improvement in QoL.

Curr Med Res Opin. 1998;14(3):127-39

EFFICACY OF PYGEUM AFRICANUM EXTRACT IN THE MEDICAL THERAPY OF URINATION DISORDERS DUE TO BENIGN PROSTATIC HYPERPLASIA: EVALUATION OF OBJECTIVE AND SUBJECTIVE PARAMETERS.

A placebo-controlled doubleblind multicenter study. The efficacy of an extract of *Pygeum africanum* in the treatment of micturitional disorders due to benign prostatic hyperplasia was tested in a multicentre doubleblind trial versus placebo. Capsules containing 50 mg of *Pygeum africanum* extract or placebo were administered at a dosage of 1 capsule in the morning and 1 capsule in the evening over a period of 60 days. 263 patients were included in this study, which was carried out in 8 centers in Germany, France, and Austria. Evaluation was mainly based on quantitative parameters such as residual urine, uroflowmetry and the precise monitoring of diurnal and nocturnal pollakiuria. Treatment with the *Pygeum africanum* extract led to a marked clinical improvement: a comparison of the quantitative parameters showed a significant difference between the *Pygeum africanum* group and the placebo group with respect to therapeutic response. The characteristic subjective symptoms of micturitional disorders, which were evaluated by the patients in a qualitative manner, were also significantly improved by administration of *Pygeum africanum* extract. Overall assessment at the end of therapy, showed that micturition improved in 66% of the patients treated with *Pygeum africanum* extract, as compared with an improvement of 31% in the placebo group. The difference was significant at the statistical level of p less than 0.001. During therapy with *Pygeum africanum* extract, gastrointestinal side effects occurred in 5 patients. Treatment was discontinued in three of those cases.

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