東海大學畜產學研究所

博士論文

老化與鹿茸給予對早老化小鼠骨骼動態及其相關內泌素變化之影響

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Dissertation

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Effects of Aging and Dietary Antler Supplementation on Bone Status and Changes of Related Hormones in SAM Mice

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中英文縮寫對照表

英文縮寫	英文全名	中文
ALP	alkaline phosphatase	鹼性磷酸鹽酶
CT	calcitonin	降鈣素
Ca	calcium	鈣
CaBP	calcium-binding protein	鈣結合蛋白質
cAMP	cyclic AMP	環狀腺苷單磷酸
DPD	deoxypyridinoline crosslinks	去氧比林二酚胺交叉連結物
ICTP	type I collagen C-terminal crosslinked telopeptide	第一型膠原蛋白羧基末端胜肽
Ig G	immunoglobulin G	免疫球蛋白 G
IL-1	interleukin-1	介白素-1
IL-6	interleukin-6	介白素-6
LH	luteinizing hormone	排卵素
M	months of age	月齡
MAO	monoamine oxidase	單胺氧化酶
OHPr	hydroxyproline	羥基脯胺酸
Orx	orchidectomy	睪丸切除術
Ovx	ovariectomy	卵巢切除術

英文縮寫	英文全名	中文
P	phosphorus	磷
PICP	procollagen type I C-terminal propeptide	前膠原蛋白羧基前胜肽
PTH	parathyroid hormone	甲狀旁腺素
SAM	senescence accelerated mice	早老化小鼠
Sham	sham operation	僞手術
VDR	vitamin D receptor	維生素 D 受體
$1,25(OH)_2D_3$	1,25-dihydroxycholecalciferol	1,25-二羥基膽利鈣醇

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摘　要

本論文之研究目的，乃在探討老化對 SAMP8 小鼠鈣原狀穩定 (calcium homeostasis) 及其骨骼動態之影響，以評估 SAMP8 小鼠是否適合作爲研究骨質疏鬆症之動物模式，並探討鹿茸給予對於骨骼代謝相關參數之影響。本研究計分五個試驗進行。試驗一：雌性早老化小鼠 (senescence accelerated mouse, SAM) — SAMP8 (早老化品系之一) 與 SAMR1 (對照品系) 二品系小鼠，分別於 2.5 月齡及 3-12 月齡間每隔一個月，收集其血液及股骨樣品一次，每次每一品系各犧牲 8 隻小鼠，分析其與骨骼代謝有關之各項參數，包括血漿中之鈣、磷、降鈣素 (calcitonin, CT)、甲狀旁腺素 (parathyroid hormone, PTH) 與 1,25-dihydroxycholecalciferol [1,25$(OH)_2D_3$] 濃度，以及股骨之密度與骨鈣含量 (以上參數在其他四個試驗中亦被測定之)。結果顯示，雌性 SAM 小鼠之血鈣濃度於試驗期間，並不隨年齡而變，始終維持於一狹小範圍。雌性 SAMP8 與 SAMR1 小鼠血漿中之磷、CT 濃度皆隨年齡之增加而下降，血漿中之 PTH 與 1,25$(OH)_2D_3$ 濃度則皆隨年齡之增加而上升。此等參數之變化曲線，在 SAMP8 者皆較在 SAMR1 者爲左移。二品系 SAM 小鼠之股骨密度與骨鈣含量，於試驗初期皆隨年齡之增加而增加，

並於 6 月齡時達到顛峰，之後逐漸減少，而此等參數之變化曲線，在 SAMP8 者亦皆較在 SAMR1 者爲低。試驗二：以雄性 SAMP8 與 SAMR1 小鼠爲試驗動物，其餘與試驗一相同。所有參數之分析結果，大致與試驗一所見者相似。試驗三：雌、雄性 SAMP8 與 SAMR1 小鼠分別於 2 月齡時，施以性腺切除術或僞手術，並於 3、6 與 12 月齡時收集樣品。結果顯示，雌性 SAM 小鼠血漿中磷濃度較雄性者爲低，$1,25(OH)_2D_3$ 濃度則較雄性者爲高，而其他參數在兩性別間則無差異。去除性腺可使血漿中 PTH 與 $1,25(OH)_2D_3$ 濃度上升，而使血漿中磷、CT 濃度與骨密度、骨鈣含量下降。試驗四：雌性 SAMP8 與 SAMR1 小鼠分別於 2 月齡時，施以卵巢切除術或僞手術，並分別餵予添加 0.2% 鹿茸飼糧或一般飼糧。於 3、6、9、12 與 15 月齡時，分別收集樣品一次。另外，並於上述月齡時，進行爲期 7 天之代謝試驗，收集其糞便及尿液樣品，記錄其採食量、糞便重量及尿液體積，以測定鈣與磷之表相消化率及尿中排出量。結果顯示，血漿中及股骨中之參數變化，與試驗一、三所見者相似。隨年齡之增加，雌性 SAMP8 與 SAMR1 小鼠腸道鈣與磷之表相消化率皆下降，而尿液中之鈣與磷排泄量則上升。去除卵巢可使腸道鈣與磷之表相消化率下降，而使尿液中之鈣與磷排泄量增加。長期餵予鹿茸飼糧，可延緩 SAM 小鼠血漿中磷、CT 濃度與骨密度、

骨鈣含量之下降，以及血漿中 PTH 濃度之上升，但對血漿中之 $1,25(OH)_2D_3$ 濃度則無影響，並可提昇腸道對鈣與磷之吸收作用及腎臟對鈣與磷之重吸收作用。試驗五：雄性 SAMP8 與 SAMR1 小鼠分別於 2 月齡時，施以睪丸切除術或僞手術，其餘處理與試驗四相同。所有參數之分析結果，大致與試驗四所見者相似。本研究顯示：以 SAMP8 小鼠從事有關老化及骨骼生理之研究，較正常品系更爲適合；SAMP8 小鼠在去除性腺後，從事骨質疏鬆症研究極爲適合，可謂係一理想之骨質疏鬆症動物模式；長期鹿茸給予對骨質流失具有緩和之效果。

參考文獻

毛鳳志、李武軍與高松。1983。鹿茸精對心血管的藥理作用。中成藥研究 12：28-30。

王本祥與陳曉光。1989。次黃嘌呤對單胺氧化酶的抑制作用。藥學學報 8：573-577。

王本祥與周秋麗。1991。鹿茸的化學、藥理及臨床研究進展。藥學學報 26：714-720。

王本祥、劉愛晶、王慶貴、魏廣仁、崔景朝、楊娜與程秀娟。1985。鹿茸多糖的藥理研究。中國藥理通訊 3：9-12。

王本祥、楊明、程欣、程秀娟、邸琳、劉愛晶與崔志勇。1987。胃特靈對各種實驗性胃潰瘍影響的研究。中藥藥理與臨床 4：32-37。

王本祥、陳曉光與張偉。1990。鹿茸有效成分對小鼠肝臟 RNA 和蛋白質合成的影響。藥學學報 25：321-325。

王本祥、張偉與王學農。1994。鹿茸多肽對雄鼠黃體生成素和睪丸酮分泌的影響。中成藥研究 16：33-34。

王家沖。1989。慢性腎衰腎虛型大鼠氨基酸代謝與中藥治療實驗觀察。現代中醫 4：33-34。

庄司政滿。1988。麝香代用品鹿茸的藥理作用。國外醫學：中醫中藥分冊 10：39。

李時珍 (明)。1988。本草綱目。國立中國醫藥研究所。臺北。

李鳳林。1989。鹿茸精注射液對雛雞發育的影響。哈爾濱醫科大學學報 26：386-387。

李恆夫、姜樹興與楊錫坤。1993。飼糧中添加梅花鹿鹿茸對鼠生長性能及造血功能之影響。中畜會誌 22 (增刊)：61。

那琦與謝文全 (重輯)。1977。重輯名醫別錄。中國醫藥學院中國藥學研究所。

臺中。

岡西爲人 (重輯)。1982。重輯新修本草。國立中國醫藥研究所。臺北。

林培英與潘竟鏘。1984。梅花鹿茸精對小鼠血清免疫球蛋白的影響。中成藥研究 12：28-29。

郁知非 (主編)。1979。貧血及紅細胞系疾病。浙江人民出版社 21-24。

凌一揆 (主編)。1984。中藥學。上海科學技術出版社 219。

唐慎微 (宋) 撰。岡西爲人、難波恆雄與李煥燊考訂。1971。經史證類大觀本草。國立中國醫藥研究所。臺北。

唐慎微 (宋) 撰。張存惠 (元) 重刊。1976。那琦解題并序。重修政和經史證類備用本草。南天書局。臺北。

孫星衍 (清)。1985。神農本草經。五洲出版社。臺北。

孫曉波與周重楚。1986。鹿茸精對機體免疫功能的影響。中成藥研究 2：24-25。

孫曉波與周重楚。1987。鹿茸精強壯作用的研究。中藥藥理與臨床 3：11-13。

徐可福與林時田。1983。鹿茸精穴位注射治療陽萎 42 例簡介。浙江中醫雜誌 18：498。

郝朴。1984。「陽春藥」治療陽萎 105 例臨床觀察。中西醫結合雜誌 2：117。

高云瑞、孫尙奎、李柏岩、羅大力、楊帆、張麗霞與李文漢。1990。鹿茸精注射液性激素樣作用的實驗研究。中藥藥理與臨床 2：23-24。

陳梅芳。1988。大白鼠 5/6 腎切除所致慢性腎衰竭動物模型的中藥治療觀察。中國醫藥學報 6：24-27。

陳瑞楠。2001。鹿茸萃取液對鹿茸細胞增殖之影響。碩士論文。東海大學。臺中。

陳曉光、王本祥與吳延東。1990a。鹿茸總脂對單胺氧化酶的抑制作用。中草藥 21：21-24。

陳曉光、楊明、王本祥、曲文、崔勇與王岩。1990b。人工培養鹿茸細胞的藥理作用。中藥藥理與臨床 1：30-32。

許喬木、那琦、甘偉松與游春淑。1979。臺灣產鹿類藥材之藥用動物學調查研究。中國醫藥學院研究年報 10：405-467。

楊立軍。1983。單味鹿茸治癒再生障礙性貧血。湖南醫藥雜誌 1：46。

趙學敏 (清)。1978。本草綱目拾遺。旋風書局。臺北。

黎鏡。1986。鹿茸田雞散治療虛勞。四川中醫 12：21-22。

劉華昌與楊榮森。2001。骨質疏鬆症防治指引：男性骨質疏鬆症。中華民國內分泌學會。臺北。

蔡益堅與何彥瑤。1997。臺灣地區老年髖骨骨折罹病天數及經濟成本。蔡益堅 (主編)。臺灣地區衛生部門優先順序檢定之先趨研究計劃－老年髖骨骨折病患之追蹤調查研究論文集。臺灣省庭計劃研究所。臺中。

佐野昌之、今井政、田原溶夫与滝川勝雄。1972。鹿茸抽出物 (Pantocrin) の一般薬理作用および抗原性試験。応用薬理 4：717-726。

梶原大義与国分信彦。1973。鹿茸抽出剤 (Pantocrin) のラット脊髄神経の酵素活性に対する作用。応用薬理 5：741-745。

Aaron, J.E., Makins, N.B., and Sagreiya, K. 1987. The microanatomy of trabecular bone loss in normal aging men and women. *Clin. Orthop.* 15: 260-271.

Abbiati, G., Arrigoni, M., Frignani, S., Longoni, A., Bartucci, F., and Castiglioni, C. 1994. Effect of salmon calcitonin on deoxypyridinoline (Dpyr) urinary excretion in healthy volunteers. *Calcif. Tissue Int.* 55: 346-348.

Abou-Samra, A.B., Juppner, H., Force, T., Freeman, M.W., Kong, X.F., Schipani, E., Urena, P., Richards, J., Bonventre, J.V., and Potts, J.T. Jr. 1992. Expression cloning of a common receptor for parathyroid hormone and parathyroid hormone-related peptide from rat osteoblast-like cells: A single receptor stimulates intracellular accumulation of both cAMP and inositol triphosphates and increase intracellular free calcium. *Proc. Natl. Acad. Sci. U.S.A.* 89: 2732-2736.

Akatsu, T., Takahashi, N., Udagawa, N., Sato, K., Nagata, N., Moseley, J.M., Martin, T.J., and Suda, T. 1989. Parathyroid hormone (PTH)-related protein is a potent stimulator of osteoclast-like multinucleated cell formation to the same extent as PTH in mouse marrow cultures. *Endocrinology* 125: 20-35.

Akedo, Y., Hosoi, T., Mizuno, Y., Ikegami, A., Inoue, S., Nakamura, T., Ouchi, Y., and Orimo, H. 1992. Vitamin K_2 modulates proliferation and function of osteoblastic cells *in vitro*. *J. Bone Miner. Res.* 7 (Suppl. 1): 213.

Alatalo, S.L., Peng, Z., Janckila A.J., Kaija, H., Vihko, P., Vaananen, H.K., and Halleen, J.M. 2003. A novel immunoassay for the determination of tartrate-resistant acid phosphatase 5b from rat serum. *J. Bone Miner. Res.* 18: 134-139.

Alevizaki, C.C., Ikkos, D.G., and Singhelakis, P. 1973. Progressive decrease of true intestinal calcium absorption with age in normal man. *J. Nucl. Med.* 14: 760-762.

Amiel, C., Kuntziger, H., and Richet, G. 1970. Micropuncture study of handling of phosphate by proximal and distal nephron in normal and parathyroidectomized rat. Evicence for distal reabsorption. *Pfluegers. Arch* 317: 93-109.

Anonymous. 2002. MAO-B inhibitors for the treatment of Parkinson's disease. *Mov. Disord.* 17: S38-44.

AOAC. 2000. *Official methods of analysis*, 17th ed. Arlington, VA, Association of Official Analytical Chemists.

Ardaillou, R. 1982. The endocrinology of renal calcium and phosphate homeostasis. In: Parsons, J.A., ed. *Endocrinology of Calcium Metabolism.* NY, Raven Press. p.p.41-85.

Arjmandi, B.H., Hollis, B.W., and Kalu, D.N. 1994. *In vivo* effect of 17β-estradiol on intestinal calcium absorption in rats. *Bone Miner.* 26: 181-189.

Armbrecht, H.J., Forte, L.R., and Halloran, B.P. 1984. Effect of age and dietary

calcium on renal 25(OH)D metabolism, serum 1,25$(OH)_2$D and PTH. *Am. J. Physiol.* 246: E266-E270.

Armbrecht, H.J., Boltz, M.A., Christakos, S., and Bruns, M.E.H. 1998. Capacity of 1,25-dihydroxyvitamin D to stimulate expression of calbindin D changes with age in the rat. *Arch. Biochem. Biophys.* 352: 159-164.

Audi, L., Garcia-Ramirez, M., and Carrascosa, A. 1999. Genetic determinants of bone mass. *Horm. Res.* 51: 105-123.

Bae, D.S. 1975. Study on the effect of velvet on growth of animals. I. Effect of velvet of different levels on weight gain, feed efficiency and development of organs of chicken. *Korean J. Anim. Sci.* 17: 571-576.

Bae, D.S. 1976. Study on the effect of velvet on growth of animals. II. Effect of velvet on the growth internal organs and blood picture of chicken. *Korean J. Anim. Sci.* 18: 342-348.

Baille, S.P., Davison, C.E., Johnson, F.J., and Francis, R.M. 1992. Pathogenesis of vertebral crush fractures in men. *Age Ageing* 21: 139-141.

Banu, J., Wang, L., and Kalu, D.N. 2002. Age-related changes in bone mineral content and density in intact male F344 rats. *Bone* 30: 125-130.

Baran, D.T., and Braverman, L.E. 1991. Thyroid hormones and bone mass. *J. Clin. Endocrinol. Metab.* 72: 1182-1183.

Barger-Lux, M.J., Heaney, R.P., Hayes, J., DeLuca, H.F., Johnson, M.L., and Gong, G. 1995. Vitamin D receptor gene polymorphism, bone mass, body size, and vitamin D receptor density. *Calcif. Tissue Int.* 57: 161-162.

Baron, R. 1977. Importance of the intermediate phases between resorption and formation in the measurement and understanding of the bone remodeling sequence. In: *Meunier, P.J., ed. Bone Histomorphometry: Proceedings of the Second International Workshop.* Toulouse, Société de la Nouvelle Imprimerie Fournie. p.p.179-183.

Bell, N.H., Epstein, S., Greene, A., Shary, J., Oexmann, M.J., and Shaw, S. 1985.

Evidence for alteration of the vitamin D-endocrine system in obese subjects. *J. Clin. Invest.* 76: 370-373.

Bellino, F.L. 2000. Nonprimate animal models of menopause: Workshop report. *Menopause* 7: 14-24.

Beresford, J.N., Gallagher, J.A., and Russel, R.G.G. 1986. 1,25-dihydroxyvitamin D_3 and human bone-derived cells *in vitro*: Effects on alkaline phosphatase, type I collagen and proliferation. *Endocrinology* 119: 1776-1785.

Black, A., Tilmont, E.M., Handy, A.M., Scott, W.W., Shapses, S.A., Ingram, D.K., Roth, G.S., and Lane, M.A. 2001. A nonhuman primate model of age-related bone loss: A longitudinal study in male and premenopausal female rhesus monkeys. *Bone* 28: 295-302.

Bikle, D.D. 1999. Regulation of bone mineral homeostasis: An integrated view. In: Favus, M.J., 4th ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* NY, Raven Press. p.p.76-80.

Bingham, P.J., Brazell, I.A., and Owen, M. 1969. The effect of parathyroid extract on cellular activity and plasma calcium levels *in vivo*. *J. Endocrinol.* 45: 387-400.

Birge, S.J., and Miller, R. 1977. The role of phosphate in the action of vitamin D on the intestine. *J. Clin. Invest.* 60: 980-988.

Body, J.J., and Heath, H. III. 1983. Estimates of circulating monomeric calcitonin: Physiological studies in normal and thyroidectomized man. *J. Clin. Endocrinol. Metab.* 57: 897-903.

Borderie, D., Roux, C., Toussaint, B., Dougados, M., Ekindjian, O.G., and Cherruau, B. 2001. Variability in urinary excretion of bone resorption markers: Limitations of a single determination in clinical practice. *Clin. Biochem.* 34: 571-577.

Bressot, C., Meunier, P.J., Chapuy, M.C., Lejeune, E., Edouard, C., and Darby, A.J. 1979. Histomorphometric profile, pathophysiology and reversibility of

corticosteroid-induced osteoporosis. *Metab. Bone Dis. Relat. Res.* 1: 303-311.

Brickman, A.S., Harrtenbower, D.L., Norman, A.W., and Coburn, J.W. 1977. Action of 1-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 on mineral metabolism in man. *Am. J. Clin. Nutr.* 30: 1064-1069.

Burton, P., Nyssen-Behets, C., and Dhem, A. 1989. Haversian bone remodeling in human fetus. *Acta Anat.* 135: 171-175.

Burr, D.B. 1993. Remodeling and the repair of fatigue damage. *Calcif. Tissue Int.* 53 (Suppl. 1): S75-S80.

Bushinsky, D.A. 1997. Disorders of calcium and phosphorus homeostasis. In: Greenberg, A., ed. *Primer on Kidney Diseases.* San Diego, Academic Press. p.p.106-113.

Bushinsk, D.A. and Monk, R.D. 1998. Calcium. *Lancet* 352: 306-311.

Caniggia, A., Nuti, R., Galli, M., Lore, F., Turchetti, V., and Righi, G.A. 1986. Effect of a long-term treatment with 1,25-dihydroxyvitamin D_3 on osteocalcin in postmenopausal osteoporosis. *Calcif. Tissue Int.* 38: 328-332.

Cann, C.E., Martin, M.C., Genant, H.K., and Jaffe, R.B. 1984. Decreased spinal mineral content in amenorrheic women. *JAMA* 251: 626-629.

Carlsson, A. 1954. The effect of vitamin D on the absorption of inorganic phosphate. *Acta Physiol. Scand.* 31: 301-307.

Carney, S.L. 1997. Calcitonin and human renal calcium and electrolyte transport. *Miner. Electrolyte. Metab.* 23: 43-47.

Case, L.R., and Aurbach, G.D. 1970. The effect of parathyroid hormone on the concentration of adenosine 3'5'-monophosphate in skeletal tissue *in vitro*. *J. Biol. Chem.* 245: 1520-1526.

Chambers, T.J., Darby, J.A., and Fuller, K. 1985. Mamalian collagenase predisposes bone surfaces to osteoclastic resorption. *Cell Tissue Res.* 241: 671-675.

Chen, J.Y. 1973. Chinese health foods and herb tonics. *Am. J. Chin. Med.* 1: 225-247.

Chen, T.L., Cone, C.M., Morey-Holton, E., and Feldman, D. 1983. 1 alpha,25-dihydroxyvitamin D_3 receptors in cultured rat osteoblast-like cells: Glucocorticoid treatment increases receptor content. *J. Biol. Chem.* 258: 4350-4355.

Christiansen, C. 1993. Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. *Am. J. Med.* 94: 646-650.

Christensen, M.S., Hagen, C., Christiansen, C., and Transbol, I. 1982. Dose-response evaluation of cyclic estrogen/gestagen in postmenopausal women: Placebo-controlled trial of its gynecologic and metabolic actions. *Am. J. Obstet. Gynecol.* 144: 873-879.

Clemens, T.L., Zhou, X.Y., Myles, M., Endres, D., and Lindsay, R. 1986. Serum vitamin D_2 and vitamin D_3 metabolite concentrations and absorption of vitamin D_2 in elderly subjects. *J. Clin. Endocrinol. Metab.* 63: 656-660.

Clifford, D.H., Lee, M.O., Kim, Y.C., and Lee, D.C. 1979. Can an extract of deer antlers alter cardiovascular dynamics? *Am. J. Chin. Med.* 7: 345-350.

Colman, R.J., Lane, M.A., Binkley, N., Wegner, F.H., and Kemmitz, J.W. 1999. Skeletal effects of aging in male rhesus monkeys. *Bone* 24: 17-23.

Colvard, D.S., Eriksen, E.F., Keeting, P.E., Wilson, E.M., Lubahn, D.B., French, F.S., Riggs, B.L., and Spelsberg, T.C. 1989. Identification of androgen receptors in normal human osteoblastlike cells. *Proc. Natl. Acad. Sci. U.S.A.* 86: 854-857.

Cramer, C.G., Parkes, C.O., and Copp, D.H. 1969. The effect of chicken and hog calcitonin on some parameters of calcium, phosphorus and magnesium metabolism in dogs. *Can. J. Physiol. Pharmacol.* 47: 181-184.

Cuzzocrea, S., Mazzon, E., Dugo, L., Genovese, T., Di Paola, R., Ruggeri, Z., Vegeto, E., Caputi, A.P., Van De Loo, F.A., Puzzolo, D., and Maggi, A. 2003.

Inducible nitric oxide synthase mediates bone loss in ovariectomized mice. *Endocrinology* 144: 1098-1107.

Diamond, T., Stiel, D., and Posen, S. 1989. Osteoporosis in hemochromatosis: Iron excess, gonadal deficiency, or other factors? *Ann. Intern. Med.* 110: 430-436.

Diamond, T., Stiel, D., Lunzer, M., Wilkinson, M., Roche, J., and Posen, S. 1990. Osteoporosis and skeletal fractures in chronic liver disease. *Gut* 31: 82-87.

Dalsky, G., Stocke, K., Ehsani, A., Slatopolsky, E., Lee, W., and Brige, S. 1988. Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women. *Ann. Intern. Med.* 108: 824-828.

Daniell, H.W. 1976. Osteoporosis of the slender smoker. *Arch. Intern. Med.* 136: 298-304.

Davie, M., and Lawson, D.E.M. 1980. Assessment of plasma 25-hydroxyvitamin D response to ultraviolet irradiation over a controlled area in young and elderly subjects. *Clin. Sci.* 58: 235-242.

Deftos, L.J., Weisman, M.H., Williams, G.W., Karpf, D.B., Frumar, A.M., Davidson, B.J., Parthemore, J.G., and Judd, H.L. 1980. The influence of age and sex on plasma calcitonin in human beings. *N. Engl. J. Med.* 302: 1351-1353.

Delmas, P.D. 1995. Biochemicalmarkers of bone turnover in osteoporosis. In: Riggs, B.L., and Melton, L.J. III, 2nd ed. *Osteoporosis: Etiology, Diagnosis and Management.* NY, Raven Press. p.p. 319-334.

Delmas, P.D., Stenner, D., Wahner, H.W., Mann, K.G., and Riggs, B.L. 1983. Increase in serum bone gamma-corboxyglutamic acid protein with aging in women: Implications for the mechanism of age-related bone loss. *J. Clin. Invest.* 71: 1316-1321.

Dequeker, J., Nijs, J., Verstraeten, A., Geusens, P., and Gevers, G. 1987. Genetic determinants of bone mineral content at the spine and radius: A twin study.

Bone 8: 207-209.

Diamond, T., Stiel, D., Lunzer, M., Wilkinson, M., and Posen, S. 1989. Ethanol reduces bone formation and may cause osteoporosis. *Am. J. Med.* 86: 282-288.

Donahue, H., Fryer, M., Eriksen, E.F., and Heath, H. 1988. Differential effects of parathyroid hormone fragment PTH(1-34) on cytosolic calcium in cultured osteoblast like cells. *J. Biol. Chem.* 263: 13522-13527.

Donaldson, C., Hulley, S., Vogel, J., Hattner, R., Bayers, J., and McMillan, D. 1970. Effects of prolonged bed rest on bone mineral. *Metabolism* 19: 1071-1084.

Dykman, D.R., Gluck, D.S., Murphy, W.A., Hahn, T.J., and Hahn, B.H. 1985. Evaluation of factors associated with glucocorticoid-induced osteopenia in patients with rheumatic diseases. *Arthritis Rheum.* 28: 361-368.

Eastell, R., Yergey, A.L., Vieira, N.E., Cedel, S.L., Kumar, R., and Riggs, B.L. 1991. Interrelationship among vitamin-D metabolism, true calcium-absorption, parathyroid function, and age in women: Evidence of an age-related intestinal resistance to 1,25-dihydroxyvitamin-D action. *J. Bone Miner. Res.* 6: 125-132.

Ebeling, P.R., Sandgren, M.E., DiMagno, E.P., Lane, A.W., DeLuca, H.F., and Riggs, B.L. 1992. Evidence of an age-related decrease in intestinal responsiveness to vitamin D: Relationship between serum 1,25-dihydroxyvitamin D_3 and intestinal vitamin D receptor concentrations in normal women. *J. Clin. Endocrinol. Metab.* 75: 176-182.

Einhorn, T.A. 1996. The bone organ system: Form and function. In: Marcus, R., Feldman, D., and Kelsy, J., eds. *Osteoprosis.* San Diego, Academic Press. p.p.3-22.

Epstein, S., Bryce, G., Hinman, J.W., Miller, O.N., Riggs, B.L., Hui, S.L., and Johnston, C.C. 1986. The influence of age on bone mineral regulating

hormones. *Bone* 7: 421-425.

Eriksen, E.F., Colvard, D.S., Berg, N.J., Graham, M.L., Mann, K.G., Spelsberg, T.C., and Riggs, B.L. 1988. Evidence of estrogen receptors in normal human osteoblast-like cells. *Science* 241: 84-86.

Eriksen, E.F., Hodgson, S.F., Eastell, R., Cedel, S.L., O'Fallon, W.M., and Riggs, B.L. 1990. Cancellous bone remodeling in type I (postmenopausal) osteoporosis: Quantitative assessment of rates of formation, resorption, and bone loss at tissue and cellular levels. *J. Bone Miner. Res.* 5: 311-319.

Farach-Carson, M.C. 2001. Bioactive analogs that simulate subsets of biological activities of 1 alpha, $25(OH)_2D_3$ in osteoblasts. *Steroids* 66: 357-361.

Fares, J.E., Choucair, M., Nabulsi, M., Salamoun, M., Shahine, C.H., and Fuleihan, G.E-H. 2003. Effect of gender, puberty, and vitamin D status on biochemical markers of bone remodeling. *Bone* 33: 242-247.

Favus, M.J. 1985. Factors that influence absorption and secretion of calcium in the small intestine and colon. *Am. J. Physiol.* 248: G147-G157.

Fauvs, M.J. 2002. Intestinal absorption of calcium, magnesium, and phosphorus. In: Coe, F.L., and Favus, M.J., 2nd ed. *Disorders of Bone and Mineral Metabolism.* NY, Lippincott Williams & Wilkins. p.p.48-73.

Fedarko, N.F., Vetter, U.K., and Gehron Robey, P. 1992. Age-related changes in hyaluronan, proteoglycan, collagen and osteonectin synthesis by human bone cells. *J. Cell Physiol.* 151: 215-227.

Festing, M.F.W. 1993. Origins and characteristics of inbred strain of mice. *Mouse Genome.* 91: 471-472.

Finkelstein, J.S., Klibanski, A., Neer, R.M., Greenspan, S.L., Rosenthal, D.I., and Crowley, W.F. Jr. 1987. Osteoporosis in men with idiopathic hypogonadotropic hypogonadism. *Ann. Intern. Med.* 106: 354-361.

Fisher, E.C., Nelson, M.E., Frontera, W.R., Turksoy, R.N., and Evans, W.J. 1986. Bone mineral content and levels of gonadotropins and estrogens in

amenorrheic running women. *J. Clin. Endocrinol. Metab.* 62: 1232-1236.

Fleet, J.C., Harris, S.S., Wood, R.J., and Dawson-Hughes, B. 1995. The BsmI vitamin D receptor restriction fragment length polymorphism (BB) predicts low bone density in premenopausal black and white women. *J. Bone Miner. Res.* 10: 985-990.

Foresta, C., Ruzza, G., Mioni, R., Guarneri, G., Gribaldo, R., Meneghello, A., and Mastrogiacomo, I. 1984. Osteoporosis and decline of gonadal function in the elderly male. *Horm. Res.* 19: 18-22.

Fox, K.M., Magaziner, J., Sherwin, R., Scott, J.C., Plato, C.C., Nevitt, M., Cummings, S., and The Study of Osteoporotic Fractures Research Group. 1993. Reproductive correlates of bone mass in elderly women. *J. Bone Miner. Res.* 8: 901-908.

Fraher, L.J. 1993. Biochemical markers of bone turnover. *Clin. Biochem.* 26: 431-432.

Francis, R.M., Peacock, M., and Barkworth, S.A. 1984a. Renal impairment and its effects on calcium metabolism in elderly women. *Age Ageing* 13: 14-20.

Francis, R.M., Peacock, M., Taylor, G.A., Storer, J.H., and Nordin, B.E. 1984b. Calcium malabsorption in elderly women with vertebral fractures: Evidence for resistance to the action of vitamin D metabolites on the bowel. *Clin. Sci.* 66: 103-107.

Francis, R.M., Peacock, M., Aaron, J.E., Selby, P.L., Taylor, G.A., Thompson, J., Marshall, D.H., and Horsman, A. 1986. Osteoporosis in hypogonadal men: Role of decreased plasma 1,25-dihydroxyvitamin D, calcium malabsorption, and low bone formation. *Bone* 7: 261-268.

Franklyn, J.A., Betteridge, J., and Daykin, J. 1992. Long-term thyroxine treatment and bone mineral density. *Lancet* 340: 9-13.

Freudenheim, J.L., Johnson, N.E., and Smith, E.L. 1986. Relationship between usual nutrient intake and bone mineral content of owmen 35-65 years of age:

Longitudinal and cross sectional analysis. *Am. J. Clin. Nutr.* 44: 863-876.

Friedman, P.A. 1988. Basal and hormone-activated calcium absorption in mouse renal thick ascending limbs. *Am. J. Physiol.* 254: F62-F70.

Frizzell, R.A., and Schultz, S.G. 1972. Ionic conductances of extracellular shunt pathway in rabbit ileum. *J. Gen. Physiol.* 59: 318-346.

Frost, H.M. 1988. Vital biomechanics: Proposed general concepts for skeletal adaptations to mechanical usage. *Calcif. Tissue Int.* 42: 145-156.

Fujimoto, D., Morigachi, T., Ishida, T., and Hayashi, H. 1978. The structure of pyridinoline, a collagen crosslink. *Biochem. Biophys. Res. Commun.* 84: 52-57.

Gallagher, J.C. 1990. The pathogenesis of osteoporosis. *Bone Miner.* 9: 215-227.

Gallagher, J.C., Riggs, B.L., Eisman, J., Hamstra, A., Amaud, S.B., and DeLuca, H.F. 1979. Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients. *J. Clin. Invest.* 64: 729-736.

Gallagher, J.C., Riggs, B.L., and DeLuca H.F. 1980. Effect of estrogen on calcium absorption and serum vitamin D metabolites in post-menopausal osteoporosis. *J. Clin. Endocrinol. Metab.* 51: 1359-1364.

Gardiner, E.M., Baldock, P.A., Thomas, G.P., Sims, N.A., Henderson, N.K., Hollis, B., White, C.P., Sunn, K.L., Morrison, N.A., Walsh, W.R., and Eisman, J.A. 2000. Increased formation and decreased resorption of bone in mice with elevated vitamin D receptor in mature cells of the osteoblastic lineage. *FASEB J.* 14: 1908-1916.

Gärdsell, P., Johnell, O., Nilsson, B.E., and Sernbo, I. 1991. Bone mass in an urban and a rural population: A comparative, population-based study in southern Sweden. *J. Bone Miner. Res.* 6: 67-75.

Gaumet-Meunier, N., Coxam, V., Robins, S., Pastoureau, P., Pointillart, A., Davicco, M.J., Lebecque, P., and Barlet, J.P. 2000. Gonadal steroids and bone metabolism in young castrated male rats. *Calcif. Tissue Int.* 66: 470-475.

Glorieux, F.H., Travers, R., Taylor, A., and Norman, M. 1992. Normative data for iliac crest bone histomorphometry in growing children. *Bone* 13: A12.

Goret-Nicaise, M., and Dhem, A. 1984. The mandibular body of the human fetus: Histological analysis of the basilar part. *Anat. Embryol.* 169: 231-236.

Gowen, M., Wood, D.D., Ihrie, E.J., McGuire, M.K.B., and Russel, R.G.G. 1983. An interleukin 1-like factor stimulates bone resorption *in vitro*. *Nature* 306: 378-380.

Gruber, H.E., Ivey, J.L., Baylink, D.J., Matthews, M., Nelp, W.B., Sisom, K., and Chesnut, C.H. 1984. Long-term calcitonin therapy in postmenopausal osteoporosis. *Metabolism* 33: 295-303.

Gundberg, C.M., Looker, A.C., Nieman, S.D., and Calvo, M.S. 2002. Patterns of osteoclacin and bone specific alkaline phosphatase by age, gender, and race or ethnicity. *Bone* 31: 703-708.

Gurkan, L., Ekeland, A., Gautvik, K.M., Langeland, N., Ronningen, H., and Solheim, L.F. 1986. Bone changes after castration in rats. A model for osteoporosis. *Acta Orthop. Scand.* 57: 67-70.

Hammerman, M.R., Karl, I.E., and Hruska, K.A. 1980. Regulation of canine renal vesicle Pi transport by growth hormone and parathyroid hormone. *Biochim. Biophys. Acta* 603: 322-335.

Harrison, E., Adjei, A., Ameho, C., Yamamoto, S., and Kono, S. 1998. The effect of soybean protein on bone loss in a rat model of postmenopausal osteoporosis. *J. Nutr. Sci. Vitaminol.* 44: 257-268.

Hartwell, D., Riis, B.J., and Christiansen, C. 1990. Comparison of vitamin D metabolism in early healthy and late osteoporotic postmenopausal women. *Calcif. Tissue Int.* 47: 332-337.

Hasen, M.A., Hassager, C., Jensen, S.B., and Christiansen, C. 1992. Is heritability a risk factor for postmenopausal osteoporosis? *J. Bone Miner. Res.* 7: 1037-1043.

Hauge, E.M., Qvesel, D., Eriksen, E.F., Mosekilde, L., and Melsen, F. 2001. Cancellous bone remodeling occurs in specialized compartments lined by cells expressing osteoblastic markers. *J. Bone Miner. Res.* 16: 1575-1582.

Heaney, R.P. 1985. A unified concept of osteoporosis. *Am. J. Med.* 39: 377-380.

Heaney, R.P. 1993a. Nutritional factors in osteoporosis. *Ann. Rev. Nutr.* 13: 287-316.

Heaney, R.P. 1993b. Protein intake and the calcium economy. *J. Am. Diet Assoc.* 93: 1259-1260.

Heaney, R.P. 2003. How does bone support calcium homeostasis? *Bone* 33: 264-268.

Heaney, R.P., Gallagher, J.C., Johnston, C.C., Neer, R., Parfitt, A.M., and Whedon, G.D. 1982. Calcium nutrition and bone health in the elderly. *Am. J. Clin. Nutr.* 36: 986-1013.

Heaney, R.P., Recker, R.R., and Saville, P.D. 1990. Calcium balance and calcium requirements in middle-aged women. *Am. J. Clin. Nutr.* 30: 1603-1611.

Heaney, R.P., BargerLux, M.J., Davies, K.M., Ryan, R.A., Johnson, M.L., and Gong, G. 1997. Bone dimensional change with age: Interactions of genetic, hormonal, and body size variables. *Osteoporos. Int.* 7: 426-431.

Herzberg, M., Foldes, J., Steinberg, R., and Menczel, J. 1990. Zinc excretion in osteoporotic women. *J. Bone Miner. Res.* 5: 251-257.

Herzog, W., Minne, H., Deter, C., Leidig, G., Schellberg, D., Wüster, C., Gronwald, R., Sarembe, E., Kröger, F., Bergmann, G., Petzold, E., Hahn, P., Schepank, H., and Ziegler, R. 1993. Outcome of bone mineral density in anorexia nervosa patients 11.7 years after first admission. *J. Bone Miner. Res.* 8: 597-605.

Hock, J.M., Gera, I., Fonseca, J., and Raisz, L.G. 1988. Human parathyroid hormone-(1-34) increases bone mass in ovariectomized and orchidectomized rats. *Endocrinology* 122: 2899-2904.

Holick, M.F., Matsuoka, L.Y., and Wortsman, J. 1989. Age, vitamin D, and solar ultraviolet. *Lancet* 2: 1104-1105.

Holtrop, M.E., and Raisz, L.G. 1979. Comparison of the effects of 1,25-dihydroxycalciferol, prostaglandin E_2, and osteoclast activating factor with parathyroid hormone on the ultrastructure of osteoclasts in cultured long bones of fetal rats. *Calcif. Tissue Int.* 29: 201-205.

Holtrop, M.E., Raisz, L.G., and Simmons, H.A. 1974. The effects of parathyroid hormone, colchicines, and calcitonin on the ultrastructure and the activity of osteoclasts in organ culture. *J. Cell Biol.* 60: 346-355.

Hopper, J.L., and Seeman, E. 1994. The bone density of female twins discordant for tobacco use. *N. Engl. J. Med.* 330: 387-392.

Hosokawa, M. 1994. Grading score system: A method of evaluation of the degree of senescence in senescence-accelerated mouse (SAM). In: Takeda, T., ed. *The SAM Model of Senescence.* Amsterdam, Elsevier Science B.V. pp.23-28.

Hosokawa, M., Kasai, R., Higuchi, K., Takeshita, S., Shimizu, K., Hamamoto, H., Honma, A., Irino, M., Toda, K., Matsumura, A., Matsushita, M., and Takeda, T. 1984. Grading score system: A method for evaluation of the degree of senescence in Senescence Accelerated Mouse (SAM). *Mech. Aging Dev.* 26: 91-102.

Hosokawa, M., Abe, T., Higuchi, K., Shimakawa, K., Omori, Y., Matsushita, T., Kogishi, K., Deguchi, E., Kishimoto, Y., Yasuoka, K., and Takeda, T. 1997. Management and design of the maintenance of SAM mouse strains: An animal model for accelerated senescence and age-associated disorders. *Exp. Gerontol.* 32: 111-116.

Hosokawa, M., Umezawa, M., Higuchi, K., and Takeda, T. 1998. Interventions of senescence in SAM mice. *J. Anti-aging Med.* 1: 27-37.

Huang, S.L., Kakiuchi, N., Hattori, M., and Namba, T. 1991. A new monitoring system of cultured myocardial cell motion: Effect of pilose antler extract and

cardioactive agents on spontaneous beating of myocardial cell sheets. *Chem. Pharm. Bull.* 39: 384-387.

Hui, S.L., Slemenda, C.W., and Johnston, C.C. 1990. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporosis* 1: 30-34.

Isaia, G., Mussetta, M., Pecchio, F., Sciolla, A., di Stefano, M., and Molinatti, G.M. 1992. Effect of testosterone on bone in hypogonadal males. *Matrritas* 15: 47-51.

Ivey, J.L., and Baylink, D.J. 1981. Postmenopausal osteoporosis: Proposed roles of defective coupling and estrogen deficiency. *Metab. Bone Dis. Rel. Res.* 67: 75-78.

Jemmerson, R., and Low, M.G. 1987. Phosphotidylinositol anchor of HeLa cell alkaline phosphatase. *Biochemistry* 26: 5703-5709.

Jensen, J., Christiansen, C., and Rodbro, P. 1985. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. *N. Engl. J. Med.* 313: 973-975.

Jilka, R.L., Hangoc, G., Giarasole, G., Passeri, G., Williams, D.C., Abrams, J.S., Boyce, B., Broxmeyer, H., and Manolagas, S.C. 1992. Increased osteoclast development after estrogen loss: Mediation by interleukin-6. *Science* 257: 88-91.

Jowsey, J., and Riggs, B.L. 1970. Bone formation in hypercortisonism. *Acta Endocrinol.* 63: 21-28.

Jowsey, J., Riggs, B.L., Kelly, P.J., and Hoffman, D.L. 1978. Calcium and salmon calcitonin in treatment of osteoporosis. *J. Clin. Endocrinol.* 47: 633-639.

Kalu, D.N., and Chen, C. 1999. Ovariectomized murine model of postmenopausal calcium malabsorption. *J. Bone Miner. Res.* 14: 593-601.

Kalu, D.N., Cockerham, R., Yu, B.P., and Roos, B.A. 1983. Lifelong dietary modulation of calcitonin levels in rats. *Endocrinology* 113: 2010-2016.

Kalu, D.N., Hardin, R.R., and Cockerham, R. 1984. Evaluation of the pathogenesis of skeletal changes in ovariectomized rats. *Endocrinology* 115: 507-512.

Kalu, D.N., Masoro, E.J., Yu, B.P., Hardin, R.R., and Hollis, B.W. 1988. Modulation of age-related hyperparathyroidism and senile bone loss in Fischer rats by soy protein and food restriction. *Endocrinology* 122: 1847-1854.

Kalu, D.N., Liu, C.C., Hardin, R.R., and Hollis, B.W. 1989. The aged rat model of ovarian hormone deficiency bone loss. *Endocrinology* 124: 7-16.

Kanis, J.A. 1994. *Osteoporosis.* Oxford, Blackwell Science.

Kano, J., Sugimoto, T., Fukase, M., and Fujita, T. 1991. Activation of cAMP-dependent protein kinase is directly linked to the regulation of osteoblast proliferation by PTH. *Biochem. Biophys. Res. Commun.* 177: 365-369.

Kelly, P.J., Nguyen, T., Hopper, J., Pocock, N., Sambrook, P., and Eisman, J. 1993. Changes in axial bone density with age: A twin study. *J. Bone Miner. Res.* 8: 11-17.

Kent, N. 1997. Markers of bone turnover. *J. Int. Fed. Clin. Chem.* 9: 31-35.

Kiebzak, G.M., Smith, R., Gundberg, C.C., Howe, J.C., and Sacktor, B. 1988a. Bone status of senescent male rats: Chemical, morphometric, and mechanical analysis. *J. Bone Miner. Res.* 3: 37-45.

Kiebzak, G.M., Smith, R., Howe, J.C., and Sacktor, B. 1988b. Bone mineral content in the senescent rat femur: An assessment using single photon absorptiometry. *J. Bone Min. Res.* 3: 311-317.

Kiebzak, G.M., Smith, R., Howe, J.C., Gundberg, C.M., and Sacktor, B. 1988c. Bone status of senescent female rats: Chemical, morphometric, and biomechanical analyses. *J. Bone Miner. Res.* 3: 439-446.

Knapen, M.H.J., Hamuiyàk, K., and Vermeer, C. 1989. The effect of vitamin K supplementation on circulating osteocalcin (bone Gla protein) and urinary

calcium excretion. *Ann. Intern. Med.* 111: 1001-1005.

Kobayashi, S., Inoue, S., Hosoi, T., Ouchi, Y., Shiraki, M., and Orimo, H. 1996. Association of bone mineral density with polymorphism of the estrogen receptor gene. *J. Bone Miner. Res.* 11: 306-311.

Kobayshi, Y., Goto, S., Tanno, T., Yamazaki, M., and Moriya, H. 1998. Regional variations in the progression of bone loss in two different mouse osteopenia models. *Calcif. Tissue Int.* 62: 426-436.

Koeppen, B.M., and Stanton, B.A. 1997. *Renal Physiology.* 2nd ed. Missouri, Mosby-Year Book, Inc. USA.

Koh, E.T., Yeh, J.K., Bourdeau, J.E., Chen, M.M., and Om, A.S. 1996a. Bone histomorphometry of ovariectomized or orchiectomized rats fed a moderately magnesium-deficient fructose diet and treated with exogenous oestrogen or testosterone. *Magnes. Res.* 9: 13-21.

Koh, E.T., Owen, W.L., and Om, A.S. 1996b. Exogenous oestrogen affects calcium metabolism differently from exogenous testosterone in ovariectomized or orchiectomized rats fed a high fructose diet severely deficient in magnesium. *Magnes. Res.* 9: 23-31.

Kong, Y.C., and But, P.P.H. 1985. Deer: The ultimate medicinal animal (antler and deer parts in medicine). In: Fennessy, P.F., and Drew, K.R., eds. *Biology of Deer Production.* Royal Wellington, Soc. NZ Bull. p.p.311-324.

Koshihara, Y., Hoshi, K., and Shiraki, M. 1992. Enhancement of mineralization in human osteoblast-like cells by vitamin K_2 (menatetrenone). *J. Bone Miner. Res.* 7 (Suppl.): 209.

Kotowicz, M.A., Klee, G.G., Kao, P.C., O'Fallon, W.M., Hodgson, S.F., Cedel, S.L., Eriksen, E.F., Gonchoroff, E., Judd, H.L., and Riggs, B.L. 1990a. Relationship between serum intact parathyroid hormone concentrations and bone remodeling in type I osteoporosis: Evidence that skeletal sensitivity is increased. *Osteoporosis Int.* 1: 14-22.

Kotowicz, M.A., Melton, L.J., Cedel, S.L., O'Fallon, W.M., and Riggs, B.L. 1990b. Effect of age on variables relating to calcium and phosphorus-metabolism in women. *J. Bone Miner. Res.* 5: 345-352.

Kowarski, S., and Schachter, D. 1969. Effects of vitamin D on phosphate transport and incorporation into mucosal constituents of rat intestinal mucosa. *J. Biol. Chem.* 244: 211-217.

Kraenzlin, M.E., Seibel, M.J., Trechsel, V., Boerlin, V., Azria, M., Kraenzlin, C.A., and Haas, H.G. 1996. The effect of intranasal salmon calcitonin on postmenopausal bone turnover as assessed by biochemical markers: Evidence of maximal effect after 8 weeks of continuous treatment. *Calcif. Tissue Int.* 58: 216-220.

Krall, E.A., and Dawson-Hughes, B. 1991. Smoking and bone loss among postmenopausal women. *J. Bone Miner. Res.* 6: 331-337.

Krall, E.A., and Dawson-Hughes, B. 1993. Heritable and life-style determinants of bone mineral density. *J. Bone Miner. Res.* 8: 1-9.

Krall, E.A., Sahyoun, N., Tannenbaum, S., Dallal, G.E., and Dawson-Hughes, B. 1989. Effect of vitamin D intake on seasonal variations in parathyroid hormone secretion in postmenopausal women. *N. Engl. J. Med.* 321: 1777-1783.

Krawitt, E.L. 1967. Effects of thyrocalcitonin in duodenal calcium transport. *Proc. Soc. Exp. Biol. Med.* 125: 1084-1086.

Kream, B.E., Rowe, D.W., Gworek, S.C., and Raisz, L.G. 1980. Parathyroid hormone alters collagen synthesis and procollagen mRNA levels in fetal rat calvaria. *Proc. Natl. Acad. Sci. U.S.A.* 77: 5654-5658.

Kuntziger, H., Amiel, C., Roinel, N., and Morel, F. 1974. Effects of parathyroidectomy and cyclic AMP on renal transport of phosphate, calcium and magnesium. *Am. J. Physiol.* 227: 905-911.

Kurnik, B.R., Huskey, M., and Hruska, K.A. 1987. 1,25-Dihydroxycholecalciferol

stimulates renal phosphate transport by directly altering membrane phosphatidylcholine composition. *Biochim. Biophys. Acta* 917: 81-85.

Laitinene, K., Lamberg-Allardt, C., Tunninen, R., Karonen, S-L., Tahtela, R., Ylikahri, R., and Välimäki, M. 1991a. Transient hypoparathyroidism during acute alcohol intoxication. *N. Engl. J. Med.* 324: 721-727.

Laitinen, K., Lamberg-Allardt, C., Tunninen, R., Sirkka-Liisa, K., Ylikahri, R., and Välimäki, M. 1991b. Effects of 3 weeks' moderate alcohol intake on bone and mineral metabolism in normal men. *Bone Miner.* 13: 139-151.

Lanyon, L.E. 1987. Functional strain in bone tissue as an objective and controlling stimulus for adaptive bone remodeling. *J. Biomech.* 20: 1083-1093.

Lassiter, W.E., Gottschalk, C.W., and Mylle, M. 1963. Micropuncture study of renal tubular reabsorption of calcium in normal rodents. *Am. J. Physiol.* 204: 771-775.

Lau, E.M.C., Woo, J., Leung, P.C., Swaminathan, R., and Leung, D. 1992. The effects of calcium supplementation and exercise on bone density in elderly Chinese women. *Osteoporosis Int.* 2: 168-173.

Ledger, G.A., Burritt, M.F., Kao, P.C., O'Fallon, W.M., Riggs, B.L., and Khosla, S. 1994. Abnormalities of parathyroid hormone secretion in elderly women that are reversible by short term therapy with 1,25-dihydroxyvitamin D_3. *J. Clin. Endocrinol. Metab.* 79: 211-216.

Le Grimellec, C., Roinel, N., and Morel, F. 1973. Simultaneous Mg, Ca, P, K, Na and Cl analysis in rat tubular fluid. *Pfluegers Arch.* 340: 181-196.

Lian, J.B., and Gundberg, C.M. 1988. Osteocalcin: Biochemical considerations and clinical applications. *Clin. Orthop. Relat. Res.* 226: 267-291.

Lips, P., Courpron, P., and Meunier, P.J. 1978. Mean wall thickness of trabecular bone packets in human iliac crest: Changes with age. *Calcif. Tissue Res.* 26: 13-17.

Lu, C.C., Tsai, S.C., Wang, S.W., Tsai, C.L., Lau, C.P., Shih, H.C., Chen, Y.H.,

Chiao, Y.C., Liaw, C., and Wang, P.S. 1998a. Effects of ovarian steroid hormones and thyroxine on calcitonin secretion in pregnant rats. *Am. J. Physiol.* 274: E246-E252.

Lu, C.C., Tsai, S.C., Wang, S.W., Huang, W.J.S., and Wang, P.S. 1998b. Age-related differences in the secretion of calcitonin in female rats. *Am. J. Physiol.* 275: E735-E739.

Lu, C.C., Tsai, S.C., Chien, E.J., Tsai, C.L., and Wang, P.S. 2000. Age-related differences in the secretion of calcitonin in male rats. *Metabolism* 49: 253-258.

Lukert, B.P., and Raisz, L.G. 1994. Glucocorticoid-induced osteoporosis. *Rheum. Dis. Clin. North Am.* 20: 629-650.

Lukert, B., Higgins, J., and Stoskopf, M. 1992. Menopausal bone loss is partially regulated by dietary intake of vitamin D. *Calcif. Tissue Int.* 51: 173-179.

Lutz, J., and Tesar, R. 1990. Mother-daughter pairs: Spinal and femoral bone densities and dietary intakes. *Am. J. Clin. Nutr.* 52: 872-877.

Majeska, R.J., and Rodan, G.A. 1982a. Alkaline phosphatase inhibition by parathyroid hormone and isoproterenol in a clonal rat osteosarcoma cell line: Possible mediation by cAMP. *Calcif. Tissue Int.* 34: 59-66.

Majeska, R.J., and Rodan, G.A. 1982b. The effect of $1,25(OH)_2D_3$ on alkaline phosphatase in osteoblastic osteosarcoma cells. *J. Biol. Chem.* 257: 3362-3365.

Mann, D.R., Gould, K.G., and Collins, D.C. 1990. A potential primate model for bone loss resulting from medical oophorectomy or menopause. *J. Clin. Endocrinol. Metab.* 71: 105-110.

Marie, P.J., and Travers, R. 1983. Continuous infusion of 1,25 dihydroxyvitamin D_3 stimulates bone turnover in normal young mice. *Calcif. Tissue Int.* 35: 418-425.

Martin, R.B. 2000. Toward a unifying theory of bone remodeling. *Bone* 26: 1-6.

Matsushima, N., and Hikichi, K. 1989. Age changes in the crystallinity of bone mineral and in the disorder of its crystal. *Biochim. Biophys. Acta* 992: 155-159.

Mazess, R.B., Barden, H.S., Drinka, P.J., Bauwens, S.F., Orwoll, E.S., and Bell, N.H. 1990. Influence of age and body weight on spine and femur bone density in U.S. white men. *J. Bone Miner. Res.* 5: 645-652.

McKane, W.R., Khosla, S., Burritt, M.F., Kao, P.C., Wilson, D.M., Ory, S.J., and Riggs, B.L. 1995. Mechanism of renal calcium conservation with estrogen replacement therapy in women in early postmenopause: A clinical research center study. *J. Clin. Endocrinol. Metab.* 80: 3458-3464.

McLean, W., and Olsen, B.R. 2001. Mouse models of abnormal skeletal development and homeostasis. *Trends Genet.* 17: S38-43.

McSheety, P.M.J., and Chambers, T.J. 1987. 1,25-dihydroxyvitamin D_3 stimulates rat osteoblastic cells to release a soluble factor that increases osteoclastic bone resorption. *J. Clin. Invest.* 80: 425-429.

Meier, D.E., Orwoll, E.S., Keenan, E.J., and Fagerstrom, R.M. 1987. Marked decline in trabecular bone mineral content in healthy men with age: Lack of association with sex steroid levels. *J. Am. Geriatr. Soc.* 35: 189-197.

Meller, Y., Kestenbaum, R.S., Galinsky, D., and Shany, S. 1986. Seasonal variation in serum levels of vitamin D metabolites and parathormone in geriatric patients with fractures in southern Israel. *Isr. J. Med. Sci.* 22: 8-11.

Mellish, R.W.E., Garrahan, N.J., and Compston, J.E. 1989. Age-related changes in trabecular width and spacing in human iliac crest bone biopsies. *Bone Miner.* 6: 331-338.

Melton, L.J. III, Wahner, H.W., Richelson, L.S., O'Fallon, W.M., and Riggs, B.L. 1986. Osteoporosis and the risk of hip fracture. *Am. J. Epidemiol.* 124: 254-261.

Mentaverri, R., Lorget, F., Wattel, A., Maamer, M., Kamel, S., and Brazier, M.

2000. Osteoblastic regulation of osteoclast survival: Effect of calcitriol. *C. R. Acad. Sci. III* 323: 951-957.

Meunier, P.J., Aaron, J., Edouard, G., and Vignon, G. 1971. Osteoporosis and the replacement of cell populations of the marrow by adipose tissue *Clin. Orthop.* 80: 147-154.

Miller, A. III, Ueng, T-H., and Bronner, F. 1979. Isolation of a vitamin D-dependent, calcium-binding protein from brush borders of rat duodenal mucosa. *FEBS Lett.* 103: 319-322.

Minaire, P., Meunier, P., Edouard, C., Bernard, J., Courpron, P., and Bourret, J. 1974. Quantitative histological data on disuse osteoporosis: Comparison with biological data. *Calcif. Tissue Res.* 17: 57-73.

Morris, H.A., Need, A.G., Horowitz, M., O'Loughlin, P.D., and Nordin, B.E.C. 1991. Calcium absorption in normal and osteoporotic postmenopausal women. *Calcif. Tissue Int.* 49: 240-243.

Morrison, N.A., Qi, J.C., Tokita, A., Kelly, P.J., Crofts, L., Nguyen, T.V., Sambrook, P.N., and Eisman, J.A. 1994. Prediction of bone density from vitamin D receptor alleles. *Nature* 367: 284-287.

Mosekilde, L. 1993. Normal age-related changes in bone mass, structure, and strength: Consquences of the remodeling process. *Dan. Med. Bull.* 40: 65-83.

Mundy, G.R. 1999. Bone remodeling. In: Favus, M.J., ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* Philadelphia, Lippincott Williams & Wilkins. p.p. 30-38.

Mundy, G.R., and Roodman, G.D. 1987. Osteoclast oncogeny and function. In: Peck, W.A., ed. *Bone and Mineral Research/5.* Amsterdam, Elsevier Publishers B.V. p.p.204-274.

Murray, E.J.B., Beamer, W.G., Duarte, M.E., Behnam, K., Grisanti, M.S., and Murray, S.S. 2001. Effects of dietary restriction on appendicular bone in the SENCAR mouse. *Metabolism* 50: 436-442.

Naeraa, R.W., Brixen, K., Hansen, R.M., Hasling, C., Mosekilde, L., Andresen, J-H., Charles, P., and Nielsen, J. 1991. Skeletal size and bone mineral content in Turner's syndrome: Relation to karyotype, estrogen treatment, physical fitness, and bone turnover. *Calcif. Tissue Int.* 49: 77-83.

Nakamura, T., Kurokawa, T., and Orimo, H. 1988. Increase of bone volume in vitamin D-repleted rats by massive administration of 24R,25$(OH)_2D_3$. *Calcif. Tissue Int.* 43: 235-243.

Nellans, H.N., and Kimberg, D.V. 1978. Cellular and paracellular calcium transport in rat ileum: Effects of dietary calcium. *Am. J. Physiol.* 236: E726-E737.

Nicholson, G.C., Moseley, J.M., Sexton, P.M., Mendelsohn, F.A., and Martin, T.J. 1986. Abundant calcitonin receptors in isolated osteoclasts. *J. Clin. Invest.* 78: 355-360.

Noda, M., Yoon, K., and Rodan, G.A. 1988. Cyclic AMP-mediated stabilization of osteocalcin mRNA in rat osteoblast-like cells treated with parathyroid hormone. *J. Biol. Chem.* 263: 18574-18577.

Nomura, A., Wasnich, R.D., Heilbrun, L.K., Ross, P.D., and Davis, J.W. 1989. Comparison of bone mineral content between Japan-born and U.S.-born Japanese subjects in Hawaii. *Bone Miner.* 6: 213-223.

Notelovitz, M., Martin, D., Tesar, R., Khan, F.Y., Probart, C., Fields, C., and McKenzie, L. 1991. Estrogen therapy and variable-resistance weight training increase bone mineral in surgically menopausal women. *J. Bone Miner. Res.* 6: 583-590.

Olson, E.B., DeLuca, H.F., and Potts, J.T. Jr. 1972. Calcitonin inhibition of vitamin D-induced intestinal calcium absorption. *Endocrinology* 90: 151-157.

Ono, T., Tanaka, H., Yamate, T., Nagai, Y., Nakamura, T., and Seino, Y. 1996. 24R,25-dihydroxyvitamin D_3 promotes bone formation without causing excessive resorption in hypophosphatemic mice. *Endocrinology* 137:

2633-2637.

Orwoll, E. 2000. Assessing bone density in men. *J. Bone Miner. Res.* 15: 1867-1870.

Orwoll, E.S., and Meier, D.E. 1986. Alterations in calcium, vitamin D, and parathyroid hormone physiology in normal men with aging: Relationship to the development of senile osteopenia. *J. Clin. Endocrinol. Metab.* 63: 1262-1269.

Orwoll, E.S., Oviatt, S.K., McClung, M.R., Deftos, L.J., and Sexton, G. 1990. The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation. *Ann. Intern. Med.* 112: 29-34.

Orwoll, E.S., Stribrska, L., Ramsey, E.E., and Keenan, E.J. 1991. Androgen receptors in osteoblast-like cell lines. *Calcif. Tissue Int.* 49: 183-187.

Oursler, M.J., Pederson, L., Fitzpatrick, L., Riggs, B.L., and Spelsberg, T. 1994. Human giant cell tumors of the bone (osteoclastomas) are estrogen target cells. *Proc. Natl. Acad. Sci. U.S.A.* 91: 5227-5231.

Pacifici, R., Brown, C., Puscheck, E., Friedrich, E., Slatopolsky, E., Maggio, D., McCracken, R., and Avioli, L.V. 1991. Effect of surgical menopause and estrogen replacement on cytokine release from human blood mononuclear cells. *Proc. Natl. Acad. Sci. U.S.A.* 88: 5134-5138.

Parfitt, A.M. 1994. Osteonal and hemi-osteonal remodeling: The spatial and temporal framework for signal traffic in adult human bone. *J. Cell Biochem.* 55: 273-286.

Parfitt, A.M. 2002. Physiologic and pathogenetic significance of bone histomorphometric data. In: Coe, F.L., and Favus, M.J., 2nd ed. *Disorders of Bone and Mineral Metabolism.* NY, Raven Press. p.p.469-485.

Parfitt, A.M., Mathews, H.E., Villanueva A.R., Kleerekoper, M., and Frame, B. 1983. Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis: Implications for the

microanatomic and cellular mechanisms of bone loss. *J. Clin. Invest.* 72: 1396-1409.

Peng, T.C., Cooper, C.W., and Garner, S.C. 1976. Thyroid and blood thyrocalcitonin concentrations and C-cell abundance in two strains of rats at different ages. *Proc. Soc. Exp. Biol. Med.* 153: 268-272.

Peterlik, M., and Wasserman, R.H. 1978. Effect of vitamin D on transepithelial phosphate transport in chick intestine. *Am. J. Physiol.* 234: E379-E388.

Pocock, N.A., Eisman, J.A., Hopper, J.L., Yeates, M.G., Sambrook, P.N., and Eberl, S. 1987. Genetic determinats of bone mass in adults: A twin study. *J. Clin. Invest.* 80: 706-710.

Prentice, A. 2001. The relative contribution of diet and genotype to bone development. *Proc. Nutr. Soc.* 60: 45-52.

Price, P.A., and Baukol, S.A. 1980. 1,25-dihydroxyvitamin D_3 increases synthesis of the vitamin-K dependent bone protein by osteosarcoma cells. *J. Biol. Chem.* 255: 11660-11663.

Price, P.A., and Baukol, S.A. 1981. 1,25-dihydroxyvitamin D_3 increases serum levels of vitamin K-dependent bone protein. *Biochem. Biophys. Res. Commun.* 99: 928-935.

Price, P.A., Parthemore, J.G., and Deftos, L.J. 1980. New biochemical marker for bone metabolism. *J. Clin. Invest.* 66: 878-883.

Prince, R.L., Smith, M., Dick, I.M., Price, R.I., Webb, P.G., Henderson, N.J., and Harris, M.M. 1991. Prevention of postmenopausal osteoporosis. *N. Engl. J. Med.* 325: 1189-1195.

Prockop, D.J., Kivirikko, K.I., Tuderman, L., and Guzman, N.A. 1979. The biosynthesis of collagen and its disorders. *N. Engl. J. Med.* 301: 13-23.

Quesada, J.M., Coopmans, W., Ruiz, B., Aljama, P., Jans, I., and Bouillon, R. 1992. Influence of vitamin D on parathyroid function in the elderly. *J. Clin. Endocrinol. Metab.* 75: 494-501.

Raisz, L.G. 1963. Stimulation of bone resorption by parathyroid hormone in tissue culture. *Nature* 197: 1015-1016.

Recker, R.R., Lappe, J.M., Davies, K.M., and Kimmel, D.B. 1992. Changes in bone mass immediately before menopause. *J. Bone Miner. Res.* 7: 857-862.

Reginster, J.Y., Strause, L., Deroisy, R., Lecart, M.P., Saltman, P., and Franchimont, P. 1989. Preliminary report of decreased serum magnesium in postmenopausal osteoporosis. *Magnesium* 8: 106-109.

Reichel, H., Koeffler, H.P., and Norman, A.W. 1989. The role of the vitamin D endocrine system in health and disease. *N. Engl. J. Med.* 320: 980-991.

Reid, I.R., Plank, L.D., and Evans, M.C. 1992. Fat mass is an important determinant of whole body bone density in premenopausal women but not in men. *J. Clin. Endocrinol. Metab.* 75: 779-782.

Ribot, C., Tremollieres, F., Pouilles, J-M., Bonneu, M., Germain, F., and Louvet, J-P. 1988. Obesity and postmenopausal bone loss: The influence of obesity on vertebral density and bone turnover in postmenopausal women. *Bone* 8: 327-331.

Rico, H., Cabranes, J.A., Cabello, J., Gomez-Castresana, F., and Hernandez, E.R. 1987. Low serum osteocalcin in acute alcohol intoxication: A direct toxic effect of alcohol on osteoblasts. *Bone Miner.* 2: 221-225.

Riggs, B.L. 1989. Osteoporosis. In: DeGroot, L.J., 2nd ed. *Endocrinology*. Philadelphia, WB Saunders. p.p.1188-1207.

Riggs, B.L., and Melton, L.J. III. 1983. Evidence for two distinct syndromes of involutional osteoporosis. *Am. J. Med.* 75: 899-901.

Riggs, B.L., and Melton, L.J. III. 1986. Involutional osteoporosis. *N. Engl. J. Med.* 314: 1676-1686.

Riggs, B.L., and Melton, L.J. III. 1990. Clinical heterogeneity of involutional osteoporosis: Implications for prevention therapy. *J. Clin. Endocrinol. Metab.* 70: 1229-1232.

Riggs, B.L., Wahner, H.W., Dunn, W.L., Mazess, R.B., Offord, K.P., and Melton, L.J. III. 1981. Differential changes in bone mineral density of the appendicular and axial skeleton with aging: Relationship to spinal osteoporosis. *J. Clin. Invest.* 67: 328-335.

Riggs, B.L., Wahner, H.W., Melton, L.J., Richelson, L.S., Judd, H.L., and Offord, K.P. 1986. Rates on bone loss in the appendicular and axial skeletons of women. *J. Clin. Invest.* 77: 1487-1491.

Rodan, S.B., and Rodan, G.A. 1986. Dexamethasone effects on β-adrenergic receptors and adenylate cyclase regulatory proteins Gs and Gi in ROS 17/2.8 cells. *Endocrinology* 118: 2510-2518.

Rodan, S.B., Fischer, M.K., Egan, J.J., Epstein, P.M., and Rodan, G.A. 1984. The effect of dexamethasone on parathyroid hormone stimulation of adenylate cyclase in ROS 17/2.8 cells. *Endocrinology* 115: 951-958.

Roodman, G.D., Ibbotson, K.J., MacDonald, B.R., Kuehl, T.J., and Mundy, G.R. 1985. 1,25-dihydroxyvitamin D_3 causes formation of multinucleated cells with several osteoclast characteristics in cultures of primate marrow. *Proc. Natl. Acad. Sci. U.S.A.* 82: 8213-8217.

Roux, S. 2001. The genetics of osteoporosis. *Joint Bone Spine* 68: 482-486.

Ruegsegger, P., Dambacher, M.A., Ruegsegger, E., Fischer, J.A., and Anliker, M. 1984. Bone loss in premenopausal and postmenopausal women. *J. Bone Joint Surg. (Am.)* 66-A: 1015-1023.

Salamone, L.M., Ferrell, R., Black, D.M., Palermo, L., Epstein, R.S., Petro, N., Steadman, N., Kuller, L.H., and Cauley, J.A. 1996. The association between vitamin D receptor gene polymorphisms and bone mineral density at the spine, hip and whole-body in premenopausal women. *Osteoporosis Int.* 6: 63-68.

SAS Institute Inc. 2000. *SAS/STAT Software: Changes and Enhancements, Release 8.1*. Cary, NC, USA.

Schapira, D., Linn, S., Sarid, M., Mokadi, S., Kabala, A., and Silbermann, M. 1995. Calcium and vitamin D enriched diets increase and preserve vertebral mineral content in aging laboratory rats. *Bone* 16: 575-582.

Seeman, E., Melton, L.J.III, O'Fallon, W.M., and Riggs, B.L. 1983. Risk factors for spinal osteoporosis in men. *Am. J. Med.* 75: 977-983.

Seeman, E., Szmukler, G.I., Formica, C., Tsalamandris, C., and Mestrovic, R. 1992. Osteoporosis in anorexia nervosa: The influence of peak bone density, bone loss, oral contraceptive use, and exercise. *J. Bone Miner. Res.* 7: 1467-1474.

Seibel, M.J., Cosman, F., Shen, V., Gordon, S., Dempster, D.W., Ratcliffe, A., and Lindsay, R. 1993. Urinary hydroxypyridinium crosslinks of collagen as markers of bone resorption and estrogen efficacy in postmenopausal osteoporosis. *J. Bone Miner. Res.* 8: 881-889.

Shai, F., Baker, R.K., and Wallach, S. 1971. The clinical and metabolic effects of porcine calcitonin on Paget's disease of bone. *J. Clin. Invest.* 50: 1927-1940.

Shapiro, S., Kaufman, D.W., Slone, D., Rosenberg, L., Miettinen, O.S., Stolley, P.D., Rosenshein, N.B., Watring, W.G., Leavitt, T. Jr., and Knapp, R.C. 1980. Recent and past use of conjugated estrogens in relation to adenocarcinoma of the endometrium. *N. Engl. J. Med.* 303: 485-489.

Shapiro, S., Kelly, J.P., Rosenberg, L., Kaufman, D.W., Helmrich, S.P., Rosenshein, N.B., Lewis, J.L. Jr., Knapp, R.C., Stolley, P.D., and Schottenfeld, D. 1985. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. *N. Engl. J. Med.* 313: 969-972.

Sherman, S.S., Hollis, B.W., and Tobin, J.D. 1990. Vitamin D status and related parameters in a healthy population: The effects of age, sex, and season. *J. Clin. Endocrinol. Metab.* 71: 405-413.

Shevde, N.K., Plum, L.A., Clagett-Dame, M., Yamamoto, H., Pike, J.W., and

DeLuca, H.F. 2002. A potent analog of 1 alpha,25-dihydroxyvitamin D_3 selectively induces bone formation. *Proc. Natl. Acad. Sci. U.S.A.* 99: 13487-13491.

Sibilia, V., Cocchi, D., Pagani, F., Lattuada, N., Moro, G.L., Pecile, A., Rubinacci, A., Muller, E.E., and Netti, C. 1999. Hexarelin, a growth hormone-releasing peptide, counteracts bone loss in gonad-ectomized male rats. *Growth Horm. IGF Res.* 9: 219-227.

Silve, C.M., Hradek, G.T., Jones, A.L., and Arnaud, C.D. 1982. Parathyroid hormone receptor in intact embryonic chicken bone: Characterization and cellular localization. *J. Cell Biol.* 94: 379-386.

Slemenda, C., Longcope, C., Peacock, M., Hui, S., and Johnston, C.C. 1996. Sex steroids, bone mass, and bone loss. A prospective study of pre-, peri-, and postmenopausal women. *J. Clin. Invest.* 97: 14-21.

Slemenda, C.W., Hui, S.L., Longcope, C., and Johnston, C.C. Jr. 1989. Cigarette smoking, obesity, and bone mass. *J. Bone Miner. Res.* 4: 737-741.

Slemenda, C.W., Hui, S.L., Williams, C.J., Christian, J.C., Meaney, F.J., and Johnston, C.C. Jr. 1990. Bone mass and anthropometric measurements in adult females. *Bone Miner.* 11: 101-109.

Snow-Harter, C., Bouxsein, M.L., Lewis, B.T., Carter, D.R., and Marcus, R. 1992. Effects of resistance and endurance exercise on bone mineral status of young women: A randomized exercise intervention trial. *J. Bone Miner. Res.* 7: 761-769.

Song, S.K. 1970. Influence of deer horn on erythropoietin activity and radioactive iron uptake in rabbits. *J. Cathol. Med. Coll.* 18: 51-60.

Sparrow, D., Beausoleil, N.I., Garvey, A.J., Rosner, B., and Silvert, J.E. 1982. The influence of cigarette smoking and age on bone loss in men. *Arch. Environ. Health* 37: 246-249.

Spencer, E.M., and Tobiassen, O. 1981. The mechanism of the action of growth

hormone on vitamin D metabolism in the rat. *Endocrinology* 108: 1064-1070.

Stanbury, S.W. 1962. Osteomalacia. *Schweiz. Med. Wochenschr.* 92: 883-891.

Stepán, J.J., and Musilová Pacovsky, V. 1989. Bone demineralization, biochemical indices of bone remodeling, and estrogen replacement therapy in adults with Turner's syndrome. *J. Bone Miner. Res.* 4: 193-198.

Stevenson, J.C., Lees, B., Devenport, M., Cust, M.P., and Ganger, K.F. 1989. Determinants of bone density in normal women: Risk factors for future osteoporosis? *Br. Med. J.* 298: 924-928.

Szulc, P., Garnero, P., Munoz, F., Marchand, F., and Delmas, P.D. 2001. Cross-sectional evaluation of bone metabolism in men. *J. Bone Miner. Res.* 16: 1642-1650.

Takeda, T. 1999. SAM Animal Model. *The Medical Progression* 188: 68-74.

Takeda, T., Hosokawa, M., Takeshita, S., Irino, M., Higuchi, K., Matsushita, T., Tomita, Y., Yasuhira, K., Shimizu, K., Ishii, M., and Yamamuro, T. 1981. A new murine model of accelerated senescence. *Mech. Aging Dev.* 17: 183-194.

Takeda, T., Hosokawa, M., and Higuchi, K. 1991. Senescence-accelerated mouse (SAM): A novel murine model of accelerated senescence. *J. Am. Geriatr. Soc.* 39: 911-919.

Takeda, T., Hosokawa, M., Higuchi, K., Hosono, M., Akiguchi, I., and Katoh, H. 1994. A novel murine model of aging, senescence-accelerated mouse (SAM). *Arch. Gerntol. Geriatr.* 19: 185-192.

Takeda, T., Hosokawa, M., and Higuchi, K. 1997. Senescence-accelerated mouse (SAM): A novel murine model of senescence. *Exp. Geronol.* 32: 105-109.

Thomas, T. 2000. Monoamine oxidase-B inhibitors in the treatment of Alzheimer's disease. *Neurobiol. Aging* 21: 343-348.

Tiegs, R.D., Body, J-J., Barta, J.M., and Heath, H. III. 1986. Secretion and metabolism of monomeric human calcitonin: Effects of age, sex, and thyroid

damage. *J. Bone Miner. Res.* 1: 339-349.

Tietz, N.W., Shuey, D.F., and Wekstein, D.R. 1992. Laboratory values in fit aging individuals: Sexagenarians through centenarians. *Clin. Chem.* 38: 1167-1185.

Tran Van, P., Vignery, A., and Baron, R. 1982a. Cellular kinetics of the bone remodeling sequence in the rat. *Anat. Rec.* 202: 441-451.

Tran Van, P., Vignery, A., and Baron, R. 1992b. An electron microscopic study of the bone-remodeling sequence in the rat. *Cell Tissue Res.* 225: 283-292.

Trevisan, C., Ortolani, S., Bianchi, M.L., Caraceni, M.P., Ulivieri, F.M., Gandolini, G., and Polli, E.E. 1991. Age, time since menopause, and body parameters as determinants of female spinal bone mass: A mathematical model. *Calcif. Tissue Int.* 49: 1-5.

Tsai, K.S., Heath, H. III, Kumar, R., and Riggs, B.L. 1984. Impaired vitamin D metabolism with aging in women: Possible role in pathogenesis of senile osteoporosis. *J. Clin. Invest.* 73: 1668-1672.

Tsai, K.S., Wahner, H.W., Offord, K.P., Melton, J. III, Kumar, R., and Riggs, B.L. 1987. Effect of aging on vitamin D stores and bone density in women. *Calcif. Tissue Int.* 40: 241-243.

Tsai, C.L., Pu, H.F., Lau, C.P., Wang, P.S., and Liu, T.K. 1992. Age-related differences in basal and calcium-stimulated plasma calcitonin levels in female rats. *Am. J. Physiol.* 262: E557-E560.

Tsai, K.S., Pan, W.H., Hsu, S.H., Cheng, W.C., Chen, C.K., Chieng, P.U., Yang, R.S., and Twu, S.T. 1996. Sexual differences in bone markers and bone mineral density of normal Chinese. *Calcif. Tissue Int.* 59: 454-460.

Tsujibo, H., Miyake, Y., Maruyama, K., and Inamori, Y. 1987. Hypotensive compounds isolated from alcohol extract of the unossified horn of *Cervus elaphus* L. var. xanthopygus Milne-Edwarg (Rokujo). I. Isolation of lysophosphatidyl choline as a hypotensive principle and structure-activity study of related compounds. *Chem. Pharm. Bull.* 35: 654-659.

Tucker, K.L., Chen, H, Hannan, M.T., Cupples, L.A., Wilson, P.W., Felson, D., and Kiel, D.P. 2002. Bone mineral density and dietary patterns in older adults: The Framingham Osteoporosis Study. *Am. J. Clin. Nutr.* 76: 245-252.

Turner, R.T., Riggs, B.L., and Spelsberg, T.C. 1994. Skeletal effects of estrogen. *Endocr. Rev.* 15: 275-300.

Uden, P., Halloran, B., Daly, R., Duh, Q.Y., and Clark, O. 1992. Set-point for parathyroid hormone release increases with postmaturational aging in the rat. *Endocrinology* 131: 2251-2256.

Uebelhart, D., Gineyts, E., Chapuy, M.C., and Delmas, P.D. 1990. Urinary excretion of pyridinium crosslinks: A new marker of bone resorption in metabolic bone disease. *Bone Miner.* 8: 87-96.

Väänänen, H.K., and Härkönen, P.L. 1996. Estrogen and bone metabolism. *Maturitas* 23: S65-S69.

Vanderjagt, D.J., Bond, B., Dulai, R., Pickel, A., Ujah, I.O., Wadinga, W.W., Scariano, J.K., and Glew, R.H. 2001. Assessment of the bone status of Nigerian women by ultrasound and biochemical markers. *Calcif. Tissue Int.* 68: 277-284.

Vanderschueren, D., and Bouillon, R. 1995. Androgens and bone. *Calcif. Tissue Int.* 56: 341-346.

Vanderschueren, D., Van Herck, E., Suiker, A.M., Visser, W.J., Schot, L.P., and Bouillon, R. 1992. Bone and mineral metabolism in aged male rats: Short and long term effects of androgen deficiency. *Endocrinology* 130: 2906-2916.

Verhas, M., Schoutens, A., L'hermite-Baleriaux, M., Dourov, N., Verschaeren, A., Mone, M., and Heilporn, A. 1986. The effect of orchidectomy on bone metabolism in aging rats. *Calcif. Tissue Int.* 39: 74-77.

Viitanen, A-M., Kärkkäinen, M., Laitinen, K., Lamberg-Allardt, C., Kainulainen, K., Räsänen, L., Viikari, J., Välimäki, M.J., and Kontula, K. 1996. Common polymorphism of the vitamin D receptor gene is associated with variation of

peak bone mass in young Finns. *Calcif. Tissue Int.* 59: 231-234.

Walling, M.W., and Rothman, S.S. 1970. Apparent increase in carrier affinity for intestinal calcium transport following dietary calcium restriction. *J. Biol. Chem.* 245: 5007-5011.

Wang, B.X., Zhao, X.H., Qi, S.B., Yang, X.W., Kaneko, S., Hattori, M., Namba, T., and Nomura, Y. 1988a. Stimulating effect of deer antler extract on protein synthesis in senescence-accelerated mice *in vivo*. *Chem. Pharm. Bull.* 36: 2593-2598.

Wang, B.X., Zhao, X.H., Yang, X.W., Kaneko, S., Hattori, M., Namba, T., and Nomura, Y. 1988b. Indentification of the inhibitor for monoamine oxidase B in the extract from deer antler (Rokujo). *J. Med. Pharm. Soc. Wakan-Yaku* 111-122.

Wang, L., Orhii, P.B., Banu, J., and Kalu, D.N. 2001a. Effects of separate and combined therapy with growth hormone and parathyroid hormone on lumbar vertebral bone in aged ovariectomized osteopenic rats. *Bone* 28: 202-207.

Wang, L., Banu, J., McMAHAN, C.A., and Kalu, D.N. 2001b. Male rodent model of age-related bone loss in men. *Bone* 29: 141-148.

Webb, A.R., Kline, L., and Holick, M.F. 1988. Influence of season and latitude on the cutaneous synthesis of vitamin D_3: Exposure to winter sunlight in Boston and Edmonton will not promote vitamin D_3 synthesis in human skin. *J. Clin. Endocrinol. Metab.* 67: 373-378.

Webb, A.R., DeCosta, B.R., and Holick, M.F. 1989. Sunlight regulates the cutaneous production of vitamin D_3 by causing its photodegradation. *J. Clin. Endocrinol. Metab.* 68: 882-887.

Whalen, R.T., Carter, D.R., and Steele, C.R. 1988. Influence of physical activity on the regulation of bone density. *J. Biomech.* 21: 825-837.

Wong, R.G., and Norman, A.W. 1975. Studies on the mechanism of action of calciferol. *J. Biol. Chem.* 250: 2411-2419.

Wronski, T.J., and Yen, C.F. 1991. The ovariectomized rat as an animal model for postmenopausal bone loss. *Cells Matr.* 1: 69-74.

Wu, J., Wang, X.X., Chiba, H., Higuchi, M., Takasaki, M, Ohta A., and Ishimi, Y. 2003. Combined intervention of exercise and genistein prevented androgen deficiency-induced bone loss in mice. *J. Appl. Physiol.* 94: 335-342.

Youdim, M.B., and Weinstock, M. 2002. Novel neuroprotective anti-Alzheimer drugs with anti-depressant activity derived from the anti-Parkinson drug, rasagiline. *Mech. Ageing Dev.* 123: 1081-1086.

Yudin, A.M., and Dobryakov, Y.I. 1974. A guide for the preparation and storage of uncalcified male antlers as a medicinal raw material. In: *Reindeer Antlers.* Acad. Sci. USSR. p.p.65-72.

Zadik, Z., Chalew, S.A., McCarter, R.J., Meistas, M., and Kowarski, A.A. 1985. The influence of age on the 24-hour integrated concentration of growth hormone in normal individuals. *J. Clin. Endocrinol. Metab.* 60: 513-516.

Zhang, Z.Q., Zhang, Y., Wang, B.X., Zhou, H.O., Wang, Y., and Zhang, H. 1992. Purification and partial characterization of anti-inflammatory peptide from pilose antler of *Cervus nippon* Temminck. *Yao Hsueh Hsueh Pao-Acta Pharm. Sinica* 27: 321-324.

Zhao, W., Byrne, M.H., Boyce, B.F., and Krane, S.M. 1999. Bone resorption induced by parathyroid hormone is strikingly diminished in collagenase-resistant mutant mice. *J. Clin. Invest.* 103: 517-524.

Zhou, Q.L., Guo, Y.J., Wang, L.J., Wang, Y., Liu, Y.Q., Wang, Y., and Wang, B.X. 1999. Velvet antler polypeptides promoted proliferation of chondrocytes and osteoblast precursors and fracture healing. *Chung-Kuo Yao Li Hsueh Pao-Acta Pharm. Sinica* 20: 279-282.

Effects of Aging and Dietary Antler Supplementation on Bone Status and Changes of Related Hormones in SAM Mice

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Abstract

In this dissertation, the effects of aging on calcium homeostasis and bone status of senescence accelerated mice P8 (SAMP8) were investigated to evaluate the suitability of SAMP8 mice as an animal model for osteoporosis and the effects of dietary antler supplementation on bone metabolism-related parameters. Five experiments were conducted.

In Experiment 1, female SAMP8 and SAMR1 (control strain) mice were sacrificed and the blood and femur samples were collected initially at 2.5 months of age, and then monthly from 3 to 12 months of age. The determined bone metabolism-related parameters were plasma levels of calcium, phosphorus, calcitonin (CT), parathyroid hormone (PTH), and 1,25-dihydroxycholecalciferol ($1,25(OH)_2D_3$), and density and calcium content of femur. All parameters above were

also determined in other 4 individual experiments. The results indicated that the plasma calcium levels did not change with age and were maintained within a narrow range throughout the experiment. The plasma levels of phosphorus and CT decreased, and PTH and $1,25(OH)_2D_3$ increased with age in female mice. The curves of these parameters were shifted to the left in SAMP8, as compared to SAMR1. The femoral densities and calcium contents increased with age from the beginning of the experiment, peaked at 6 months of age, then followed by a decline in both strains. The curves for SAMP8 were lower than those for SAMR1.

In Experiment 2, the male SAMP8 and SAMR1 mice were sampled as their female counterparts in Experiment 1. The results and conclusions were similar to those obtained in Experiment 1.

In Experiment 3, the female and male SAM mice were gonadectomized or sham operated at 2 months of age, and the animals were sacrificed at 3, 6, and 12 months of age. The results showed that the plasma phosphorus levels were lower, and the $1,25(OH)_2D_3$ levels were higher in the females than those in the males. However, there were no significant differences in the other parameters between genders. Gonadectomy increased the plasma PTH and $1,25(OH)_2D_3$

levels, but decreased the plasma phosphorus and CT levels and the femoral densities as well as calcium contents.

In Experiment 4, the female SAMP8 and SAMR1 were ovariectomized or sham operated at 2 months of age and fed with either 0.2% antler containing diet or control diet. Animals were sacrificed at 3, 6, 9, 12, and 15 months of age. In the meanwhile, the feces and urine were collected and analyzed, and the amounts of dietary intake were recorded for 7 days in each occasion to determine the apparent digestibility and urinary excretion of calcium and phosphorus. The results showed that the apparent digestibility of calcium and phosphorus decreased and the urinary excretion of calcium and phosphorus increased with age. The apparent digestibility of calcium and phosphorus was lower, and the urinary calcium and phosphorus level was higher in the ovariectomized mice than that in the intact mice. The decrease of plasma phosphorus and CT levels, the femoral densities and calcium contents, and the increase of plasma PTH levels were moderated, and the intestinal absorption and the renal reabsorption of calcium and phosphorus were promoted by antler administration in both ovariectomized and intact mice. However, there was no effect of the dietary antler supplementation on the plasma

$1,25(OH)_2D_3$ level in the female mice.

In Experiment 5, the male SAMP8 and SAMR1 were orchidectomized or sham operated at 2 months of age, and the rest of the treatments was the same as that in Experiment 4. The results and conclusions were similar to those in Experiment 4.

It is concluded that SAMP8 is more valuable in studying age-related bone metabolism as compared to normal strains, and the gonadectomized SAMP8 is a good animal model for osteoporosis research. In addition, the prolonged dietary antler supplementation has the positive effects on bone loss.