

<p><b>Bone Cell Biology</b></p>	<ul style="list-style-type: none"> <li>• reservoir for <ul style="list-style-type: none"> <li>-Ca<sup>2+</sup></li> <li>-phosphorous</li> <li>-Mg<sup>2+</sup></li> <li>-Na<sup>+</sup></li> <li>-citrate carbonate</li> <li>-hydroxyl ions</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• 2 types of bone <ul style="list-style-type: none"> <li>-compact (cortical) <ul style="list-style-type: none"> <li>-comprises 80% of skeleton</li> <li>-very hard, dense</li> <li>-forms <ul style="list-style-type: none"> <li>-outer casing of most bones</li> <li>-tubular shafts of long bones</li> </ul> </li> </ul> </li> <li>-cancellous bone <ul style="list-style-type: none"> <li>-in vertebral bodies</li> <li>-at the ends of long bones</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• bone remodeling <ul style="list-style-type: none"> <li>-serves 2 functions <ul style="list-style-type: none"> <li>-preventive maintenance <ul style="list-style-type: none"> <li>-old bone continually replaced by new healthy bone</li> </ul> </li> <li>-provides access to skeletal store of minerals <ul style="list-style-type: none"> <li>-Ca<sup>2+</sup> can be <b>rapidly</b> transferred to bloodstream</li> <li>-Ca<sup>2+</sup> replaced more <b>slowly</b></li> </ul> </li> </ul> </li> </ul> </li> </ul>
<p><b>Bone Remodeling Cycle</b></p>	<p><u>Activation</u></p> <ul style="list-style-type: none"> <li>• initiating event that converts resting bone surface into remodeling surface <ul style="list-style-type: none"> <li>-occurs once every 10sec. in normal adult</li> </ul> </li> <li>• involves <ul style="list-style-type: none"> <li>-recruitment of mononucleated <b>osteoclast</b> precursors <ul style="list-style-type: none"> <li>-hematopoietic origin</li> </ul> </li> <li>-penetration of bone lining cells <ul style="list-style-type: none"> <li>-derived from <b>osteoblasts</b></li> </ul> </li> <li>-fusion of precursor cells ? functional <b>osteoclasts</b> in contact w/mineralized bone matrix</li> </ul> </li> <li>• possible factors ? remodeling a particular piece of bone <ul style="list-style-type: none"> <li>-local ? in mechanical properties</li> <li>-?s in electrical signals</li> <li>-substances released by aging bone</li> <li>-<b>osteocyte</b> induced activation</li> </ul> </li> </ul>	<p><u>Resorption</u></p> <ul style="list-style-type: none"> <li>• newly formed <b>osteoclasts</b> have concerted action</li> <li>• remove mineral &amp; organic bone matrix <ul style="list-style-type: none"> <li>-in cancellous bone <ul style="list-style-type: none"> <li>-create Howship's lacunae <ul style="list-style-type: none"> <li>-saucer-shaped cavity ~50µm deep</li> <li>-takes approx. <b>1wk.</b></li> </ul> </li> </ul> </li> <li>-in cortical bone <ul style="list-style-type: none"> <li>-“cutting cones” <ul style="list-style-type: none"> <li>-<b>osteoclasts</b> drill thru matrix parallel to long axis ? cylindrical tunnel ~ 2.5mm long &amp; 200µm diameter</li> <li>-takes approx. <b>2wks.</b></li> </ul> </li> </ul> </li> </ul> </li> <li>-<b>osteoclast</b> attaches firmly to bones via <b>integrin</b> receptors ? circular sealing zone ? extracellular micro-environment <ul style="list-style-type: none"> <li>-highly acidic &amp; rich in proteolytic enzymes</li> </ul> </li> </ul>	
<p><u>Reversal</u></p> <ul style="list-style-type: none"> <li>• switch from destruction to repair <ul style="list-style-type: none"> <li>-takes 7-14days</li> </ul> </li> <li>• resorption bays <ul style="list-style-type: none"> <li>-devoid of <b>osteoclasts</b></li> <li>-filled w/ mononucleated cells <ul style="list-style-type: none"> <li>-osteocytes <ul style="list-style-type: none"> <li>-freed from the matrix</li> </ul> </li> <li>-MF-like cells <ul style="list-style-type: none"> <li>-probably derived from <b>osteoclasts</b></li> <li>-smooth resorbed surface</li> <li>-deposit collagen deficient cement-like substance ? binds new bone to old</li> </ul> </li> </ul> </li> <li>-pre-<b>osteoblasts</b> <ul style="list-style-type: none"> <li>-further from the surface</li> <li>-divide ? <b>osteoblasts</b></li> <li>-derived from osteogenic precursor cells present in marrow stroma &amp; periosteum</li> </ul> </li> <li>• <b>osteoblast</b> recruitment <ul style="list-style-type: none"> <li>-uncertain mechanism</li> <li>-probably “coupling factors” (i.e. paracrine) <ul style="list-style-type: none"> <li>-released by resorptive cells (e.g. lining cells) or <b>osteoclasts</b> <ul style="list-style-type: none"> <li>-or bone matrix in resorptive phase</li> </ul> </li> </ul> </li> <li>-possible coupling factors <ul style="list-style-type: none"> <li>-IGF-II</li> <li>-TGF-β</li> </ul> </li> </ul> </li> </ul> </li></ul>	<p><u>Formation</u></p> <p><b>Stage 1:</b> <b>osteoblasts</b> deposit osteoid</p> <ul style="list-style-type: none"> <li>• matrix 1° comprised of <ul style="list-style-type: none"> <li>-Type I collagen</li> <li>-other components: proteoglycans, carbohydrates, lipids</li> <li>-non-collagenous proteins: bone GIa protein, matrix GIa protein, osteonectin</li> </ul> </li> <li>• osteoid laid down in discrete layers (lamellae) ~3µm thick <ul style="list-style-type: none"> <li>-in both cancellous &amp; cortical</li> <li>-consistent collagen fiber orientation <b>w/in</b> each lamellae</li> <li>-varied collagen fiber orientation amongst lamellae</li> </ul> </li> <li>• cancellous bone <ul style="list-style-type: none"> <li>-lamellae deposited in curved sheets <ul style="list-style-type: none"> <li>-follow contours of trabeculae</li> </ul> </li> </ul> </li> <li>• cortical bone <ul style="list-style-type: none"> <li>-<b>osteoblasts</b> &amp; blood vessels follow <b>osteoclasts</b> thru tunnels ? successive concentric lamellae from outer walls towards the center (“closing cone”) ? narrow central canal <ul style="list-style-type: none"> <li>-contains blood vessel</li> </ul> </li> </ul> </li> </ul> <p><b>Stage 2:</b> mineralization of organic matrix</p> <ul style="list-style-type: none"> <li>• occurs after a 20day delay (mineralization lag time)</li> <li>• 1° mineralization: 75% of final mineral content generated of 1<sup>st</sup> few days</li> <li>• 2° mineralization: takes up to 1yr. to reach maximal mineral content</li> <li>• hydroxyapatite is the principal mineral component</li> <li>• <b>osteoblasts</b> refill resorption cavity <ul style="list-style-type: none"> <li>-takes ~65 days in cancellous bone, ~95 days in cortical bone</li> </ul> </li> <li>• completed piece of new bone (BSU) called <ul style="list-style-type: none"> <li>-“packet” (cancellous bone) or “Haversian system” (cortical bone)</li> </ul> </li> </ul>		

<p><b>Remodeling in Different Skeletal Compartments</b></p>	<ul style="list-style-type: none"> <li>• turnover rate varies among various bones and bone types</li> <li>• greater surface-to-volume ratio in cancellous bone ? higher remodeling rate</li> <li>-more surface is in contact w/marrow in cancellous bone</li> <li>-marrow contains <b>osteoclast</b> precursors</li> <li>-cancellous bone is more vascular</li> <li>-cancellous bone <ul style="list-style-type: none"> <li>-12 BRUs activated per min.</li> <li>-annual turnover rate ~ 25%</li> </ul> </li> <li>-cortical bone <ul style="list-style-type: none"> <li>-3 BRUs per min.</li> <li>-annual turnover rate ~ 2-3%</li> </ul> </li> <li>• difference between volume removed and replaced depends on anatomical location w/in bone</li> <li>-4 distinct “envelopes”</li> <li>-periosteal <ul style="list-style-type: none"> <li>-slightly <b>positive</b> net bone balance</li> </ul> </li> <li>-Haversian <ul style="list-style-type: none"> <li>-slightly <b>negative</b> net bone balance</li> <li>-esp. in the inner 1/2 of the cortex</li> </ul> </li> <li>-cortical-endosteal <ul style="list-style-type: none"> <li>-<i>significantly</i> <b>negative</b> bone balance</li> </ul> </li> <li>-trabecular <ul style="list-style-type: none"> <li>-slightly <b>negative</b> bone balance</li> </ul> </li> <li>• decrements (of bone loss) accumulate w/age</li> <li>• periosteal &amp; cortical-endosteal surfaces ? in circumference</li> <li>-cortical-endosteal surface moves outward at a greater rate ? cortical thickness</li> <li>• <b>amt. of cortical &amp; cancellous bone ? w/ age</b></li> </ul>	<p><b>Changes in Remodeling w/ Age and Menopause</b></p>	<ul style="list-style-type: none"> <li>• very high freq. of BRUs in children</li> <li>-? during teens &amp; 20s ? nadir in mid-30s</li> </ul> <p>Aging</p> <ul style="list-style-type: none"> <li>• ? in cancellous &amp; cortical bone mass</li> <li>-accompanied by modest ? in remodeling activation w/ age</li> <li>-both men &amp; women</li> <li>• <b>cancellous</b> bone loss</li> <li>-occurs in men &amp; women</li> <li>-however, there are differences in <ul style="list-style-type: none"> <li>-<b>pattern</b></li> <li>-<b>mechanism</b></li> <li>-<b>magnitude</b></li> </ul> </li> </ul> <table border="0" style="width: 100%;"> <thead> <tr> <th style="text-align: left;">BONE LOSS</th> <th style="text-align: left;">MEN</th> <th style="text-align: left;">WOMEN</th> </tr> </thead> <tbody> <tr> <td>-predominant mechanism</td> <td>-trabecular thinning</td> <td>-trabecular <b>plate removal</b></td> </tr> <tr> <td></td> <td></td> <td>-1° cause rapid post-menopausal bone loss</td> </tr> <tr> <td></td> <td></td> <td>-hyperactive “killer osteoclasts” are proposed mechanism</td> </tr> <tr> <td>-linear ? w/age</td> <td>-yes</td> <td>-yes, but after age 55 (menopause) ? is accelerated</td> </tr> <tr> <td></td> <td></td> <td>-also ? bone turnover rate</td> </tr> <tr> <td></td> <td></td> <td>-<b>accelerated</b> bone loss continues for <b>5yrs.</b></td> </tr> <tr> <td></td> <td></td> <td>-<b>most important reason for ? osteoporosis</b></td> </tr> <tr> <td></td> <td></td> <td>-after 5yrs, bone loss returns to previous level</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>• ?osteoblast synthetic capacity and/or ?osteoblast recruitment during reversal phase ? generalized ? in osteoblast activity w/age ? age-related ? in wall thickness of cancellous bone packets ? gradual bone loss</li> <li>-same mechanism in both sexes</li> </ul>	BONE LOSS	MEN	WOMEN	-predominant mechanism	-trabecular thinning	-trabecular <b>plate removal</b>			-1° cause rapid post-menopausal bone loss			-hyperactive “killer osteoclasts” are proposed mechanism	-linear ? w/age	-yes	-yes, but after age 55 (menopause) ? is accelerated			-also ? bone turnover rate			- <b>accelerated</b> bone loss continues for <b>5yrs.</b>			- <b>most important reason for ? osteoporosis</b>			-after 5yrs, bone loss returns to previous level
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<p><b>Bone Cell Communication &amp; Osteoclast Formation</b></p>	<ul style="list-style-type: none"> <li>• RANKL (receptor activator of NF-?B ligand)</li> <li>-osteoclast stimulating factor</li> <li>-PTH stimulates osteoblast/stromal cells</li> <li>? RANKL synthesis ? RANKL binds RANK on osteoclast precursor ? differentiation into mature osteoclast</li> <li>? OPG (decoy receptor) synthesis ? binds RANKL ? ?osteoclast formation ? ?bone loss</li> <li>• <b>estrogen</b></li> <li>? ?RANKL</li> <li>? ?OPG</li> </ul>																													

<p><b>Bone &amp; Calcium Disorders</b></p>	<p><u>Serum Calcium</u></p> <ul style="list-style-type: none"> <li>• circulating serum Ca<sup>2+</sup> comprised of <ul style="list-style-type: none"> <li>-bound to albumin (40%)</li> <li>-complexed w/anions (5-10%)</li> <li>-free ionized form (50%)</li> </ul> </li> <li>• thus, Ca<sup>2+</sup> ion conc. can remain nl. even if total Ca<sup>2+</sup> is low <ul style="list-style-type: none"> <li>-e.g. nephrotic syndrome ? hypoalbuminemia</li> </ul> </li> <li>-<b>every 1gm/dl ? in serum albumin ? 0.8mg/dl ? in total Ca<sup>2+</sup> conc.</b></li> <li>• normal total Ca<sup>2+</sup>: 8.4-10.2 mg/dl</li> </ul>	<p><u>Serum Phosphorus</u></p> <ul style="list-style-type: none"> <li>• phosphorus conc.: 2.5-4.5mg/dl</li> <li>• more sensitive to fluctuations in dietary sources than serum Ca<sup>2+</sup></li> </ul>	<p><u>Bone X-rays</u></p> <ul style="list-style-type: none"> <li>• can detect ? mineralization in <ul style="list-style-type: none"> <li>-osteoporosis <ul style="list-style-type: none"> <li>-usually must be at advanced stage to visualize <ul style="list-style-type: none"> <li>- &gt;30% loss of bone mineral necessary to visualize by x-ray</li> </ul> </li> </ul> </li> <li>-subperiosteal resorption in 1° hyper-PTH</li> <li>-metastatic lesions</li> <li>-disorganized pattern of Paget's</li> <li>-pseudofractures of osteomalacia</li> </ul> </li> </ul>	<p><u>Bone Density Determination</u></p> <ul style="list-style-type: none"> <li>• dual energy x-ray absorptiometry (DXA) <ul style="list-style-type: none"> <li>-accurate</li> <li>-reproducible</li> <li>-facile</li> <li>-minimal x-ray exposure</li> </ul> </li> <li>• areas routinely measured <ul style="list-style-type: none"> <li>-lumbar vertebrae (1° cancellous bone)</li> <li>-forearm (1° cortical bone)</li> <li>-hip (cancellous &amp; cortical)</li> </ul> </li> <li>• performed each year to monitor results of Tx.</li> </ul>
<p><b>Bone Formation Markers</b></p>	<p><u>Alkaline Phosphatase</u></p> <ul style="list-style-type: none"> <li>• produced by osteoblasts</li> <li>• important in bone remodeling processes</li> <li>• may reflect activity of other organs <ul style="list-style-type: none"> <li>-esp. liver</li> </ul> </li> <li>• a bone-specific isoenzyme of alkaline phosphatase is measured</li> </ul>	<p><u>Osteocalcin</u></p> <ul style="list-style-type: none"> <li>• osteoblast product</li> <li>• Vit K dependent for post-translational modification of ?-carboxy glutamic acid</li> </ul>	<p><u>N-terminal &amp; C-terminal propeptides</u></p> <ul style="list-style-type: none"> <li>• cleaved from procollagen during collagen synthesis</li> <li>?bone formation ? ?amt. of propeptides</li> </ul>	
<p><b>Bone Resorption Markers</b></p>	<p><u>Urinary cross-links of collagen</u></p> <ul style="list-style-type: none"> <li>• 2 cross-links <ul style="list-style-type: none"> <li>-pyridinoline (PYD)</li> <li>-deoxypyridinoline (DPD) <ul style="list-style-type: none"> <li>-found exclusively in Type I collagen <ul style="list-style-type: none"> <li>-Type I collagen found 1° in bone</li> </ul> </li> </ul> </li> </ul> </li> <li>• formed between after collagen fibrils are laid down</li> <li>• ?bone turnover ? ?urinary collagen cross-links</li> <li>-diseases such as: hyper-PTH, Paget's, osteoporosis, malignancy</li> </ul>	<p><u>Collagen telopeptides</u></p> <ul style="list-style-type: none"> <li>• terminal fragments of Type I collagen released during resorption</li> <li>• 2 types <ul style="list-style-type: none"> <li>-N-terminal (N-telopeptide)</li> <li>-C-terminal (C-telopeptide)</li> </ul> </li> <li>• measured in urine or serum assoc. w/ bone resorption</li> </ul>		
<p><b>Calcitropic Hormones</b></p>	<p><u>Plasma PTH conc.</u></p> <ul style="list-style-type: none"> <li>• concentration of intact hormone <ul style="list-style-type: none"> <li>-best methods are either <ul style="list-style-type: none"> <li>-immunoradiometric assay (IRMA)</li> <li>-immunochemiluminometric assay (ICMA)</li> </ul> </li> </ul> </li> <li>• <b>always</b> consider result in relation to serum Ca<sup>2+</sup></li> <li>-PTH secretion mechanism are extremely sensitive to ?s in serum Ca<sup>2+</sup></li> <li>• hypercalcemia (NOT due to 1° parathyroid abnormality) ? ?PTH <ul style="list-style-type: none"> <li>-if PTH and serum Ca<sup>2+</sup> are simultaneously ?, then 1° hyper-PTH is likely</li> </ul> </li> <li>• hypocalcemia ? ?PTH <ul style="list-style-type: none"> <li>-if PTH and serum Ca<sup>2+</sup> are simultaneously ?, then hypoparathyroidism is likely</li> </ul> </li> </ul>	<p><u>Plasma PTH-related protein conc.</u></p> <ul style="list-style-type: none"> <li>• similarities to PTH</li> <li>• causative factor in some malignancies assoc. w/hypercalcemia</li> <li>• NOT yet proved clinically useful</li> </ul>	<p><u>Vitamin D metabolites</u></p> <ul style="list-style-type: none"> <li>• 25-hydroxyvitamin D <ul style="list-style-type: none"> <li>-considered a marker of vitamin D stores</li> <li>-most useful clinical assay</li> <li>-?in states of vitamin D deficiency <ul style="list-style-type: none"> <li>-except renal failure</li> </ul> </li> </ul> </li> <li>• 1,25-hydroxyvitamin D <ul style="list-style-type: none"> <li>-true active form of vitamin D</li> <li>-levels do NOT always reflect sufficient vitamin D <ul style="list-style-type: none"> <li>-?Ca<sup>2+</sup> or ?phosphorus ? ?renal 1-a-hydroxylase ? paradoxical ? of 1,25-hydroxyvitamin D (despite vitamin D deficiency)</li> </ul> </li> <li>• renal insufficiency ? ?renal mass &amp; hyperphosphatemia ? ?1-a-hydroxylase ? ?1,25-hydroxyvitamin D and nl. 25-hydroxyvitamin D</li> <li>1° hyper-PTH ? ?renal conversion of 25-hydroxyvitamin D to 1, 25-hydroxyvitamin D ? ?1, 25-hydroxyvitamin D in 25% of pts.</li> </ul> </li> </ul>	<p><u>Plasma Calcitonin conc.</u></p> <ul style="list-style-type: none"> <li>• radioimmunoassay</li> <li>• medullary thyroid carcinoma <ul style="list-style-type: none"> <li>-1° disorder w/ abnormal serum calcitonin</li> <li>-fasting calcitonin ?</li> <li>-abnormal response to Ca<sup>2+</sup> infusion or pentagastrin injection</li> </ul> </li> <li>• NOT clinically useful other than for medullary thyroid carcinoma</li> </ul>

	Etiology	Symptoms & Signs	Management of hypercalcemia
Disorders w/ Hypercalcemia	<ul style="list-style-type: none"> <li>• most common causes</li> <li>-1° hyper-PTH</li> <li>-neoplasma               <ul style="list-style-type: none"> <li>-multiple myeloma, bone metastases</li> </ul> </li> <li>• less common causes</li> <li>-thiazide diuretics</li> <li>-hyperthyroidism</li> <li>-vitamin D toxicity</li> <li>-granulomatous diseases (due to infectious agents)               <ul style="list-style-type: none"> <li>-TB, histoplasmosis</li> </ul> </li> <li>-milk-alkali syndrome</li> <li>-sarcoidosis</li> <li>-prolonged immobilization               <ul style="list-style-type: none"> <li>-children/young adults</li> <li>-elderly</li> <li>-pts. w/ Paget's disease</li> </ul> </li> <li>-artifactual               <ul style="list-style-type: none"> <li>-nl. ionized Ca<sup>2+</sup> but ?un-ionized or bound Ca<sup>2+</sup></li> </ul> </li> <li>• rare causes</li> <li>-recovery phase of acute renal failure               <ul style="list-style-type: none"> <li>-esp. after rhabdomyolysis</li> </ul> </li> <li>-vitamin A toxicity</li> <li>-acute adrenal insufficiency</li> <li>-hypophosphatasia</li> <li>-familial hypocalciuric hypercalcemia (FHH)</li> </ul>	<ul style="list-style-type: none"> <li>• important factors in presence or absence of symptoms</li> <li>-absolute Ca<sup>2+</sup> level</li> <li>-rate of increase</li> <li>-duration of elevation</li> <li>• polyuria</li> <li>• polydypsia</li> <li>• inability to concentrate urine</li> <li>• ?QT interval</li> <li>-hypercalcemic pts. have ?sensitivity to digitalis</li> <li>• personality changes</li> <li>• depression</li> <li>• lethargy</li> <li>• coma</li> <li>• calcification of cornea ? band keratopathy</li> <li>• anorexia</li> <li>• N/V</li> <li>• constipation</li> </ul>	<ul style="list-style-type: none"> <li>• serum Ca<sup>2+</sup> &gt; 14mg/dl</li> <li>-an emergency</li> <li>-prompt therapy needed</li> <li>• moderately ? Ca<sup>2+</sup> (12-14mg/dl)</li> <li>-requires careful attention</li> <li>-MUST assess whether hypercalcemia or another intercurrent process</li> <li>• mildly ?Ca<sup>2+</sup> (10.3-11.5mg/dl)</li> <li>-freq. finding in 1° hyper-PTH</li> <li>-NO specific Tx necessary to ? serum Ca<sup>2+</sup> acutely</li> <li>• pts. vary greatly in tolerance of hypercalcemia</li> <li><u>Renal</u></li> <li>• Ca<sup>2+</sup> excreted in direct proportion to Na<sup>+</sup></li> <li>• IV NaCl ? ?renal Na<sup>+</sup> excretion ? temp. ?in Ca<sup>2+</sup></li> <li>• furosemide (NOT thiazides) ? ?cardiovascular burden</li> <li>-pt. MUST <b>1<sup>st</sup></b> be <b>rehydrated</b></li> <li>-furosemide <b>before</b> rehydration ? ?hypercalcemia</li> <li>• peritoneal or hemodialysis</li> <li>-reserved for pts. w/ renal insufficiency</li> <li><u>Skeletal</u></li> <li>• goal is to ?Ca<sup>2+</sup> flux from bone to ECF</li> <li>• bisphosphonates are potent</li> <li>• calcitonin is NOT very potent</li> <li><u>Other</u></li> <li>• steroids (glucocorticoids) ? ?serum Ca<sup>2+</sup> in pts. w/ multiple myeloma, sarcoidosis, vitamin D intoxication, bone metastases</li> <li>• early mobilization</li> </ul>

	Etiology	Signs and Symptoms
<p>1° Hyper-PTH</p>	<ul style="list-style-type: none"> <li>excessive PTH secretion from parathyroid glands</li> <li>under normal circumstances</li> <li>ionized <math>Ca^{2+}</math> is 1° regulator of PTH secretion</li> <li>in 1° hyper-PTH regulation by <math>Ca^{2+}</math> ion is impaired</li> <li>single, benign parathyroid adenoma</li> <li>most cases (80%)</li> <li>multiple hyperplastic parathyroid glands</li> <li>up to 20% of cases</li> <li>parathyroid carcinoma</li> <li>&lt; 1% of cases</li> <li>genes implicated in 1° hyper-PTH</li> <li>proto-oncogenes: PRAD1 (aka cyclin D)</li> <li>tumor suppressor genes: MENIN</li> <li>peak incidence during 5<sup>th</sup> &amp; 6<sup>th</sup> decades</li> <li>women &gt; men (ratio is 3:1)</li> </ul>	<ul style="list-style-type: none"> <li>in adenomatous disease</li> <li>adenomatous gland is usually 300mg-1gm</li> <li>normal gland = 25-30mg</li> <li>despite enlargement, adenomatous gland is still difficult to identify</li> <li>does NOT always have brownish, oval appearance</li> <li>may be found in atypical locations (e.g. thyroid)</li> <li><b>most pts. are completely asymptomatic</b></li> <li>this is the major current clinical presentation</li> </ul> <p><u>Bone</u></p> <ul style="list-style-type: none"> <li>severe bone disease uncommon (&lt; 5%)</li> <li>Osteitis fibrosa cystica is most severe form</li> <li>involves</li> <li>generalized demineralization</li> <li>bone cysts</li> <li>brown tumors</li> <li>fractures</li> <li>pts. very debilitated</li> <li>short duration of symptoms (&lt; 3yrs)</li> <li>marked hypercalcemia (&gt; 13mg/dl)</li> <li>other radiologic changes</li> <li>resorptive ?s of distal phalanges</li> <li>salt-&amp;-pepper skull erosion</li> <li>thinning of distal clavicles</li> <li>radiological manifestation of 1° hyper-PTH are uncommon</li> <li>bone mineral densitometry may show selective demineralization of cortical bone</li> <li>cortical bone is the most sensitive to PTH</li> <li>cortical is predominantly in appendicular skeleton</li> <li>cancellous bone may be protected in hyper-PTH</li> </ul> <p><u>Kidney</u></p> <ul style="list-style-type: none"> <li>nephrocalcinosis (<math>Ca^{2+}</math> deposition)</li> <li>nephrolithiasis (growth of calculi)</li> <li>?incidence of 1° hyper-PTH ? ?incidence of stone disease</li> <li>stone disease in 15-20% of pts. w/ 1° hyper-PTH</li> <li>was ~35-40% 20yrs ago</li> <li>renal involvement may be limited to</li> <li>unexplained ? in Cr clearance</li> <li>mild RTA</li> <li>? concentrating ability</li> </ul>
	<p><u>Labs</u></p> <ul style="list-style-type: none"> <li>hypercalcemia is an essential feature</li> <li>indicated by <math>Ca^{2+}</math> values of 10.2-11.2mg/dl</li> <li>uncommonly <math>Ca^{2+}</math> level is &gt; 15mg/dl</li> <li>serum phosphorous</li> <li>often &lt; 3.5mg/dl</li> <li>&lt; 2.5mg/dl (i.e. frankly low) in 1/3 of pts.</li> <li>alkaline phosphatase and osteocalcin levels are ?</li> <li>PYD, DPD, and N-telopeptides are ?</li> <li>circulating 1,25-hydroxyvitamin D is ?</li> <li>possible <b>hypercalciuria</b></li> <li>occurs despite PTH's effect to conserve <math>Ca^{2+}</math> in renal tubules b/c of ?<math>Ca^{2+}</math> filtered at glomerulus</li> <li>thus, <b>PTH level is MOST useful in differential dx. of hypercalcemia</b></li> <li><b>PTH is ? in all hypercalcemia states except 1° hyper-PTH</b></li> </ul>	<p><u>Other systems</u></p> <ul style="list-style-type: none"> <li>uncommon associations</li> <li>HTN</li> <li>peptic ulcer disease</li> <li>pancreatitis</li> <li>gout</li> <li>pseudogout</li> <li>corneal calcification (band keratopathy)</li> <li>soft tissue calcification</li> <li>hypotonia</li> <li>muscular weakness</li> <li>loose teeth</li> <li>?memory</li> <li>personality disturbances</li> <li>?level of consciousness</li> <li>anemia</li> </ul>

	Etiology	Treatment
Malignant Neoplasms	<ul style="list-style-type: none"> <li>• breast or lung carcinomas</li> <li>-neighboring tumor cells ? osteoclast activation ? direct lytic destruction of bone ? hypercalcemia</li> <li>• multiple myeloma and lymphomas</li> <li>-hypercalcemia caused by either <ul style="list-style-type: none"> <li>-local release of bone-resorbing cytokines</li> <li>-?conversion of vitamin D to 1,25-hydroxyvitamin D</li> </ul> </li> </ul>	
Humoral Hypercalcemia of Malignancy (HHM)	<ul style="list-style-type: none"> <li>• hypercalcemia is absence of overt metastatic bone destruction</li> <li>• tumors produce either <ul style="list-style-type: none"> <li>-a parathyroid-like protein</li> <li>-PTHrp <ul style="list-style-type: none"> <li>-homologous w/PTH for 1<sup>st</sup> 13 amino acids at amino terminal</li> <li>-different structural features ? LACK of cross reactivity of PTHrP on assays for PTH</li> </ul> </li> </ul> </li> </ul>	
Vitamin D Intoxcation	<ul style="list-style-type: none"> <li>• may be severe and prolonged hypercalcemia</li> <li>-due to large storage capacity of Vitamin D in fat</li> <li>• ?Vitamin D ? ?GI absorption of Ca<sup>2+</sup> and excessive bone mobilization ? hypercalcemia</li> <li>-excess <b>25-hydroxyvitamin D</b> is responsible <ul style="list-style-type: none"> <li>-NOT 1, 25-hydroxyvitamin D</li> </ul> </li> <li>• <b>Sarcoidosis</b> <ul style="list-style-type: none"> <li>- &lt; 10% of pts. have hypercalcemia</li> <li>-hypercalciuria is common</li> <li>-granulomatous tissue produces 1, 25-hydroxyvitamin D</li> </ul> </li> <li>• rare lymphomas <ul style="list-style-type: none"> <li>-produce 1, 25-hydroxyvitamin D</li> </ul> </li> <li>• other granulomatous disorders (TB, histoplasmosis) <ul style="list-style-type: none"> <li>-1, 25-hydroxyvitamin D production ? hypercalcemia</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• glucocorticoids are very effective</li> </ul>
Thyrotoxicosis	<ul style="list-style-type: none"> <li>• mild hypercalcemia</li> <li>-related to ?bone turnover</li> </ul>	•
Thiazide Diuretics	<ul style="list-style-type: none"> <li>• ? urinary excretion of Ca<sup>2+</sup></li> <li>• many pts. who develop hypercalcemia while on thiazide diuretics prove to have 1° hyper-PTH</li> </ul>	•
Familial Hypocalciuric Hypercalcemia	<ul style="list-style-type: none"> <li>• disorder of Ca<sup>2+</sup> sensor (receptor) gene</li> <li>• assoc. w/ mild hypercalcemia</li> <li>• <b>NO signs of hyper-PTH</b></li> <li>-distinguished from 1° hyper-PTH by: <ul style="list-style-type: none"> <li>-autosomal dominant transmission (w/ high penetrance)</li> <li>-very low Ca<sup>2+</sup> excretion</li> <li>-always a benign clinically</li> <li>-parathyroidectomy is ineffective</li> <li>-nl. PTH level</li> </ul> </li> </ul>	•

	Symptoms & Signs	Treatment
Disorders w/ Hypocalcemia	<ul style="list-style-type: none"> <li>neuromuscular irritability</li> <li>-perioral numbness</li> <li>-sacral numbness</li> <li>-parasthesias</li> <li>-tetany</li> <li>-muscle cramps</li> <li>-carpal-pedal spasm</li> <li>-seizures</li> <li>-abnormal Chvostek's sign</li> <li>-tapping CN VII ? ipsilateral contraction of facial muscles</li> <li>-Trousseau's sign</li> <li>-occluding venous return in forearm ? carpopedal spasm</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>
2° Hyper-PTH	<ul style="list-style-type: none"> <li>normally, any disorder ? ? Ca<sup>2+</sup> ? ?PTH secretion</li> <li>2° (compensatory) hyper-PTH assoc. w/ <ul style="list-style-type: none"> <li>-renal disease</li> <li>-Vitamin D deficiency (classical rickets)</li> <li>-acquired vitamin D-resistant states</li> <li>-renal tubular disease</li> </ul> </li> <li>in mild disease, ?PTH ? nl. serum Ca<sup>2+</sup></li> <li>in progressive disease, ?PTH becomes unable to compensate</li> <li>-lack of active Vitamin D ? ? ability of PTH to mobilize Ca<sup>2+</sup> from bone</li> <li>hypercalcemia is NOT seen in 2° hyper-PTH</li> <li>occasionally, end-stage renal disease ? <b>severe</b> 2° hyper-PTH ? overt hypercalcemia</li> <li>-esp. following renal transplantation</li> </ul> <p><u>3° hyper-PTH</u></p> <ul style="list-style-type: none"> <li>long-term compensatory hyperactivity ? autonomous PTH release</li> </ul>	<ul style="list-style-type: none"> <li></li> <li>often managed w/ control of renal disease</li> <li>occasionally partial parathyroidectomy required</li> </ul>
Pseudo-hypo-parathyroidism	<ul style="list-style-type: none"> <li>genetically determined ? in a guanine nucleotide regulatory protein (G<sub>s</sub>)</li> <li>-?G<sub>s</sub> may also ? hormone-resistant states (gonadotropin, TSH, vasopressin, glucagons)</li> <li>-regulatory protein normally couples PTH receptor to adenylyl cyclase</li> </ul> <p><b>target organ resistance to PTH</b></p> <ul style="list-style-type: none"> <li>-major defect</li> <li>-phenotype</li> <li>-short stature</li> <li>-round facies</li> <li>-short neck</li> <li>-brachydactyly (shortened 4<sup>th</sup> metacarpals &amp; metatarsals)</li> <li>-mental retardation</li> <li>-seizures</li> </ul> <ul style="list-style-type: none"> <li>symptoms</li> <li>-ectopic calcifications (esp. in basal ganglia)</li> <li>-nl. or ? bone density</li> </ul> <ul style="list-style-type: none"> <li>labs</li> <li>-hypocalcemia</li> <li>-hyperphosphatemia</li> <li>-?PTH</li> <li><b>-PTH infusion does NOT ? ?phosphate &amp; ?cAMP in urine</b></li> <li>-diagnostic hallmark of this disease</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>
Pseudo-pseudo-Hypo-parathyroidism	<ul style="list-style-type: none"> <li>genetic variant of pseudo-hypo-PTH</li> <li><b>-NO hypocalcemia</b></li> <li>reflects a stage in expression of pseudo-hypo-PTH</li> <li>imprinting may explain difference in phenotype from pseudo-hypo-PTH</li> </ul>	<ul style="list-style-type: none"> <li></li> </ul>
Hypo-PTH	<ul style="list-style-type: none"> <li>occurs commonly after neck exploration for parathyroid or thyroid disease</li> <li>also seen as either</li> <li>-1° acquired disorder</li> <li>-multiple endocrine end organ failure <ul style="list-style-type: none"> <li>-parathyroids, pituitary thyroid, adrenals, gonads, &amp; endocrine pancreas may fail in any order or combination</li> <li>-unpredictable time sequence</li> </ul> </li> <li>-also see: pernicious anemia &amp; myasthenia gravis</li> <li>-rarely occurs as: DiGeorge's syndrome—abnormality of 3<sup>rd</sup> &amp; 4<sup>th</sup> brachial pouches w/ thymus aplasia</li> <li>hypocalcemia is assoc. w/ absent PTH secretion,</li> <li>-thus [in contrast w/pseudo-hypo-PTH] <b>PTH infusion ? ?? in urinary phosphate &amp; cAMP</b></li> </ul>	<p><b>Other Causes of Hypocalcemia</b></p> <ul style="list-style-type: none"> <li>renal failure</li> <li>-hyperphosphatemia</li> <li>-unable to convert 25-Vitamin D to 1,25-Vitamin D</li> <li>acute pancreatitis</li> <li>-transient hypocalcemia</li> <li>Hypomagnesemia</li> <li>-Mg<sup>2+</sup> deficiency ? defect in PTH release ? hypocalcemia</li> </ul>

	Epidemiology	Risk Factors	Clinical	Diagnosis
Osteoporosis	<ul style="list-style-type: none"> <li>• affects 10-12million people in US</li> <li>• causes</li> <li>- &gt; 300,000 <b>hip fractures</b> per yr.</li> <li>-most occur in women &gt; 65y.o. and men &gt; 75y.o.</li> <li>-most serious effect of osteoporosis</li> <li>-assoc. w/ high morbidity &amp; mortality</li> <li>- <b>12-25% mortality in 1<sup>st</sup> yr. after fracture</b></li> <li>-leading cause of disability in the elderly</li> <li>- &gt; 500,000 <b>vertebral</b> fractures per yr.</li> <li>-many are <b>asymptomatic</b></li> <li>• probability of a fall directly related to loss of: <ul style="list-style-type: none"> <li>-muscle strength, coordination, balance, eyesight, &amp; meds</li> </ul> </li> <li>• skeletal growth &amp; development</li> <li>-consolidated by accrual of bone mass <ul style="list-style-type: none"> <li>-continues until 'peak' bone mass at skeletal maturity</li> <li>-afterwards, bone mass plateaus for ~ 15-20yrs</li> </ul> </li> <li>• after age 40, bone density ?</li> <li>-in <b>both men &amp; women</b></li> <li>-accelerated ? in women during 5yrs. post-menopause</li> <li>• <b>higher the peak bone mass, the longer it takes to reach level of significantly ?fracture risk</b></li> </ul>	<p><u>Genetic</u></p> <ul style="list-style-type: none"> <li>• Caucasian &amp; Asian women have lower peak bone mass</li> <li>-thus, ?hip fracture rate vs. AA &amp; Hispanic women</li> <li>• ?susceptibility to hip fracture in women w/family h/o osteoporosis</li> <li>-slightly ? susceptibility in <ul style="list-style-type: none"> <li>-homocystinuria</li> <li>-osteogenesis imperfecta</li> </ul> </li> </ul> <p><u>Dietary factors</u></p> <ul style="list-style-type: none"> <li>• lower bone mass in pts. w/ <ul style="list-style-type: none"> <li>-lactose intolerance</li> <li>-h/o adolescent eating disorders</li> </ul> </li> </ul> <p><u>Physical activity</u></p> <ul style="list-style-type: none"> <li>• athletic activity (weight-bearing exercises) important to peak bone mass development during <b>adolescence</b></li> <li>• in adults, exercise adds <b>little bone mass</b>, but does add strength</li> </ul> <p><u>Lifestyle</u></p> <ul style="list-style-type: none"> <li>• excessive EtOH ? bone loss</li> </ul> <p><u>Endocrine factors</u></p> <ul style="list-style-type: none"> <li>• gonadal failure, hyperthyroidism, hyper-PTH, &amp; hypercortisolism all cause bone loss</li> </ul> <p><u>Gender</u></p> <ul style="list-style-type: none"> <li>• bone <b>density</b> is the <b>same</b> in age-matched men &amp; women</li> <li>• men have <b>wider</b> bones ? ?susceptibility to fractures</li> </ul> <p><u>Medications</u></p> <ul style="list-style-type: none"> <li>• ?bone loss w/: <ul style="list-style-type: none"> <li>-glucocorticoids,</li> <li>-high dose Vitamin A or D</li> <li>-immunosuppressants</li> <li>-thyroid hormone in excess</li> <li>-some anticonvulsants</li> <li>-chronic heparin</li> </ul> </li> </ul> <p><u>Chronic inflammation</u></p> <ul style="list-style-type: none"> <li>• Rheumatoid arthritis ? cytokine activation of bone resorption</li> </ul>	<ul style="list-style-type: none"> <li>• fractures most often at <ul style="list-style-type: none"> <li>-spine</li> <li>-hip</li> <li>-distal radius</li> <li>-proximal humerus</li> </ul> </li> </ul> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p><u>Bone Densitometry</u></p> <ul style="list-style-type: none"> <li>• measures amt. of Ca<sup>2+</sup></li> <li>-precise, accurate, safe</li> <li>• related to reference of nl. pts. age 25-30 who have reached peak bone mass</li> <li>• <b>relate older pt's bones density to younger pt's</b></li> <li>-basis of modern diagnosis</li> <li>-comparison between older and younger gives measure of <b>how much bone is lost since peak</b> bone mass</li> <li>• T-score</li> <li>-comparison between older pt. &amp; younger pt.</li> <li>-for <b>every S.D.</b> ? in bone density, fracture <b>risk ? 2X</b></li> <li>-<b>osteoporosis = 2.5 S.D.</b>s below reference (young adult) <ul style="list-style-type: none"> <li>-T &lt; -2.5</li> </ul> </li> <li>-<b>osteopenia</b> <ul style="list-style-type: none"> <li>-T is between -1.0 and -2.5</li> </ul> </li> <li>• ? rate of bone <b>remodeling</b> in adults is assoc. w/ ?rate of bone <b>loss</b></li> </ul> </div> <p><u>Histopathology</u></p> <ul style="list-style-type: none"> <li>• iliac biopsy</li> <li>-used to rule out osteomalacia, mastocytosis or Gaucher disease</li> <li>-important in adult w/bone pain, low mineral density, &amp; profile suggestive of osteomalacia</li> <li>• hip fracture</li> <li>-histology of femoral head can rule out pathologic (metastatic disease) fracture</li> </ul>	<p><u>Plain Radiographs</u></p> <ul style="list-style-type: none"> <li>• insensitive</li> <li>-unsuitable for early detection</li> <li>• advanced diseases shows</li> <li>-severe osteopenia</li> <li>-“fish-mouth” deformity of intervertebral spaces</li> <li>-thinning of cortices</li> <li>-old or current fractures</li> </ul>

	Definition	Etiology	Clinical	Labs	Histology
Rickets	<ul style="list-style-type: none"> <li>disease of bone matrix mineralization</li> <li>childhood disease during period of growth</li> <li>severely impacts immature, partly cartilaginous skeleton</li> <li>mineralization defect affects both bone &amp; cartilage</li> <li>-inadequate calcification of newly formed bone matrix &amp; cartilage at <b>active growth zones</b> (epiphyses) ? interferes w/ normal growth</li> </ul>	<u>Causes</u> <ul style="list-style-type: none"> <li>Vit. D dietary deficiency</li> <li>GI or hepatobiliary diseases ? malabsorption of Vit. D calcium</li> <li>drugs ? abnormal Vit. D metabolism</li> <li>causes of chronic hypophosphatemia</li> <li>-RTA</li> <li>-hereditary syndromes ? renal phosphate wasting</li> <li>-rare mesenchymal tumors ? acquired phosphate wasting</li> </ul> <u>Pathogenesis</u> <ul style="list-style-type: none"> <li>prolonged ? in ionized <math>Ca^{2+}</math> or phosphate ? failure to mineralize osteoid</li> <li>-?extracellular <math>Ca^{2+}</math> <b>or</b> phosphate ? ?<math>Ca^{2+}</math>-phosphate molar product ? defective mineralization</li> <li>osteoclasts do NOT resorb osteoid effectively ? excess unmineralized osteoid on bone surfaces</li> <li>new bone lacks strength</li> <li>-tensile &amp; compressive</li> <li>in children</li> <li>-?mineralization of chondrocyte columns ? overgrowth &amp; ?in irregular cartilage nodules ?</li> <li>?cartilage turnover ? cartilage retention in 1°metaphyseal bone ? widened &amp; irregular growth plates</li> <li>-microfractures ? capillary overgrowth w/in growth plates</li> <li>-eventually, impaired growth in length of skeleton</li> <li>bones formed by <b>intramembranous ossification</b> (flat bones) NOT affected the same way</li> <li>-does NOT involve calcification of cartilage</li> </ul>	<ul style="list-style-type: none"> <li>depends on severity &amp; age</li> <li>infants</li> <li>-skull</li> <li>-flattened occipital bones</li> <li>-widely opened fontanels</li> <li>-frontal bossing &amp; buckling</li> <li>-due to excess osteoid</li> <li>-chest</li> <li>-“beading” of costo-chondral junction</li> <li>-causes “rachitic rosary”</li> <li>-inward traction of resp. muscles</li> <li>-“pigeon-breast” deformity</li> <li>-inward pull of diaphragm</li> <li>-“Harrison groove”</li> <li>older child</li> <li>-pelvic deformities</li> <li>-spine: “lumbar lordosis”</li> <li>-swollen wrists &amp; ankles</li> <li>-long bones: “knock knees”</li> <li>-due to mechanically deficient osteoid</li> </ul>	<ul style="list-style-type: none"> <li>low to nl. serum <math>Ca^{2+}</math></li> <li>low serum phosphorus</li> <li>?serum alkaline phosphatase, osteocalcin, N-telopeptides</li> <li>low 24 urine <math>Ca^{2+}</math></li> <li>serum 25(OH)D</li> <li>-? in Vit. D deficiency</li> <li>-nl. in other states</li> <li>serum 1,25(OH)<sub>2</sub>D</li> <li>-? in severe Vit. D deficiency</li> <li>-?when Vit.D is slightly ?</li> </ul>	<ul style="list-style-type: none"> <li>abnormal chondrocyte alignment in growth plates</li> <li>unmineralized cartilage retained ? irregular nodules</li> <li>irregular vascular ingrowth</li> </ul>
Osteomalacia	<ul style="list-style-type: none"> <li>disease of bone matrix mineralization</li> <li>adult disease</li> <li>involves mature skeleton <b>after epiphyses close</b></li> <li>affects only newly formed bone</li> </ul>	<ul style="list-style-type: none"> <li>overgrowth &amp; ?in irregular cartilage nodules ?</li> <li>?cartilage turnover ? cartilage retention in 1°metaphyseal bone ? widened &amp; irregular growth plates</li> <li>-microfractures ? capillary overgrowth w/in growth plates</li> <li>-eventually, impaired growth in length of skeleton</li> <li>bones formed by <b>intramembranous ossification</b> (flat bones) NOT affected the same way</li> <li>-does NOT involve calcification of cartilage</li> </ul>	<ul style="list-style-type: none"> <li><b>pain</b> from</li> <li>-stress fractures</li> <li>-completed fracture</li> <li>proximal myopathy ? muscle weakness ? waddling gait</li> <li>bowing of lower extremities</li> <li>“Looser’s lines” on X-ray</li> <li>-bilateral &amp; symmetrical</li> <li>-located in femoral neck, pubis, ischium</li> <li>-due to excess osteoid along blood vessels</li> </ul>		<ul style="list-style-type: none"> <li>?bone surface covered by osteoid</li> <li>?thickness of osteoid seams ? ? or nl. cancellous bone volume despite evidence of osteopenia</li> <li>tetracycline labeling</li> <li>-very sensitive in detection of osteomalacia</li> <li>-shows ?bone formation &amp; mineralization</li> </ul>
Renal Osteodystrophy	<ul style="list-style-type: none"> <li>heterogeneous bone &amp; soft tissue disorders assoc. w/ renal failure</li> <li>renal failure (GFR &lt; 30%) ? widespread pathological ?s in skeleton &amp; soft tissues</li> </ul>	<ul style="list-style-type: none"> <li>chronic renal insufficiency</li> <li>-?renal parenchyma ? ?phosphate excretion ? hyperphosphatemia ? <math>Ca^{2+}</math>-phosphate precipitates ? ?serum <math>Ca^{2+}</math> ? hypocalcemia ? ?PTH secretion (if prolonged ? 2° hyper-PTH)</li> <li>-also important: ?renal parenchyma ? ?Vit. D 1-<math>\alpha</math>-hydroxylase activity ? ?25(OH)-D conversion to 1,25(OH)<sub>2</sub>-D ? ?intestinal <math>Ca^{2+}</math> absorption ? worsened hypocalcemia</li> <li><u>High Turnover Disease</u> (Osteitis Fibrosa) <ul style="list-style-type: none"> <li>most common form of uremic osteodystrophy</li> <li>?PTH, ?bone turnover, ?cell #, ?bone formation, marrow fibrosis</li> </ul> </li> <li><u>Low Turnover Disease</u> <ul style="list-style-type: none"> <li>nl. (or slightly ?) PTH, ?osteoblastic &gt;&gt; ?osteoclastic activity</li> <li>related to aluminum toxicity</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>in children: similar signs and symptoms to rickets</li> <li>-other factors contributing to growth retardation are</li> <li>-chronic acidosis</li> <li>-protein malnutrition</li> <li>-lack of IGF-1 ? skeletal resistance to GH</li> </ul>	<ul style="list-style-type: none"> <li>X-ray findings are similar to rickets and osteomalacia</li> <li>in children</li> <li>-“Rugger Jersey” spine</li> <li>-characteristic of 2° hyper-PTH</li> <li>-extension of sclerotic trabeculae ? vertical striations</li> <li>-slipped epiphyses in femur or tibia ? deformities</li> <li>in adults</li> <li>-“salt &amp; pepper” skull</li> </ul>	

