Vitamin D And Prostate Cancer Prevention And Treatment

The fifth of the annual research conferences of the American Institute for Cancer Research was held September l-2, 1994, at the L'Enfant Plaza Hotel in Washington, DC. Appropriately, in view of current directions in research, the theme was "Diet and Cancer: Molecular Mechanisms of Interactions". This proceedings volume contains chapters from the platform presentations and abstracts from the poster session held on the end of the first day. The subtopics for the tl;rree sessions held were "Retinoids, Vitamins A and Din Cancer Prevention and Therapy," "Choline and Lipids: Signal Transduction, Gene Expression and Growth Regulation," and "Dietary Factors and Regulation of Oncogenes, Growth and Differentiation. " A general overview on vitamins A and D emphasized that A and D, in addition to their established roles in vision, reproduction, and bone mineral homeostasis, may play significant roles in regulating cell function. Vitamin A metabolites, trans-retinoic acid and 9-cis-retinoic acid, regulate growth and differentiation. Furthermore, vitamin A deprived animals were more susceptible to both spontaneous and carcinogen-induced tumors. Epidemiological studies showed a correlation between low A intake and higher incidences of certain types of human cancers. Conversely, all-trans retinoic acid is useful in treatment and control of certain types of cancer. Physiologically, Vitamin D is converted to the active form, l ,25-dihydroxyvitamin D (VD). VD regulates hormone production and secretion, myocardial contractility, vascu 3 3 3 lar tone, and growth inhibition and differentiation.

"Sunlight, Vitamin D, and Prostate Cancer Risk" P. J. Hyde This science-based book is the first to demonstrate that in prostate cancer, insufficient access to the sun's short wavelength ultraviolet-B irradiance, necessary for photosynthesis of vitamin D, increases the risk of progression. The author surveys five populations with steeply elevated mortality from prostate cancer: African-North Americans, Norwegians, Swedes, Swiss and Danes. He finds that insufficient exposure to UV-B and inadequate photosynthesis of vitamin D is common to them all. Based on data extracted from World Health Statistics Annuals published in hard copy by the World Health Organization (WHO) in the 1980s, graphs depicting age-specific rates of prostate cancer mortality in Western European countries show that the Swiss rates are anomalously high for the country's latitude and may even surpass the rates for Norway and Sweden. Age-standardized (world) statistics published on-line by the WHO's International Agency for Research into Cancer (IARC) in its Globocan 2000 Cancer Epidemiology Database list identical rates for Norway, Sweden and Switzerland. The age-specific and age-standardized rates of prostate cancer mortality reported for other northern alpine countries are normal for the latitudes. Their more extensive surface areas and dispersed populations, with the great majority of their citizens residing far from the Alps, are consistent with this. In a population survey conducted by Swiss scientists from two institutions, blood levels of calcidiol (25-hydroxyvitamin D), the body's major circulating reservoir of the vitamin, were measured in a large representative sample of adults in all age groups. Subjects older than 65 were found to be spending less than 30 minutes a day outdoors in the summer. This is significant, because the capacity of exposed skin to photosynthesize vitamin D declines with age. Moreover, its inverse correlation with the intensiveness of pigmentation means that African-North Americans in particular need to spend longer periods of time in direct sunlight than may be possible for a variety of reasons. The book contends that many aging individuals residing far from the Equator can achieve year-round sufficiency in vitamin D through relatively frequent, brief periods of exposure to sunlight, reinforced in winter by adequate supplementation. Published research indicating how many international units of the vitamin may be needed daily is also discussed. There is a detailed description of the mechanism whereby minute quantities of a powerful steroid hormone (calcitriol) metabolized from calcidiol, bind to the hormone's receptors (VDR) within the nuclei of the cells. By a signalling procedure involving "cross talk" between the hormone and the VDR, and resulting changes in the transcription of genes within the nuclei, proliferation of malignant cells can be inhibited. Besides prostate cancer, several other common cancers are reported to be associated with deficiencies of vitamin D. "Recommended reading for anyone interested in lowering their risk of prostate cancer"---Christopher Morash, MD, FRCSC, Chief of Urosurgical Oncology, Ottawa Regional Cancer Centre, Ottawa, Ontario. ISBN: 1-4010-8258-0 (paperback) and 1-4010-8259-9 (hardback). Surface: Xlibris Corporation at International Plaza II, Suite 340, Philadelphia, PA, U.S.A. 19113 Web: http://www.xlibris.com/bookstore/bookdisplay.asp'bookid=17092 Email: Orders@Xlibris.com Price (paperback): U

Cancer Treatment: Conventional and Innovative Approaches is an attempt to integrate into a book volume the various aspects of cancer treatment, compiling comprehensive reviews written by an international team of experts in the field. The volume is presented in six sections: i) Section 1: Cancer treatment: Conventional and innovative pharmacological approaches; ii) Section 2: Combinatorial strategies to fight cancer: Surgery, radiotherapy, backytherapy, chemotherapy, and hyperthermia; iii) Section 3: The immunotherapy of cancer; iv) Section 4: Multidisciplinarity in cancer therapy: nutrition and beyond; v) Section 5: Supportive care for cancer patients; vi) Section 6: Perspectives in cancer biology and modeling. Ultimately, we hope this book can enlighten important issues involved in the management of cancer, summarizing the state-of-the-art knowledge regarding the disease control and treatment; thus, providing means to improve the overall care of patients that daily battle against this potentially lethal condition.

"This report provides estimates of dietary supplement use for specific population groups over time. In addition to overall use of dietary supplements, this report focuses on estimates for specific nutrients consumed through dietary supplement use."--Cover.

The Nutrition and Health series of books has as an overriding mission to provide health professionals with texts that are considered essential because each includes: a synthesis of the state of the science; timely, in-depth reviews by the leading researchers in their respective fields; extensive, up-to-date fully annotated reference lists; a detailed index;

relevant tables and figures; identification of paradigm shifts and the consequences; of information between chapters, but targeted, inter-chapter refer virtually no overlap rals, suggestions of areas for future research; and balanced, data-driven answers to patient questions that are based on the totality of evidence rather than the findings of any single study. The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose training is both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authori ties from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research de findings to potential human health consequences.

The scientific rationale for this Idea Grant was to clarify whether modifiable, mainly nutritional, influence levels of IGF-l, IGFBP-3, 1,25 (OH)2 vitamin D (l,25(OH)2D), and 25(OH)vitamin D. High levels of IGF-l and low l,25(OH)2D have been shown to be related to elevated risk of prostate cancer. Some dietary factors that hypothetically impact on these serological factors, including total energy intake, calcium intake and protein intake, have been associated with prostate cancer risk. In the current study, none of the hypothesized factors showed correlations with l,25(OH)2D in 630 men. These results do not support our original hypothesis that 1,25 vitamin D is an important mediator of risk of several dietary risk factors of prostate cancer. We were able to demonstrate that intake of protein and minerals influence IGF-l levels moderately in 751 men, but men with high intakes of protein and minerals were not at higher risk of prostate cancer relative to men with low intakes of these. These findings suggest that the range of dietary influences on prostate cancer in generally well-fed populations is unlikely to have a major impact on risk of prostate cancer.

Many advances in vitamin D physiology and biochemistry have been made in recent years. Vitamin D metabolites and analogs have found increasing application in clinical medicine. The purpose of this text is to review what is known about vitamin D physiology and draw attention to areas of vitamin D research that have changed within the last 2-3 years. Additionally, information concerning clinical aspects of vitamin D is also presented. More than 40 scientists have generously contributed chapters to this text; I thank them for their efforts. As might be expected, not everyone has the same point of view. Finally, I would like to acknowledge the secretarial and editorial efforts of Mrs. Cheryl Collins without whom this book would not have been completed. CONTRIBUTORS ETSUKO ABE, Department of Biochemistry, School of Dentistry, Showa University, 1-5-8, Hatanodai, Shinagawa-KU, Tokyo 142, Japan DAVID J. BAYLINK, Department of Medicine, Loma Linda University, Loma Linda, CA, and Pettis Veterans Hospital, 11201 Benton Street, Loma Linda, CA, 92357, USA NORMAN H. BELL, Department of Medicine, Medical University of South Carolina and Veterans Administration Medical Center, 109 Bee Street, Charleston, SC, 29403, USA WARNER M. BURCH, Jr. , Departments of Medicine and Physiology, Duke Univer sity Medical Center, Durham, NC, 27710, USA DAVID V. COHN, ICCRH, Inc. , 1238 Wyncrest Court, Arden Hills, MN, 55112, USA ROBERT A. CORRADINO, Department of Physiology, New York State College of Veterinary Medicine, Cornell University, 720 VRT, Ithaca, NY, 14853, USA HECTOR F.

Recent, groundbreaking medical research has made a connection between Vitamin D deficiency and 17 types of cancers, including breast, colon, and prostate. Illnesses such as influenza, diabetes, multiple sclerosis, and coronary heart disease have also been connected to a lack of this vitamin. Until not too long ago, not getting enough Vitamin D (the sunshine vitamin) was only associated with rickets, the childhood bone disease. Now, Soram Khalsa, M. D., sheds new light on the power of this long-forgotten vitamin. He reveals how to recognize signs of Vitamin D deficiency, which has reached epidemic proportions in North America, and then shares insights from his Beverly Hills medical practice, where he normalizes his own patients' Vitamin D levels for their optimal health.

Calcitriol plays a critical role in maintaining mineral homeostasis but also exhibits antiproliferative activity in many cancers. We have shown that the antiproliferative actions of calcitriol in LNCaP human prostate cancer cells are mediated mainly by induction of insulin-like growth factor binding protein 3 (IGFBP-3). We also found that androgens increase expression of IGFBP-3 and cause a major enhancement of IGFBP-3 stimulation by calcitriol. The purpose of this study was to determine the molecular mechanisms involved in calcitriol and androgen regulation of IGFBP-3. We cloned 6 kb of the IGFBP-3 promoter and demonstrated its responsiveness to calcitriol and androgen in transactivation assays. Computer analysis identified a putative vitamin D response element (VDRE) and a potential androgen response element (ARE) in the IGFBP-3 promoter. We proved each to be inducible by calcitriol or androgen. Mutations created in the VDRE or ARE resulted in a loss of IGFBP-3 induction confirming the critical response element sequences. Chromatin immunoprecipitation assays demonstrated that calcitriol recruited VDR/RXR heterodimers to the VDRE site and androgen recruited the AR/AR homodimer to the ARE site. In conclusion, we have identified a functional VDRE and ARE in the human IGFBP-3 promoter that directly mediates the action of calcitriol and androgen to regulate IGFBP-3 expression.

Genes may play a strong role in prostate cancer etiology but epidemiological studies suggest that prostate cancer risk is largely determined by gene and environmental interactions. In order to explore the effects of UV exposure, serum Vitamin D, and skin color on prostate cancer risk in African American men. Ninety affected AA men with histologically diagnosed adenocarcinoma of the prostate; PSA of> 2.5 ng/ml and a positive DRE were recruited under the direction of Dr. Mireku-Boateng from the division of Urology at the Howard University Hospital and forty age and ethnicity matched controls have been recruited through the monthly free screenings program at the Howard University Cancer Center. For each prostate cancer patient and matched control we have collected information on personal and family history, and blood samples for candidate gene testing. In order to measure the intake of dietary Vitamin D each subject completed the standardized food frequency questionnaire and the serum circulating levels of 25-OH Vitamin D have been measured by Enzyme Immunoassay for all participants. To elucidate their exposure to UV from childhood until current the UV exposure questionnaire has been completed. In addition their constitutive skin color (M-index) measured has been done by using the dermaspectrophotometer.

Abstract: Prostate cancer cells contain vitamin D receptor for 1a,25-dihydroxyvitamin D3 [1a,25(OH)2D3], which is known to inhibit the proliferation and invasiveness of these cells. Normal prostate cells and several prostate cancer cell lines convert 25-hydroxyvitamin D 3 [25(OH)D3] to 10,25(OH)2 D3 . In addition, epidemiological evidence correlated an inverse relationship between vitamin D status and prostate cancer risk, suggesting that vitamin D and its metabolism may be important in the development and growth of prostate cancer. Using a human androgen-insensitive prostate cancer xenograft mouse model,

the effect(s) of dietary vitamin D and calcium on tumor growth were evaluated. DU-145 cells were implanted in mice and monitored for 76 days. Serum, for 25(OH)D and calcium determinations, and tumors, for immunohistochemistry and gene expression analysis, were collected. Tumor growth was highest in mice fed a normal calcium, vitamin D deficient diet. Diets containing high calcium, with or without vitamin D, did not alter tumor growth compared to the normal calcium vitamin D sufficient diet. To elucidate the role of 1a,25(OH) 2 D3 production by 25-hydroxyvitamin D-1a-hydroxylase (CYP27131) on prostate cancer cell growth, LNCaP cells were stably transfected with CYP27B1 (1a-S cells). 1a-S cells converted 25(OH)D 3 to 1a,25(OH)2 D3 unlike untransfected LNCaP cells. There was a dose dependent decrease in 3 H-thymidine incorporation in 1a,25(OH)2 D3 treated LNCaP cells, not seen with 25(OH)D3 treatment, and in 1a-S cells treated with 25(OH)D3 . In DU-145 cells, the decrease in 3 H-thymidine incorporation seen with 25(OH)D3 treatment was diminished with suppression of CYP2781 with siRNA. 1a,25(OH)2 D3 treated LNCaP cells and 25(OH)D3 treated 1a-S cells demonstrated increased G1 phase accumulation and apoptosis while 25(OH)D3 treatment had no effect in LNCaP cells. 1a,25(OH) 2 D3 , but not 25(OH)D3 , in LNCaP cells and 25(OH)D 3 in la-S cells increased cell cycle regulatory gene expression; CDKN1A , CDKNIB and TP53 , and opposing apoptotic genes, BAX and BCL-2 , were induced and suppressed, respectively. 25-hydroxyvitamin D-24-hydroxylase (24-OHase) suppression enhanced 25(OH)D3 and 1a,25(OH)2 D 3 effects in LNCaP and la-S cells. This study supports the hypothesis that local production of 1a,25(OH)2 D is important to inhibiting prostate cancer growth and suggests dietary vitamin D as a preventive agent in androgen-insensitive prostate cancer.

Substantial data indicate the broad importance of vitamin D-based signaling in normal human physiology and the broad effects of vitamin D deficiency. Vitamin D may play a role not only in the control of bone and mineral metabolism, but also appears to be involved in immune function, cardiovascular health, thrombosis and vasculogenesis and neuromuscular function. Considerable epidemiologic data demonstrate that low vitamin D serum levels occur very commonly in normal adult populations and that vitamin D deficiency is associated with an enhanced risk of cancer death from lung, prostate, head & neck, colorectal and other gastrointestinal cancers. In addition, preclinical data provide evidence that calcitriol and other active analogues of calcitriol have anti-proliferative, pro-differentiative, pro-apoptotic and anti-angiogenic activity in numerous in-vitro and in-vivo models. It is quite clear that, while it requires high exposure to calcitriol to induce these effects, such exposure can be readily achieved when high dose intermittent therapy is given.

Vitamin D, a steroid hormone, has mainly been known for its effects on bone and osteoporosis. The current therapeutic practices expand into such markets as cancer research, pediatrics, nephrology, dermatology, immunology, and genetics. This 3e includes over 100 chapters covering everything from chemistry and metabolism to mechanisms of action, diagnosis and management, new analogs, and emerging therapies. This complete reference works is a must-have resource for anyone working in endocrinology, osteology, bone biology, or cancer research. *Most comprehensive, up-to-date two-volume set on Vitamin D *Initial chapters cover the chemistry and metabolism of vitamin D, role in mineralization, other target organs, and general physiological effects *Second volume is more clinically oriented addressing deficiency problems (including diagnosis, interactions in the endocrine system, and involvement in malignancies) *Further sections on emerging uses for treatments of auto-immune diseases and diabetes *New chapters on squamous cell cancer, brain cancer, thyroid cancer and many more *Over 600 illustrations and figures available on CD

Vitamin D, a steroid hormone, has mainly been known for its effects on bone and osteoporosis. The current therapeutic practices expand into such markets as cancer research, pediatrics, nephrology, dermatology, immunology, and genetics. This second edition includes over 100 chapters covering everything from chemistry and metabolism to mechanisms of action, diagnosis and management, new analogs, and emerging therapies. This complete reference works is a must have resource for anyone working in endocrinology, osteology, bone biology, or cancer research. *Most comprehensive, up-to-date two-volume set on Vitamin D *New chapters on squamous cell cancer, brain cancer, thyroid cancer and many more *Further sections on emerging uses for treatments of auto-immune diseases and diabetes *Over 600 illustrations and figures available on CD

Background: The concept that cancer incidence and mortality are related to latitude was first suggested in 1930. Since then, there have been a plethora of studies addressing that connection. Studies of vitamin D have demonstrated its anti-proliferative, anti-angiogenesis and differentiating properties which are all anti-neoplastic. The relationship between prostate cancer and latitude has long been suspected. Prostate cells have vitamin D receptors and enzymes for hydroxylation of vitamin D metabolites and enabling anti-carcinogenetic effects. As a result of these findings, many ongoing studies are evaluating whether vitamin D deficiency impacts prostate cancer risk. This review summarizes the last two years of published studies on this topic. Methods: The search used Ovid/Medline, PubMed, CINAHL and Web of Science databases limited to include clinical studies, English language, major journals and including articles from 2007 to the present. Review of the abstracts produced the relevant studies, and the bibliographies of these articles led to other sources not found in the search. Keywords: prostate cancer, risk, vitamin D and vitamin D deficiency. Results: Five studies reviewed from the end of 2007 to the present were germane to the research topic. One study was an observational study, one a prospective study and the remainder were case control studies from much larger randomized controlled trials. Only one case reviewed the relationship between solar radiation and prostate cancer risk and all the relationships were positive for low solar radiation and higher prostate cancer risk. Three studies reviewed the relationship of serum levels of vitamin D and prostate cancer risk relative to polymorphisms of the VDR and two found that low levels of serum vitamin D increase prostate cancer risk, especially aggressive prostate cancer risk. One large study examining serum concentrations of only one vitamin D metabolite found no association with PCa. Conclusions: Vitamin D deficiency is a widespread health issue. There is an increased risk of prostate cancer with low vitamin D levels. The risk is greater with more aggressive disease. Conflicting results regarding PCa risk and VDR polymorphisms in light of low vitamin D levels, and it may be a one-time serum sample which causes these discrepancies. There is an association between solar radiation and PCa risk, need to follow the serum levels or solar exposure of patients much younger. Both metabolites need to be measured to understand the impact on prostate cancer risk, especially since the data shows an increased risk with aggressive disease with the one typically not measured. One serum sample does not provide information needed for understanding the relationship between vitamin D and PCa. More prospective studies beginning at an earlier age with more serum samples and solar radiation studies are needed in order to better understand the relationship between prostate cancer and vitamin D.

It was estimated that in 2008, 1,437,180 patients would receive a new cancer diagnosisand 565,650individualswould die of cancer (Jemal et al. 2008).Since the vast majority of patients dying of cancer will have had anticancer therapy, both c- ventional chemotherapy and novel targeted therapy, it can be concluded that these patients are dying with drug resistant cancer. The term multidrug resistance is also apt – in that these patients die after having undergone multiple rounds of different and structurally unrelated cancer therapies. However, for some, the concept of m- tidrug resistance is a worn out idea, stemming from disappointment with the drug resistancereversalstrategiesthatwerecarriedoutinthe1990susingpumpinhibitors to block drug resistance mediated by P-glycoprotein, product of the MDR-1 gene. However, if one takes the larger de?nition – multidrug resistance as simultaneous resistance to multiple structurally unrelated

anticancer therapies – its existence c- not be denied. The purpose of this book is to explore new concepts related to drug resistance in cancer, including resistance to the new molecularly targeted agents. Perhaps new terminology is needed for resistance that occurs following therapy with the targeted agents: Novel Targeted Agent Resistance (NTR). Alternatively, we can return to the original de?nition of multidrug resistance as simply the res- tance to multipleagents that occurs in the course of normalcancer progression.This resistance is likely to be mediated by many factors.

This study focuses on the enzyme, CYP24 which hydroxylates vitamin D acting to catalyze the first step in the breakdown of Vitamin D, effectively limiting this growth inhibitory signaling pathway. We are testing the hypothesis that through the inhibition of CYP24 using an siRNA approach we can convert prostate cancer cells that are resistant to the antiproliferative actions of Vitamin D to cells that are growth inhibited at low concentrations of Vitamin D. Inhibition of 1,25(OH)2D3 CYP24 mediated metabolism to potentiate Vitamin D actions in prostate cancer shows great potential for both a chemopreventative approach and the treatment of advanced hormone refractory cancer in patients. We have tested CYP24 siRNA constructs, ketoconazole and silencer control siRNA on three cell lines (LNCaP, PC3 and DU145) and evaluated CYP24 protein expression, mRNA expression, and growth inhibition. We are in the process of developing the stable transfected cell lines and optimal approach to enhance Vitamin D action in resistant cells.

Prostate cancer patients receive surgery or radiation therapy (RT) as treatment for cancer. Among patients receiving RT, 50% have an elevation of PSA within five years of treatment. These patients then receive hormones. We will test the theory that chemopreventive agents, which can prevent or delay the growth of prostate cancer cells in the laboratory, may prevent or delay the reappearance of prostate cancer in patients who have undergone RT for their prostate cancer. We will have prostate cancer patients who have already undergone RT take a chemopreventive agent A SYNTHETIC FORM OF VITAMIN D, la-hydroxyvitamin D5 for two years and see if their reoccurrence rate can be decreased. Unlike vitamin D, D5 does not make calcium in the bloodstream reach levels that cause serious side effects. Forty patients will participate and be randomized to D5 or placebo arms. A biopsy will be done at the end of the study and the tissue will be analyzed for any benefit of D5 in decreasing the recurrence of prostate cancer and also for any differences between the groups in terms of expressed intermediate molecular biomarkers. We have finalized the clinical protocol in 2003-04 and earned approval, pending minor revisions, from our IRB.

The purpose of this research is to gain an understanding of the vitamin D - androgen interaction in prostate cancer. Calcitriol, the active hormonal form of vitamin D, induces androgen receptors (AR) in prostate cells. Major findings thus far involve studies in two areas. First, the ability of vitamin D and retinoids to regulate AR levels in LNCaP human prostate cancer cells. These studies have led to a publication which is included in the Appendix The major conclusion is that the growth inhibitory activity of vitamin D and retinoid hormones is androgen. dependent and the activity can be blocked by the AR antagonist, Casodex. Second, is a study of prostate cancer cells derived from a bone metastasis in a patient whose prostate cancer had progressed to become androgen independent. As detailed in a paper that is in press, the cells have a double mutation in the AR. Further study o: these cells is in progress in an attempt to determine the nature of the changes that led to androgen-independence. The significance of this work is that it will increase our understanding of factors that stimulate prostate cancer growth and will attempt to develop mechanisms to inhibit the growth and progression of prostate cancer.

While the skeletal effects of vitamin D are well-documented, the role and importance of vitamin D outside of bone health has not been well-established. Vitamin D receptors are located in nearly every tissue of the body, and low levels of vitamin D are associated with a range of various diseases. This book provides an in-depth examination of these extraskeletal effects of vitamin D and the associations between vitamin D deficiency and various disease states. Beginning with a review of the biochemistry and physiology of vitamin D, subsequent chapters investigate its relationship to autoimmune and infectious diseases, various forms of cancer, endocrine issues such as diabetes, obesity and reproductive function, cardiovascular disease and muscle weakness. Concluding chapters discuss the role of vitamin D in neurological disorders, including Alzheimer's Disease, and cognitive function. Focusing on extraskeletal effects only across a range of conditions, Extraskeletal Effects of Vitamin D will be an important resource for clinical endocrinologists and primary care physicians.

Because diseases of the bone are often less acute and less lifethreatening than dis eases of the circulatory system, gastrointestinal tract, kidney, liver, and the nervous system, they have received a disproportionately smaller amount of attention in the medical world. With the average increasing life span of man as a result of improve ments in modern medicine, espe~ially in the pediatric field, the seriousness of many metabolic bone diseases has indeed become more obvious. In addition, other improvements in medicine, such as hemodialysis for the preservation of renal failure patients, have permitted the development of other consequences of diseased kidneys, one of which is the appearance of renal osteodystrophy. Finally, the appearance of several genetic disorders in the area of metabolic bone disease has been underscored by the solution of other pediatric diseas~s of much more serious consequences. These emerging problems all suggest that much remains to be learned concerning the sys temic control of bone, both as a structural organ and as a reservoir for the important elements of calcium and phosphorus so essential for the support of life in complex multicellular organisms of which man is the most important. As will be demonstrated in the historical portion of this manuscript, the existence of the three most important humoral factors regulating bone metabolism and func tion are now known.

A comprehensive, highly readable overview of the topics discussed at the First International Symposium on "Vitamin D Analogs in Cancer Prevention and Therapy" held in Homburg/Saar, Germany in May 2002. Leading researchers discuss our present knowledge of the vitamin D system in cancer. Topics range from the newest findings in molecular biology, epidemiology, synthesis and metabolism of vitamin D to new concepts for the use of vitamin D analogs in cancer prophylaxis and treatment. The book provides essential up-to-date information for every researcher or clinician interested in the biology of vitamin D or cancer.

Prostate cancer (PCa) is the most commonly diagnosed malignancy and the second leading cause of cancer death in North American men [1]. According to the American Cancer Society more than 232,000 men will be diagnosed with PCa in 2005 and approximately 10% of these men will die of the disease [1]. Primary therapy for PCa involves the removal of the prostate by surgery or radiation therapy. Unfortunately, after initial treatment PCa often recurs. Androgens regulate normal prostate development and growth. Surgical or medical androgen deprivation has been used as the standard treatment for PCa that fails primary therapy [2, 3]. Although there is a good initial response to androgen ablation in most men, tumors will progress to androgen independence resulting in death [4] since there is currently no adequate treatment for this advanced disease. Our current investigation is aimed at the development of new therapies to treat PCa. la,25- Dihydroxyvitamin D3 (calcitriol), the hormonally active form of

vitamin D, is a promising new therapeutic agent for PCa therapy [5-15].

1,25-Dihydroxyvitamin D3 (1,25-(OH)2D3), the most active metabolite of vitamin D, inhibits the proliferation of a variety of cell types including adenocarcinoma of the prostate. The primary mechanism for the antiproliferative effects of 1,25-(OH)2D3 in prostate cancer cells is inhibition of G1 to S phase cell cycle progression. While 1,25-(OH)2D3-mediated growth inhibition requires the vitamin D receptor (VDR), a ligand activated transcription factor, expression of functional VDR is not sufficient. To define target genes that might participate in the antiproliferative actions of 1,25-(OH)2D3, we developed a derivative of the human prostate cancer cell line, LNCaP, which retains transcriptionally active VDRs but unlike parental LNCaP cells, is not growth inhibited by 1,25-(OH)2D3. Gene expression profiling of these resistant cells (termed VitD. R) compared to control LNCaP cells revealed two novel 1,25-(OH)2D3-inducible genes, GADD45G and MIG6. The expression of GADD45G and MIG6 genes was induced by 1,25-(OH)2D3 in LNCaP but not in the resistant VitD. R or in ALVA31 cells, human prostate cancer cells that exhibit natural resistance to growth inhibition by 1,25-(OH)2D3 despite expression of functional VDR. Ectopic expression of GADD45G but not MIG6 in either LNCaP or ALVA31 cells resulted in accumulation of cells in G1 and inhibition of proliferation equal to or greater than that caused by 1,25-(OH)2D3 treatment. While GADD45G is induced by androgens in prostate cancer cells, up-regulation of GADD45G by 1,25-(OH)2D3 was not dependent on androgen receptor signaling further refuting a requirement for androgens/androgen receptor in vitamin D-mediated growth inhibition in prostate cancer cells. These data introduce two novel 1,25-(OH)2D3-regulated genes and establish GADD45G as a growth inhibitory protein in prostate cancer. Further, defects in vitamin D-mediated induction of GADD45G may underlie vitamin D resistance in prostate cancer cells. We previously demonstrated that the antiproliferative actions of 1,25-(OH)2D3 in prostate cancer cells are associated with decreased CDK2 activity and increased stability of the cyclin dependent kinase inhibitor (CKI) p27KIP1. We defined a novel mechanism that may underlie these antiproliferative effects, 1,25-(OH)2D3 -mediated cytoplasmic relocalization of CDK2, which would provide a unifying mechanism for the observed effects of 1,25-(OH)2D3 on CDK2 and p27. In the present study, we investigated the role of CDK2 cytoplasmic relocalization in the antiproliferative effects of 1,25-(OH)2D3. CDK2 was found to be necessary for prostate cancer cell proliferation. In contrast, while p27KIP1 is induced by 1,25-(OH)2D3, this CKI was completely dispensable for 1,25-(OH)2D3-mediated growth inhibition. Reduction of CDK2 activity by 1,25-(OH)2D3 was associated with decreased T160 phosphorylation, a residue whose phosphorylation in the nucleus is essential for CDK2 activity. Since cyclin E is important for nuclear translocation of CDK2, we investigated cyclin E effects on 1,25D-mediated growth inhibition. Ectopic expression of cyclin E blocked 1,25-(OH)2D3-mediated cytoplasmic relocalization of CDK2 and all antiproliferative effects of 1,25-(OH)2D3, yet endogenous levels of cyclin E or binding to CDK2 were not affected by 1,25-(OH)2D3. Similarly, knockdown of the CDK2 substrate retinoblastoma (Rb), which causes cyclin E up-regulation, resulted in resistance to 1,25-(OH)2D3 mediated growth inhibition. VitD. R cells did not exhibit 1,25-(OH)2D3-mediated cytoplasmic relocalization of CDK2. Importantly, targeting CDK2 to the nucleus of LNCaP cells blocked G1 accumulation and growth inhibition by 1,25-(OH)2D3. These data establish central roles for CDK2 nuclear-cytoplasmic trafficking and uncoupling of VDR in the regulation of antiproliferative target genes in the mechanisms of 1,25-(OH)2D3-mediated growth inhibition in prostate cancer cells. Since 1,25-(OH)2D3 continues to be evaluated for its chemotherapeutic and chemopreventative potential, elucidating the mechanism of 1,25-(OH)2D3 antiproliferative effects is critical in the determination of 1,25-(OH)2D3 responsiveness and the design of individualized treatment strategies.

The Role of Vitamin D in the Prevention and Treatment of Prostate Cancer.

Vitamin D: Volume 2: Health, Disease and Therapeutics, Fourth Edition, authoritatively covers the evidence for new roles for vitamin D, ranging from cardiovascular disease, to cancer, diabetes, inflammatory bowel disease, multiple sclerosis and renal disease. This collection represents a who’s who of vitamin D research and the coverage is appropriately broad, drawing in internal medicine, orthopedics, oncology and immunology. Clinical researchers will gain a strong understanding of the molecular basis for a particular area of focus. Offers a comprehensive reference, ranging from basic bone biology, to biochemistry, to the clinical diagnostic and management implications of vitamin D Saves researchers and clinicians time in quickly accessing the very latest details on the diverse scientific and clinical aspects of Vitamin D, as opposed to searching through thousands of journal articles Chapter authors include the most prominent and well-published names in the field Targets chemistry, metabolism and circulation, mechanisms of action, mineral and bone homeostasis and vitamin D deficiency Presents a clinical focus on disorders, analogs, cancer, immunity, inflammation, disease and therapeutic applications

Prostate cancer is by far the most common cancer in men and the second leading cause of death due to cancer. It comprises a mixed group of tumours displaying varying clinical behaviour: while some have a very aggressive course, others are rather indolent. Prevention of prostate cancer and discrimination between aggressive and indolent forms are important clinical goals and the acquisition of significant new evidence on means of achieving these aims makes this book particularly timely. A wide range of topics are covered by leading authorities in the field. The biology and natural history of prostate cancer are reviewed and the role of lifestyle and dietary factors, assessed. Detailed attention is paid to risk prediction biomarkers and to the role of novel high-throughput nucleic acid-based technologies in improving risk prediction and thereby allowing tailored approaches to cancer prevention. Potential means of chemoprevention of prostate cancer are also reviewed in depth, covering the very positive new data on the impact of aspirin as well as evidence regarding 5?-reductase inhibitors, DFMO and lycopene. Guidance is provided on the differentiation of aggressive from indolent disease and the policy and research implications of recent findings are examined. This book will be of interest to both clinicians and researchers.

Men of African-American descent are at a significantly higher risk of developing prostate cancer than white men. There are reasons why more black people are dying of prostate cancer. Vitamin D. The deficiency of it. Black people need the sun more than white folks. It takes less time under the sun for a white skin to manufacture all the needed vitamin D. It requires more time for the dark skin to warm up and even more time to start manufacturing vitamin D. Black folks tend to shy away from the sun because the sun will make them "darker." That is a bad strategy.When you walk through a park in the summer you see sunbathers. I don’t know about you but these sunbathers are mostly white folks who need the sun far less than black folks. Ordinarily, the people that are mostly in need of sunbathing while partially naked are the black skinned people. This is because dark skin need the intense sunlight the most. Black skin is a marvel. It is black for a reason. It evolved to be black so as to be able tap into the Sun and get those properties that will give you long life, full of health, stronger and biologically efficient. The white skin needs the Sun but not that much. More than fifteen minutes in the Sun without sunscreen and they will get burns and ultimately peels. Black folks need it far more and they don’t get scorched in fifteen minutes even without sunscreen.But some Africans and other diaspora Africans avoid the Sun. Is it not ironic that while some black folks are lightening up, some white folks are darkening down? They call it tanning and it does not come cheap either. People of African descent, living in cold climate, can have a natural Sun protection factor (SPF) of up to 13 as compared to 3-4 for whites. For equatorial and other hot weather blacks, it is even better. This advantage for African Americans and black immigrants, can also be a disadvantage. It is a double edged sword for black people not living in equatorial climate. You just need to have proper information with which to turn the disadvantage into an advantage.Vitamin D is getting a lot of attention lately even in medical circles. Many people are having their vitamin D levels tested and are surprised to find out that they are low in this essential hormone. What exactly is Vitamin D and why should you care about your Vitamin D levels? How does sunscreen use, contribute to deficiency in this important vitamin, and what can we do to remedy the deficiency?This book has been written in such a way that you will be able to absorb the contents in less than it takes to travel from one point to another in a bus or train ride.

1,25-(OH)2 vitamin D3 inhibits cell proliferation of a variety of cancers including prostate. In the human prostate cancer cell line LNCaP, 1,25-(OH)2 vitamin D3-mediated growth inhibition is attributed to cell cycle G1 accumulation which correlates with a robust decrease of cyclin-dependent kinase 2 (CDK2) activity and pronounced relocalization of CDK2 into the cytoplasm. Nuclear targeting CDK2 blocks the 1,25-(OH)2 vitamin D3-mediated growth inhibition and cell cycle G1 accumulation. Further, the nuclear targeted CDK2 blocks 1,25-(OH)2 vitamin D3-mediated inhibition of CDK2 activity and nuclear exclusion in LNCaP cells. Therefore, CDK2 cytoplasmic relocalization is the key mechanism for 1,25-(OH)2 vitamin D3 effects. Since cyclin E is important for CDK2 nuclear localization and activation, 1,25-(OH)2 vitamin D3 may exert its effects through regulation of cyclin E. Cyclin E but not a cyclin E mutant deficient in CDK2 binding reverses 1,25-(OH)2 vitamin D3-mediated antiproliferation which suggests the involvement of cyclin E as a mechanism. However, the studies showed no effects of 1,25-(OH)2 vitamin D3 on cyclin E levels, intracellular localization or binding to CDK2. In order to develop a model for studying 1,25-(OH)2 vitamin D3-mediated antiproliferative effects, LNCaP vitD. R cell line, a vitamin D resistant LNCaP derivative, was generated by continuously culturing of LNCaP cells in medium supplemented with 10 nM 1,25-(OH)2 vitamin D3 for over 9 months. The initial characterization of this cell line showed complete resistance to 1,25-(OH)2 vitamin D3-mediated effects. Analysis of vitamin D regulation of VDR target gene expression revealed that vitamin D resistance in LNCaP vitD. R cells was not due to deregulation of VDR signaling. HDAC inhibitor Trichostatin A (TSA) did not confer sensitivity of LNCaP vitD. R cells to vitamin D treatment suggested the resistance to 1,25(OH)2 vitamin D3 effect of LNCaP vitD. R cells is not due to histone deacetylase remodeling of the chromatin structure which leads to inhibition of gene transcription. While the partial sensitization of LNCaP vitD. R cells to 1,25(OH)2 vitamin D3 effect by demethylation reagent 5-Aza-2-deoxycytidine treatment suggested a set of genes involved in 1,25(OH)2 vitamin D3-mediated antiproliferative effects is silenced via hypermethylation in LNCaP vitD. R cells. These results suggested LNCaP vitD. R cell line is a useful tool and further studies to elucidate the genes involved in this effect will help uncover the mechanisms of 1,25(OH)2 vitamin D3-mediated antiproliferative effects.

The third edition is a comprehensive and updated overview of positive and negative effects of UV-exposure, with a focus on Vitamin D and skin cancer. Researchers, oncologists,and students will be provided with the most significant and timely information related to topics such as the epidemiology of skin cancer, the immune system and skin cancer, ultraviolet damage, DNA repair and Vitamin D in Nonmelanoma skin cancer and malignant melanoma. There have been a number of new, scientific findings in this fast moving field that necessitated a thoroughly updated and revised edition including new Vitamin D metabolites and skin cancer, new findings on the beneficial effects of UV and solar UV and skin cancer, adverse effects of sun protection and sunscreens, sun exposure and mortality, and more. The book will summarize essential, up-to-date information for every clinician or scientist interested in how to balance the positive and negative effects of UV?exposure to minimize the risks of developing vitamin D deficiency and skin cancer.

Vitamin D is without a doubt, THE most important missing link to your best health! Vitamin D Diet: Benefits of Vitamin D for Your Optimal Health, will absolutely blow you away with the information revealed in this guide. Be aware: if you feel run-down and lousy all the time, you might have a vitamin D deficiency! Start to feel better and help protect your body from bad health with Vitamin D3. Inside this guide, you will learn about the different types of the “D” vitamin. “Imagine feeling better all year around, but especially on those gloomy gray winter days...” The solution for that and many other common health issues comes right from a bottle! If you are looking for an easy solution to start feeling much better on gray days, one scientifically proven recommendation is to add vitamin D to your diet. Peter Kornfeld reveals how you too, can benefit from increasing your daily intake of this important vitamin. Let's get started!

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