PATHOLOGY OF BONE DISEASES

Modeling/RE-modeling
CELLS of BONE

- **OSTEOPROGENITOR ("STEM")→(TGFβ)**
- **OSTEOBLASTS (surface of spicule), under control of calcitonin to take blood calcium and put it into bone.**
- **OSTEOCYTES (are osteoblasts which are now completely surrounded by bone)**
- **OSTEOCLASTS (macrophage lineage), under control of PTH to chew up the calcium of bone and put it into blood**

Proteins (organic) of BONE

- **Type 1 (TYPE [B]ONE) collagen (90%)**
- **Cell adhesion proteins, i.e. CAMs: Osteopontin, fibronectin, thrombospondin**
- **Calcium-binding proteins: Osteonectin, sialoprotein**
- **Proteins involved in mineralization: Osteocalcin Enzymes: Collagenase, Alk. Phos.**
- **Growth factors**
- IGF-1, TGF-β, PDGF **Cytokines**
  - Prostaglandins, IL-1, IL-6, RANKL
- Proteins Concentrated from Serum
  - β2 –microglobulin Albumin
  - IGF, insulin-like growth factor
  - TGF, transforming growth factor

- PDGF, platelet-derived growth factor
- IL, interleukin
- RANKL, RANK ligand

Minerals (IN-organic) of BONE
HYDROXY-APATITE
Ca5(PO4)3(OH)
Ca10(PO4)6(OH)2
ADJECTIVES of BONE

- **Compact**
  - **Dense**
  - **Cortical**
- **Spongy**
  - **Cancellous**
  - **Membranous**
  - **Endosteal**
  - **Spicular**

Woven vs. “Lamellar”

-BLASTS/-CLASTS
BONE DISEASES

- **1) MALFORMATIONS AND DISEASES CAUSED BY DEFECTS IN NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS, polydactyly, syndactyly, absence of a bone**
- **2) DISEASES CAUSED BY DEFECTS IN HORMONES AND SIGNAL TRANSDUCTION MECHANISMS, achondroplasia, thanatophoria**
- **3) DISEASES ASSOCIATED WITH DEFECTS IN EXTRACELLULAR**

STRUCTURAL PROTEINS

- **Type 1 Collagen Diseases (Osteogenesis Imperfecta)**
- **Types 2, 10, and 11 Collagen Diseases**

- **4) DISEASES ASSOCIATED WITH DEFECTS IN FOLDING AND DEGRADATION OF MACROMOLECULES**
  - **Mucopolysaccharidoses**
- **5) DISEASES ASSOCIATED WITH DEFECTS IN METABOLIC PATHWAYS (ENZYMES, ION CHANNELS, AND TRANSPORTERS)**
  - **Osteopetrosis**
- **6) DISEASES ASSOCIATED WITH DECREASED BONE MASS**
  - **Osteoporosis**
- **7) DISEASES CAUSED BY OSTEOCLAST DYSFUNCTION**
  - **Paget Disease (Osteitis Deformans)**
- **8) DISEASES ASSOCIATED WITH ABNORMAL MINERAL (Ca++) HOMEOSTASIS**
  - **Ricketts and Osteomalacia**
  - **Hyperparathyroidism**
  - **Renal Osteodystrophy**

1) MALFORMATIONS AND DISEASES CAUSED BY DEFECTS IN NUCLEAR PROTEINS AND "<u>TRANSCRIPTION FACTORS</u>"

protein→DNA□mRNA

- **Congenital absence of a, usually single, bone: phalanx, rib, clavicle**
- **Supernumerary digit (polydactyly)**
- **Syndactyly**
- **CRANIORACHISCHISIS**

2) DISEASES CAUSED BY DEFECTS IN HORMONES AND <u>SIGNAL TRANSDUCTION</u> MECHANISMS

- **Achondroplasia, dwarf (non-lethal)**
- **Thanatophoria, dwarf (lethal, FGF-3 mutations)**

- a point mutation (usually Arg for Gly375) in the gene that codes for FGF receptor 3 (FGFR3), which is located on the short arm of chromosome 4. In the normal growth plate, activation of FGFR3 *inhibits* cartilage proliferation, hence the term “achondroplastic”;
- A MUTATION causes FGFR3 to be constantly activated.

3) DISEASES ASSOCIATED WITH DEFECTS IN EXTRACELLULAR STRUCTURAL PROTEINS

- **OSTEOGENESIS IMPERFECTA TYPES**
- **(“Brittle” bone disease, too LITTLE bone), BLUE sclerae**
- **Mutations in genes which code for the alpha-1 and alpha-2 chains of COLLAGEN 1**
- **Mutations of COLLAGEN 2,10, 11 manifest themselves as CARTILAGE diseases, ranging from joint cartilage destruction to fatal sequelae**

Osteogenesis Imperfecta

4) DISEASES ASSOCIATED WITH DEFECTS IN FOLDING AND DEGRADATION OF MACROMOLECULES (glycosaminoglycans)

- **MUCOPOLYSACCHARIDOSIS (one of MANY lysosome storage diseases)**
- **DECREASES in ENZYMES which degrade:**
  - **DERMATAN**
  - **HEPARAN**
  - **KERATAN**
- **Chiefly CARTILAGE disorders: short, chest wall, malformed bones**

MUCOPOLYSACCHARIDOSES

5) DISEASES ASSOCIATED WITH DEFECTS IN METABOLIC PATHWAYS (ENZYMES, ION CHANNELS, AND TRANSPORTERS)

- **OSTEOPETROSIS, 4 types**
- **One common one has a CARBONIC ANHYDRASE deficiency, i.e., ↓ acid**
- **DECREASED osteoclast resorption**
- **"MARBLE" bone, increased bone, brittle, sclerotic bone**

OSTEOPETROSIS

6) DISEASES ASSOCIATED WITH DECREASED BONE MASS

- **OSTEOPOROSIS**
- **"PEAK" bone mass is early adulthood**
- **Normal decline, slow**
- **Osteoporosis is accelerated bone loss**
- **Factors:**
  - **AGE**
  - **Physical activity**
  - **Estrogen withdrawal (menopause)**
  - **Nutrition (Ca++)**
  - **Genetics**

OSTEOPOROSIS

7) DISEASES CAUSED BY OSTEOCLAST DYSFUNCTION

Paget Disease (Osteitis Deformans)

- **Matrix madness, Osteoblasts/-cytes gone wild**
- **THREE PHASES:**
  - **1) Increased osteoclast resorption**
  - **2) Increased "hectic" bone formation (osteoblasts)**
  - **3) Osteosclerosis**

- **ELEVATED ALKALINE-PHOSPHATASE**
- **ELEVATED urine HYDROXYPROLINE**

PAGET's DISEASE

8) DISEASES ASSOCIATED WITH ABNORMAL MINERAL HOMEOSTASIS

- **Ricketts and Osteo"malacia"**
  - **VITAMIN D deficiency/dysfunction**
- **Hyperparathyroidism, PRIMARY (PTH ADENOMA)**
  - **ENTIRE SKELETON**
  - **OSTEITIS FIBROSIS CYSTICA (von Recklinghausen's disease (of bone)**
  - **"BROWN"* TUMOR**
- **Hyperparathyroidism, SECONDARY (RENAL) (NOT AS SEVERE AS 1^{o})**
- **Renal Osteodystrophy = ANY bone disorder due to chronic renal disease**

PRIMARY HYPERPARATHYROIDISM

RENAL OSTEODYSTROPHY

- **PHOSPHATE RETENTION**

- **HYPOPHOSPHATEMIA**
- **HYPOCALCEMIA**
- **INCREASED PTH**
- **INCREASED OSTEOCLASTS**
- **METABOLIC ACIDOSIS → release of HYDROXYAPATITES from matrix**

FRACTURES
FRACTURES, adjectives

- **Complete, incomplete**
- **Closed, open (communicating)**
- **Communited (splintered, "greenstick")**
- **Displaced (NON-aligned)**
- **PATHOGENIC, (non-traumatic, 2^{o} to other disease, often metastases)**
- **"STRESS" fracture**

FRACTURES

- **THREE PHASES**
  - **HEMATOMA, minutes days→ PDGF, TGF-β, FGF**
  - **SOFT CALLUS ("PRO"-CALLUS), ~1 week**
  - **HARD CALLUS (BONY CALLUS), several weeks**
- **COMPLICATIONS**
  - **PSEUDARTHROSIS (non-union)**

- INFECTION (especially OPEN [communicating] fractures)

FRACTURES

OSTEONECROSIS

- Also called AVASCULAR necrosis
- Also called ASEPTIC necrosis

- CAUSE: ISCHEMIA
  - Trauma
  - Steroids
  - Thrombus/Embolism
  - Vessel injury, e.g., radiation
  - INCREASED intra-osseous pressure→vascular compression
  - Venous hypertension too

OSTEONECROSIS

OSTEONECROSIS

OSTEONECROSIS

OSTEOMYELITIS

- Pyogenic: Staph, E. coli, Pseudom, Kleb, Salmonella
  - Hematogenous
  - Contiguous, e.g., from a nearby joint
  - Direct implantation
- TB
- Syphilis

OSTEOMYELITIS

- **DX: X-ray, Bone scan**

OSTEOMYELITIS

- **DX: Histology**

OSTEOMYELITIS

- **COMPLICATIONS**
  - **Subperiosteal abscess**
  - **Draining sinus**
  - **Joint involvement**

- **SEQUESTRUM (dead bone)**

vs.

- **INVOLUCRUM (new bone)**

OSTEOMYELITIS

- **Tuberculous**
  - **Usually blood borne**
  - **TB of spine is known as POTTS disease**

- **Syphilis**
  - **CONGENITAL**
  - **TERTIARY, “SABRE” shins**

POTT’s DISEASE

SABER SHINS

BONE TUMORS

- BONE
- CARTILAGE
- FIBROUS
- MISC.
  - Ewing's "sarcoma"
  - Giant Cell Tumor
  - METASTASES

BONE- BONE TUMORS

- OSTEOMA
- OSTEOID OSTEOMA (nidus)
- OSTEOBLASTOMA
- OSTEOSARCOMA (OSTEOGENIC SARCOMA)

OSTEOMA

- SOLITARY
- MIDDLE AGE
- FROM SUBPERIOSTEAL or ENDOSTEAL surfaces

- **SKULL, FACE, most common**
- **Totally BENIGN**
- **To be distinguished from REACTIVE BONE, (can be difficult)**

OSTEOID OSTEOMA

- **At least 2 cm in diameter**
- **Teens, twenties, APPENDICULAR skeleton**
- **M>>F**
- **PAINFUL**
- **Has a NIDUS**
- **Responds to aspirin**
- **Induces a MARKED bony reaction**

OSTEOBLASTOMA

- **AXIAL SKELETON, i.e., SPINE**
- **NO nidus**
- **NO bony reaction**
- **NOT relieved by aspirin**

OSTEOSARCOMA (OSTEOGENIC SARCOMA)

TYPES of OSTEOSARCOMAS

- **The anatomic portion of the bone from which they arise (intramedullary, intracortical, or surface)**
- **Degree of differentiation**
- **Multicentricity (synchronous, metachronous[NOT synchronous])**
- **Primary (pre-existing bone is unremarkable) or secondary (e.g., osteosarcoma associated with pre-existing disorders such as benign tumors, Paget disease, bone infarcts, previous irradiation)**
- **Histologic variants (osteoblastic, chondroblastic, fibroblastic, telangiectatic, small cell, and giant cell)**

BONE- CARTILAGE TUMORS

- **OSTEOCHONDROMA (EXOSTOSIS)**
- **CHONDROMA**
- **CHONDROBLASTOMA**
- **CHONDROMYXOID FIBROMA**
- **CHONDROSARCOMA**

OSTEOCHONDROMA (EXOSTOSIS)

- **Common, Cartilage AND Bone present**
- **Often MULTIPLE as a hereditary syndrome**
- **M>>>F**
- **PELVIS, SCAPULAE, RIBS**

CHONDROMA

- Chondroma vs. EN-chondroma
- PURE Hyaline Cartilage
- MULTIPLE enchondromas = Ollier's dis.
- Maffucci Synd. if hemangiomas present

CHONDROBLASTOMA

- RARE, in teenagers
- M>>F
- KNEES, usually
- Epiphyses
- MUCH LESS matrix than a chondroma

CHONDROMYXOID FIBROMA

- RAREST of all
- TEENS, MALES
- "MYXOID" concept
- "ATYPIA"

CHONDROSARCOMA

- ANATOMY
  - INTRAMEDULLARY
  - JUXTACORTICAL

- **HISTOLOGY**
  - **CONVENTIONAL**
    - **HYALINE**
    - **MYXOID**
  - **CLEAR**
  - **DE-DIFFERENTIATED**
  - **MESENCHYMAL**

CHONDROSARCOMA

BONE- FIBROUS TUMORS

- **FIBROUS CORTICAL DEFECT/NON-OSSIFYING FIBROMA**
- **FIBROUS DYSPLASIA**
- **FIBROSARCOMA/MALIGNANT FIBROUS HISTIOCYTOMA**

FIBROUS CORTICAL DEFECT

- **COMMON, usually LESS THAN 1 CM**
- **CHILDREN >2**
- **IF MORE THAN 5-6 CM, they are then called NON-OSSIFYING FIBROMA**

FIBROUS "DYSPLASIA"

- **BENIGN TUMOR**
- **THREE TYPES**
  - **SINGLE BONE (70%)**

- POLY-OSTOTIC (27%)
- POLY-OSTOTIC (3%) with café-au-lait and endocrine disorders, especially precocious puberty

FIBROSARCOMA/MFH

- METAPHYSES of LONG BONES
- PELVIC FLAT BONES
- LYTIC
- FRACTURES
- OF COURSE, SARCOMATOUS METASTASIS

MISC. TUMORS of BONE

- EWING sarcoma/PNET (Primitive NeuroEctodermal Tumor)
- GIANT CELL TUMOR
- METASTASES

EWING/PNET

- SAME TUMOR
- SMALL ROUND BLUE CELL TUMOR
- NEUROENDOCRINE CELL ORIGIN
- CHROMOSOME TRANSLOCATION 11&22
- SECOND most COMMON bone malignancy in CHILDREN

- **ARISE IN MEDULLARY CAVITY of BONE**
- **LOOK LIKE LYMPHOMA**

GCT (Giant Cell Tumor), BONE METASTASES

SYNOVIAL JOINTS
TWO KINDS of cells form the synovial intima

- **1) fibroblasts**
  - **Hyaluronin**
  - **Lubricin**
- **2) macrophages**

The **SUB-intima** is loose CT or fat

JOINT DISEASES

- **"ARTHRITIS"**
  - **DEGENERATIVE (OSTEOARTHRITIS)**
  - **RHEUMATOID**
  - **"JUVENILE" RHEUMATOID**
  - **NON-INFECTIOUS: Ankylosing Spond., Reactive, Psoriasis, IBD**

- INFECTIOUS: Supp., TB, Lyme, Viral
- GOUT (URATE)
- PSEUDOGOUT (PYROPHOSPHATE)

- Tumors (all are of synovium)
  - Ganglion (Synovial Cyst), non-neoplastic
  - Giant Cell Tumor (Pigmented VilloNodular Synovitis[PVNS]), benign
  - Synovial Sarcoma, malignant

"DEGENERATIVE" ARTHRITIS
aka, "OSTEO"ARTHRITIS

- Etiology/Risk Factors: Age, Trauma, Genes
- Pathogenesis: Progressive EROSION of articular cartilage
- Morphology: X-Ray, "eburnation", "joint mice", osteophytes
- Clinical Expression: PAIN, Limitation of motion

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder that may affect many tissues and organs—skin, blood vessels, heart, lungs, and muscles—but principally attacks the joints, producing a nonsuppurative proliferative and inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints.

TWO KINDS of cells form the synovial intima

- 1) fibroblasts
  - Hyaluronin
  - Lubricin

- **2) macrophages**

The **SUB-intima** is loose CT or fat

RHEUMATOID ARTHRITIS

- **Etiology/Risk Factors: Autoimmune**
- **Pathogenesis: Progressive SYNOVITIS**
- **Morphology: Synovial lymphocytes, macrophages, plasma cells, neutrophils, osteoclasts, "pannus", hyperemia, rheumatoid "nodules", vasculitis**
- **Clinical Expression: PAIN, Limitation of motion, malaise, fatigue, rheumatoid factor IgM→IgG-Fc,**

DIAGNOSIS

- **CLINICAL FEATURES (1% of population F>>M)**
  - **MORNING STIFFNESS, MEAN AGE 45 YRS**
  - **ARTHRITIS in MORE THAN 3 JOINT AREAS**
  - **"TYPICAL" hand findings, MP ULNAR deviation**
  - **SYMMETRIC ARTHRITIS**
  - **SERUM RHEUMATOID FACTOR**
  - **"TYPICAL" X-RAY findings**

"JUVENILE" Rheumatoid Arthritis

- **Begins BEFORE age 16, by definition**
- **Generally LARGER joints than RA**

- **Often POSITIVE ANA**

  “SERONEGATIVE” ARTHRITIDES

- **ANKYLOSING SPONDYLITIS (aka, “rheumatoid” spondylitis, or Marie-Strumpell Disease [HLA-B27] (M>>F)**

- **“REACTIVE” ARTHRITIS (FOLLOWS GU or GI INFECTIONS)**

  - **REITER SYDROME (urethral & conjunctival inflammation too) [HLA-B27]**

  - **Arthritis associated with IBD**

- **PSORIATIC ARTHRITIS [HLA-B27]**

  Ankylosing Spondylitis

  INFECTIOUS ARTHRITIS

- **From OSTEOMYELITIS**

- **USUALLY SUPPURATIVE**

- **GC, staph, strep, H. flu, E. coli, (Salmonella in sicklers)**

- **4 cardinal signs, fever, leukocytosis, □ ESR**

  INFECTIOUS ARTHRITIS

- **TB**

- **LYME Disease, i.e., Borrelia burgdorferi, from Ixodes ticks**

- **VIRAL**

- **Parvovirus B19**
- **Rubella**
- **Hepatitis C**

GOUT

- **Endpoint of HYPERURICEMIA from ANY cause resulting in JOINT deposition of monosodium urate crystals (TOPHI)**
  - **ACUTE**
  - **CHRONIC**
- **10% of population has hyperuricemia (>7 mg/dl), but only 1/20 of these has gout**

HYPERURICEMIA→ GOUT

- ***Age*** **of the individual and duration of the hyperuricemia are factors. Gout rarely appears before 20 to 30 years of hyperuricemia. M>>F**
- ***Genetic predisposition*** **is another factor. In addition to the well-defined X-linked abnormalities of HGPRT, primary gout follows multifactorial inheritance and runs in families.**
- **Heavy *alcohol* consumption predisposes to attacks of gouty arthritis.**
- ***Obesity*** **increases the risk of asymptomatic gout.**
- **Certain *drugs* (e.g., thiazides) predispose to the development of gout.**
- ***Lead toxicity*** **increases the tendency to develop gout**

FEATURES

- **TOPHACEOUS ARTHRITIS**
- **GOUTY NEPHROPATHY**

GOUTY NEPHROPATHY
GOUT

- **Associated with ATHEROSCLEROSIS**
- **Associated with HYPERTENSION**

Pseudo-GOUT

- **Gout: Monosodium Urate**
- **Pseudo-GOUT: Calcium Pyrophosphate**
- **PSEUDOGOUT is also called CHONDROCALCINOSIS, or CPPD (Calcium Phosphate Deposition Disease)**
- **IDIOPATHIC, HEREDITARY, SECONDARY**
  - **Secondary→ joint damage, hyperparathyroidism, hemochromatosis, hypomagnesemia, hypothyroidism, ochronosis, and diabetes**

GOUT vs. PSEUDOGOUT
JOINT TUMORS

- **BENIGN**

- GANGLION (SYNOVIAL CYST)
- GIANT CELL TUMOR of TENDON SHEATH, aka PVNS, Pigmented VilloNodular Synovitis

- MALIGNANT
  - SYNOVIAL SARCOMA

GANGLION
PVNS/GCT
Synovial Sarcoma
"SOFT TISSUE" TUMORS

- FAT
- FIBROUS TISSUE
- FIBROHISTIOCYTIC
- SKELETAL MUSCLE
- SMOOTH MUSCLE
- VASCULAR
- PERIPHERAL NERVE
- UNCERTAIN: SYNOVIAL SARCOMA, ALVEOLAR SOFT PART SARCOMA, EPITHELIOD SARCOMA

CAUSES

- MOSTLY UNKNOWN
- RADIATION association
- CHEMICAL BURN association

- **THERMAL BURN association**
- **TRAUMA association**
- **VIRUS association (HHV8 for Kaposi)**
- **GENETICS**
- **Parts of many SYNDROMES**
- **MANY TRANSLOCATIONS**

SOFT TISSUE TUMORS

- **ALL "SPINDLY"**
- **Deep (desmoid) vs. Superficial (skin)**
- **Importance of counting MITOSES**
- **Importance of STAGING**
- **Importance of IMMUNOPEROXIDASE**
- **Importance of CONSULTATION**

FAT

- **LIPOMA**
- **LIPOSARCOMA**

FIBROUS TISSUE

- **NODULAR FASCIITIS (pseudosarcomatous)**
- **FIBROMATOSES (plantar,**

palmar, penile)

- **FIBROSARCOMA**

MYOSITIS OSSIFICANS

- **BENIGN FIBROUS TISSUE PROLIFERATION PLUS OSSEOUS "METAPLASIA"**

FIBROHISTIOCYTIC

- **FIBROUS HISTIOCYTOMA**
- **DERMATOFIBROSARCOMA PROTUBERANS**
- **MALIGNANT FIBROUS HISTIOCYTOMA**

SKELETAL MUSCLE

- **RHABDOMYOMA**
- **RHABDOMYOSARCOMA**

SMOOTH MUSCLE

- **LEIOMYOMA**
- **LEIOMYOSARCOMA**

VASCULAR

- **HEMANGIOMA**
- **LYMPHANGIOMA**
- **HEMANGIOENDOTHELIOMA**

- **HEMANGIOPERICYTOMA**
- **ANGIOSARCOMA**

PERIPHERAL NERVE

- **NEUROFIBROMA**
- **SCHWANNOMA**
- **GRANULAR CELL TUMOR**
- **MALIGNANT (SCHWANNOMA)**

UNCERTAIN

- **SYNOVIAL SARCOMA**
- **ALVEOLAR “SOFT PART” SARCOMA**
- **EPITHELIOD SARCOMA**