

TEST TIPS

Which of the following neoplasms may behave very aggressively locally but does not metastasize:

- 1--- ~~Conventional osteosarcoma~~
- 2--- ~~Ewing's tumor~~
- 3--- ~~De-differentiated chondrosarcoma~~
- 4. Desmoplastic fibroma
- 5--- ~~Sarcoma occurring in Paget's sarcoma~~

Correct answer by elimination is 4

Which of the following genetic defects is associated with Marfan's syndrome:

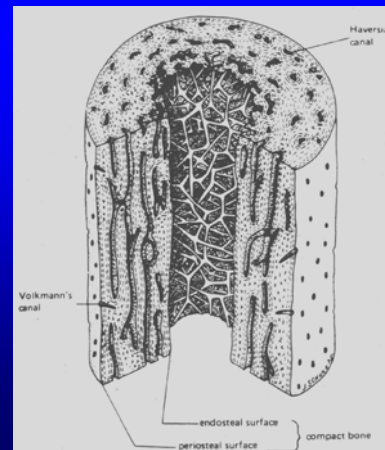
- 1- ~~Type II collagen~~ Spondyloepiphyseal dysplasia
- 2. Fibrillin
- 3- ~~Type I collagen~~ Osteogenesis imperfecta
- 4- ~~EXT1, EXT2 genes~~ **Multiple exostoses**
- 5- ~~Dystrophin~~ Duchenne muscular dystrophy

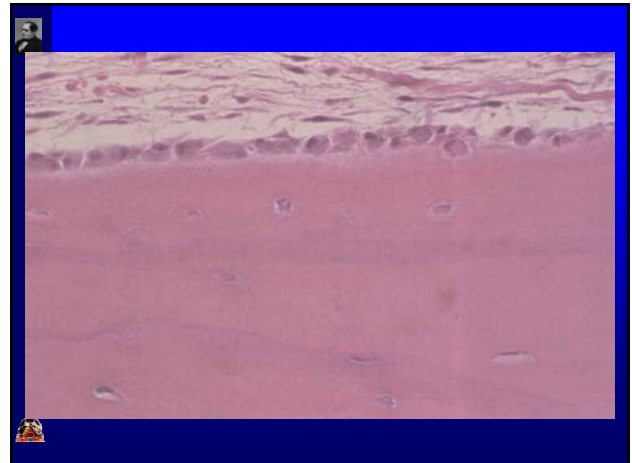
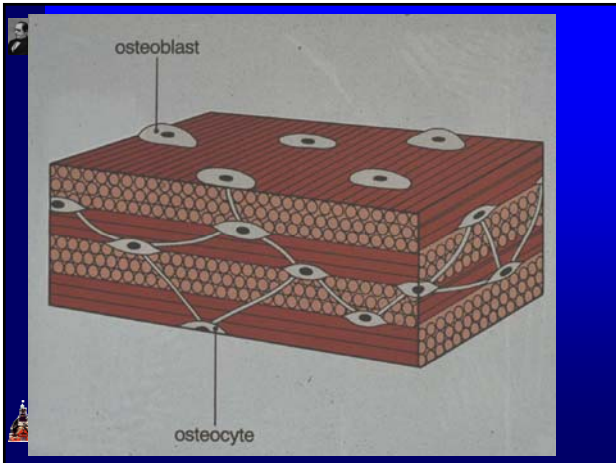
Know the answer is 2

Circle questions that you would like to come back to if you have time:

- questions in which you narrowed to 2 answers
- avoid questions in which you could not eliminate any distractors

Do not change an answer unless you are positive that your original choice was wrong

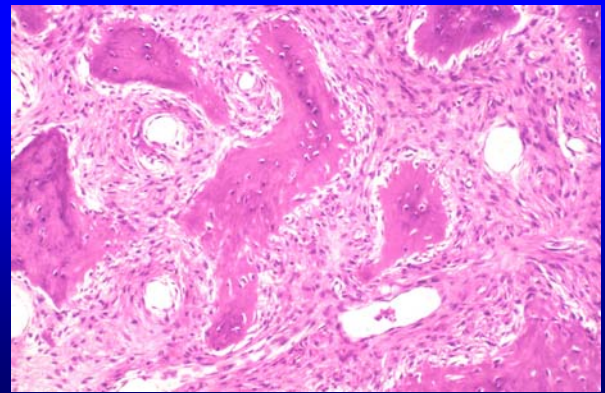




Classification: Microscopic Level

Woven Bone

- **Immature** bone found in the embryo & new bone (Fx and metaphysis)
- Found in tumors, Paget's & Osteogenesis Imperfecta
- Coarse-fibered, **no uniform pattern** of collagen
- **Isotropic** mechanical characteristics 2° to random pattern
- **More cellular** & variable mineral content

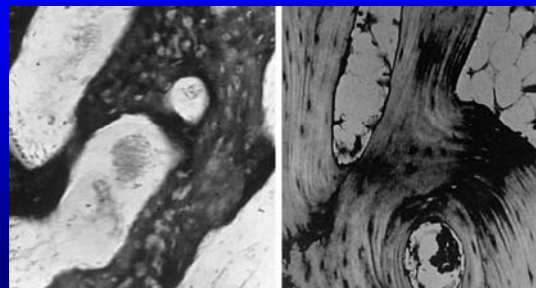


Classification: Microscopic Level

Lamellar Bone

- Begins 1 month postpartum, age 2 before most bone is lamellar
- **Mature bone** as a result of **remodeling** of woven bone
- **Cortical & trabecular** bone
- **Intramembranous** or **endochondral** ossification
- **Anisotropic** mechanical behavior 2° to parallel collagen arrangement
- Based on **orientation** of bone, greatest strength along the **long axis** of bone

Classification: Microscopic Level



Woven vs. Lamellar (random vs. circumferential layers)

Classification: Structural Level

Trabecular

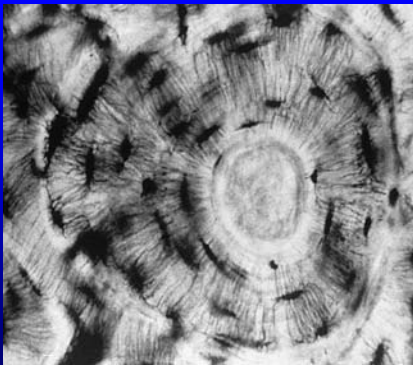
- “**Cancellous**” & “**spongy**”
- Located mainly in the **metaphysis** & **epiphysis**
- High turnover rate 2° large surface area
- Long bones and **vertebrae**

Classification: Structural Level

Cortical

- **Compact**: small animals, no vascular network, layers of lamellar bone
- **Plexiform**: large animals, facilitates rapid growth, lamellar and woven bone, vessels in woven bone
- **Haversian**: “**osteon**”, vascular channels, circumferentially around neurovascular canal, **oriented** in long axis of bone, Haversian canal & **Volkman’s canals** for nutrients transport

Haversian Canal in Osteon



Osteon with Haversian Canal & radial osteocytes

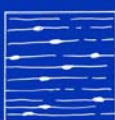
Classification: Structural Level

Differentiation

- **Porosity**: cortical <30% vs. trabecular 50-90%
- **Architecture**: **cortical**: solid with series of voids vs. **trabecular**: network of connecting plates separated by space
- **Mass**: cortical = 80% vs. trabecular = 20%

TYPES OF BONE

MICROSCOPIC



LAMELLAR

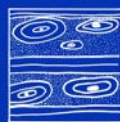


WOVEN

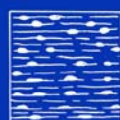
STRUCTURAL



CANCELLOUS



PLEXIFORM



COMPACT

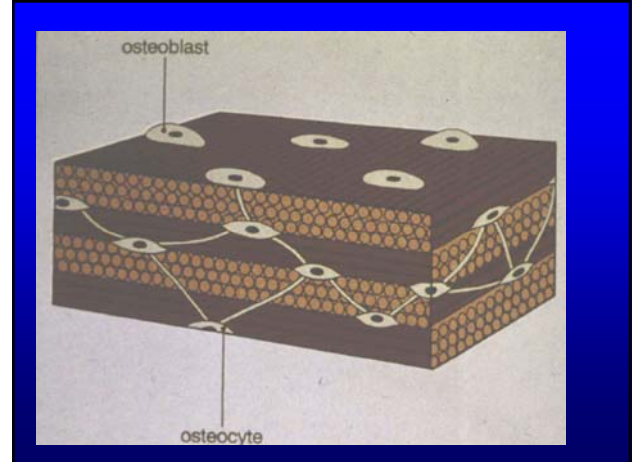
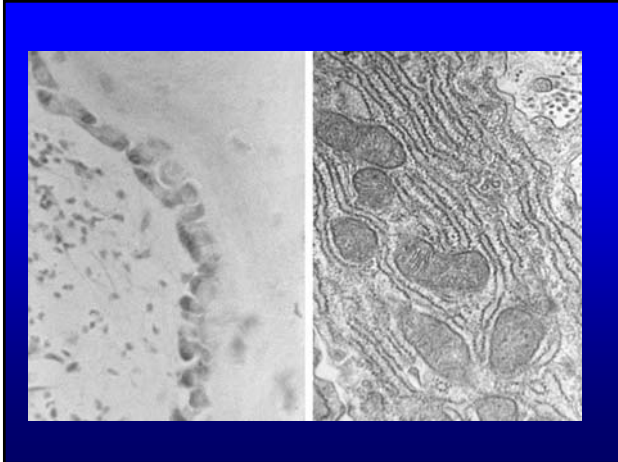


HAVERSIAN

Cell Morphology

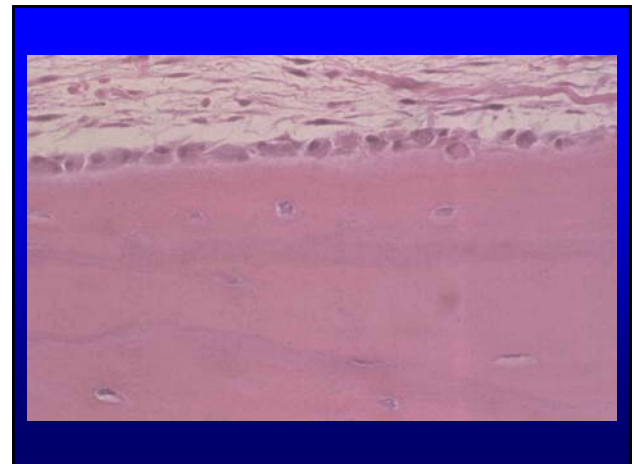
Osteoblasts

- **Bone forming** cells,
- Deposit **osteoid**, **type I collagen** & ECM proteins
- **Receptors** for **endocrine signals**



Cell Morphology: Active Osteoblasts

- Plump, **basophilic** filled with **osteoid**
- Abundant rough endoplasmic reticulum and Golgi apparatus
- **Polarized** nucleus
- Covered by **alkaline phosphatase**
- **Lining bone** and make osteoid
- Large cytoplasm



Cell Morphology: Resting Osteoblasts (resting lining cells)

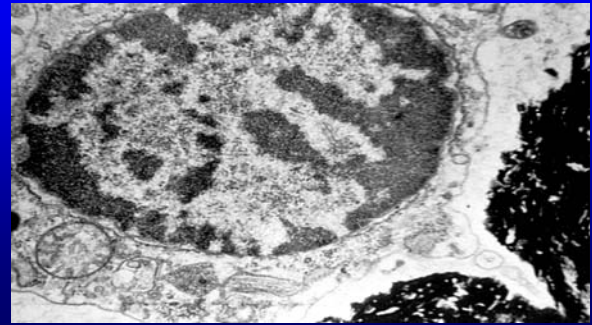
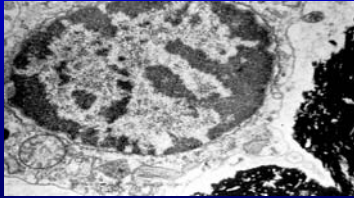
- **Flattened** cells lining the bone
- **Noncollagenous** protein synthesis
- Small gaps that expand to allow osteoclast access to osteoid
- Direct **contact** with osteocytes (caniculi)
- **Protection**

Cell Morphology: Osteocytes

- Osteoblast surrounded by **bone matrix**
- **Metabolic Management?**- exchange of Ca with ECM
- 3D structure and gap junctions allow for **large surface area**
- Response to fluid shifts involved with **stress & strain**

Cell Morphology: Osteocytes

- Concentric arrangement around osteon (**Haversian Canal**)
- **Canniculi** (radial extensions connecting cells & environment)
- Decreased organelles
- Higher nuclear:cytoplasm ratio

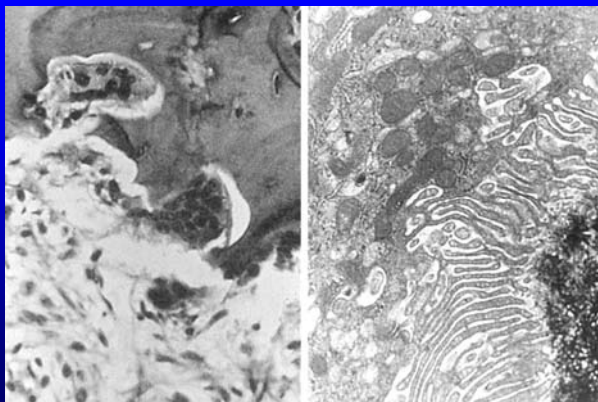


Cell Morphology: Osteoclasts

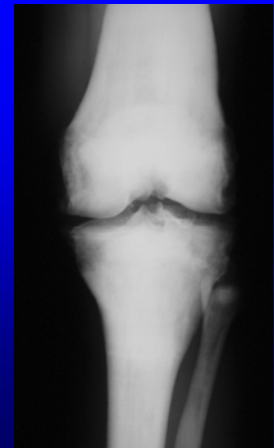
- **Monocyte** lineage- multinucleated via monocyte fusion
- Lineage Discovery: **Osteopetrosis** (defect in osteoclasts) cured via bone marrow transplant
- **Tartrate-resistant acid phosphatase**- osteoclast marker
- **Lack endocrine receptors**- activated by osteoblasts

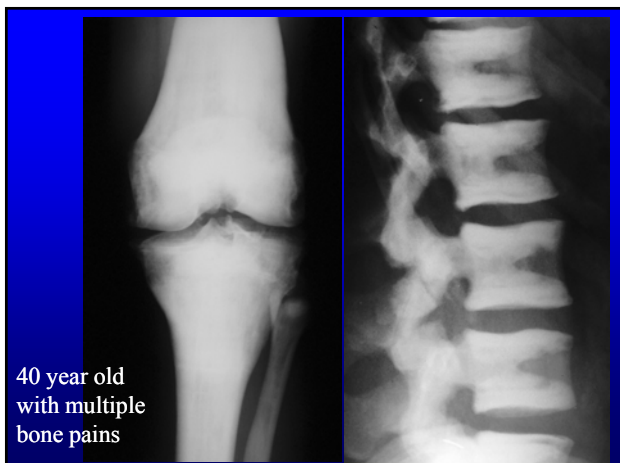
Cell Morphology: Osteoclasts

- Resorption- **Howship lacunae** (resorption pits)
- Clear zone & ruffle boarder (integrins)
- Bone Resorption- seals off clear zone, **carbonic anhydrase**, low pH (~4), dissolves mineral (solubility up), hydrolytic enzyme activation (**cathepsin & acid phosphatase**), degrade organic matrix, degrade crosslinks (urinary markers)



40 year with
chronic knee
pain





Bone Modeling

Osteoblastic Products:

- **Type I collagen**
- **Noncollagenous** proteins: (osteocalcin, osteopontin, osteonectin, & proteoglycans)
- **Regulatory factors:** (cytokines, growth factors & prostaglandins)
- **Enzymes:** (collagenase, collagenase inhibitor, plasminogen activator, neutral proteases, alkaline phosphatases)

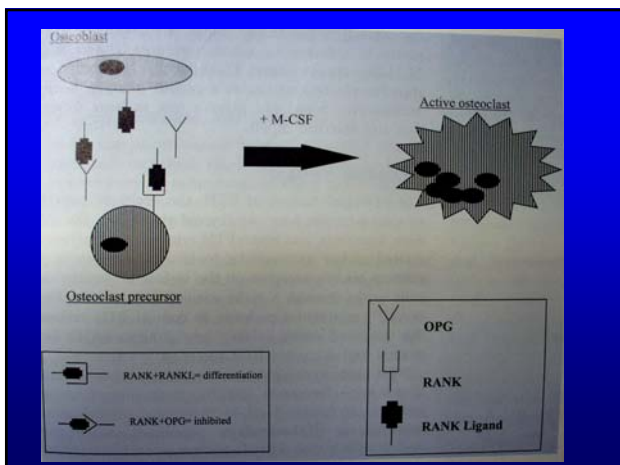
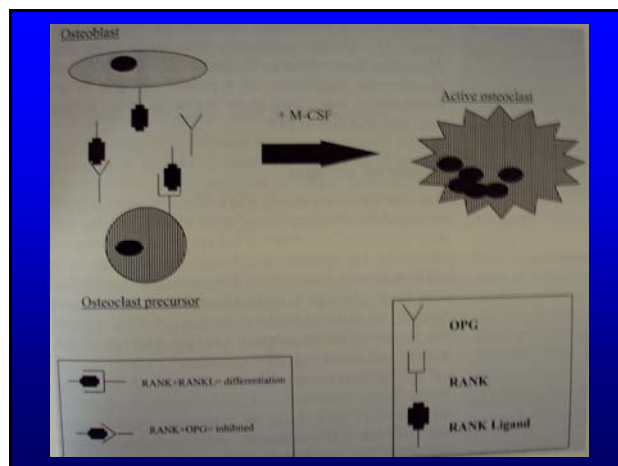
Bone Modeling

Osteoblast Receptors: Metabolic control

- PTH & prostaglandins = **cell surface & 2° messengers**
- Vit D & glucocorticoids = **cytosolic receptors**

Resorption:

- **Initiated** by osteoblasts which **contract** & release **enzymes** to degrade osteoid (collagenase)
- Bone surface **exposed** to osteoclasts



Bone Modeling

Resorption:

- **Initiating signals** = PTH, Vit D & Prostaglandin E
- Bone matrix degradation releases **Bone Morphogenic Proteins (BMP)** which help to couple formation and resorption
- BMP involved with coupled **remodeling, differentiating & chemoattracting** osteoclasts & osteoblasts

Bone Matrix Composition

Matrix Composition:

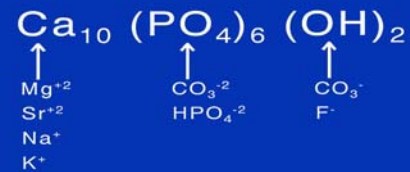
- Based on age, anatomic site, diet, disease...
- **Inorganic** = 60-70% (hydroxyapatite)
- **Organic** = 25% (90% collagen)
- **H₂O** = 5-8%

Bone Matrix Composition

Inorganic:

- Calcium phosphate mineral (calcium hydroxyapatite)
- **Impurities** (carbonate, chloride & fluoride)

Hydroxyapatite:



Bone Matrix Composition: Organic

Collagen:

- **90% type I** collagen
- **Low solubility**, **3 polypeptide chains**, ~1000 a/a long in a **triple helix**
- Two **alpha 1** chains & one **alpha 2** chain stabilized by **H bonding** between hydroxyproline & charged residues
- **Parallel alignment** in quarter-staggered array
- Gaps = “**hole zones**” & “**pores**”

Mineral accretion: biological considerations

Heterogeneity within a collagen fibril

Progressively increasing mineral mass due to:

1. Increased number of new mineral phase particles (nucleation)
 - a. Heterogeneous nucleation by matrix in collagen holes (? pores)
 - b. 2^o crystal induced nucleation in holes and pores
2. Initial growth of particles to ~ 400 Å X 15-30 Å X 50-75 Å



Bone Matrix Composition: Organic

Collagen:

- Collagen > triple helix > collagen fibril > collagen fibers, in line with long axis of bone
- **Processing: posttranslational:** hydroxylation of proline(50%) & lysine(15-20%) & subsequent glycosylation- **procollagen** secreted
- **Postsecretory:** terminal peptide cleavage & **crosslinkage** (reactivealdehydes)
- **Adlehydes** - lysine & hydroxylysine via **oxidative deamination** (**urinary marker** of bone resorption)

Bone Matrix Composition: Organic

Noncollagenous Proteins:

Osteocalcin (bone gamma-carboxyglutamic acid containing protein):

- **3 glutamic acid** residues allow **Ca binding**
- 10-20% of noncollagenous protein
- **Attracts osteoclasts** to resorption sites & regulates **maturation** of crystals (cartilage calcification)
- Produced by osteoblasts, enhanced production with **Vit D**, inhibited with **PTH** and **corticosteroids**

Bone Matrix Composition: Organic

Osteonectin:

- Produced by osteoblasts & platelets
- **Binds denatured collagen** & hydroxyapatite
- Role in regulation of Ca & **potentiation of nucleation** of Calcium phosphate

Bone Matrix Composition: Organic

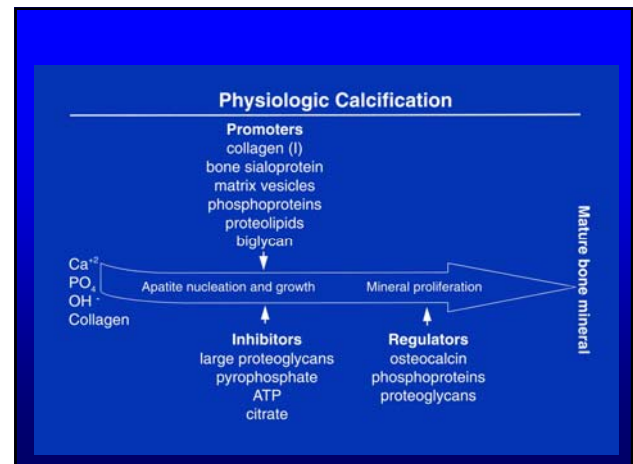
Phosphoproteins (sialoprotein):

- Produced by osteoblasts
- Localized to **“holes” & pores**
- **Nucleation** of crystals during mineralization initiation

Bone Mineralization

Phases:

- **Initiation** (small fraction in isolated sites)
 - Bone sialoproteins (phosphoproteins)
- **Growth** (bulk of mineral)
 - Maturation - osteocalcin



Bone Mineralization

Initiation:

- Increased **ion concentration**, nucleation **promoters** & removal of **inhibitor** proteins
- More energy to initiate than to add to crystals, begin in **holes**
- **Energy Reduction**- few **isolated nucleation** centers that coalesce, apatite **analog**s initiate nucleation
- **Type I collagen**- only one that can support apatite deposition

Bone Mineralization

Growth:

- Crystals impregnate holes
- Multiple discrete & **discontinuous** areas
- Spread to pores
- Initiation sites grow & **coalesce**

Bone Remodeling

Growth:

- **Long axis**- endochondral ossification
- **Width**- intramembranous (subperiosteal)

Mechanical Stress (**Wolff's law**):

- Repair of microfractures
- Regulated by electrical currents (**piezoelectrical** currents)

Bone Remodeling

Surface phenomenon:

- **Trabecular**- much more **surface area**
- Allows for more remodeling (5-10x more than cortical)

Aging:

- **Higher rates** in children (up to 50% in midshaft femur in 2yo)
- **Slows** in elderly (2-5% in healthy elderly)

Bone Remodeling

Bone Modeling Unit (**BMU**):

- **Coupled** osteoclast resorption & osteoblast formation
- In **cutting cones**
- Nutrient capillary



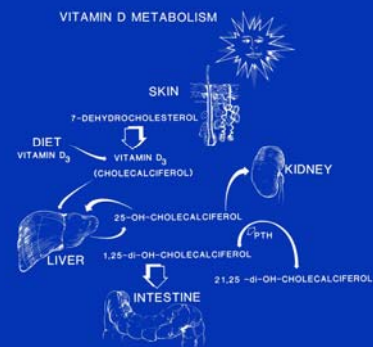
Blood Flow

Three separate but connected circulations:

Nutrient, Metaphyseal & Periosteal

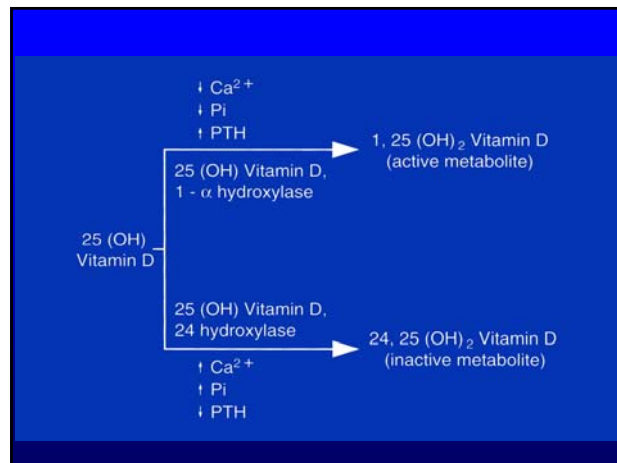
1. **Nutrient**: originates from **main arteries**, enters at **diaphysis** through nutrient foramen & branches into **ascending & descending vessels**, arterioles supply **endosteal cortex**
2. **Metaphyseal Complex**: from **periarticular plexus** (geniculate arteries), penetrates thin cortex, supply **metaphysis**, connect to medullary arteries and epiphyseal supply after plate fusion.
3. **Periosteal Capillaries**: **outer ~20% of cortical bone**, localized entrance at **muscle attachments**

Bone Metabolism & Mineral Homeostasis: Vitamin D Pathway



Bone Metabolism & Mineral Homeostasis: Vitamin D

Function: increase **serum** Ca & phosphorus via **gut** absorption and **bone** resorption



Bone Metabolism & Mineral Homeostasis: Vitamin D

Source:

- **Skin** (UV light)
- **Diet** (fortified dairy foods & cod-liver)
- 400 units/day = 1 hr direct sunlight in whites (more in darker skinned individuals)

Bone Metabolism & Mineral Homeostasis: Vitamin D

Forms:

- Skin = **7-dehydrocholesterol** into **Vit D₃**
- Diet = **Vit D₂**
- **Liver** converts to **25-Hydroxyvitamin D₃**
- **Kidney** converts to **1,25-dihydroxyvitamin D₃**
- 24,25-dihydroxyvitamin D₃- inactive form

Bone Metabolism & Mineral Homeostasis: Vitamin D

Homeostasis:

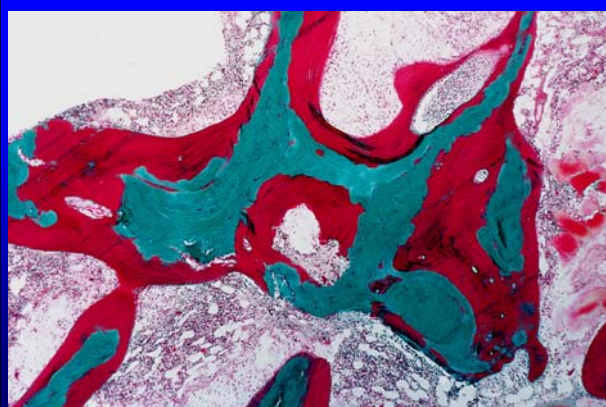
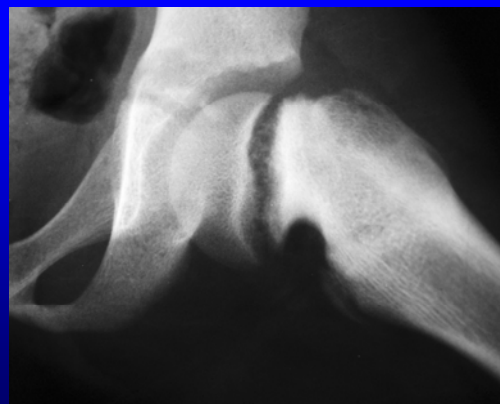
- **99%** of Calcium is stored in the bone
- Extracellular 10⁵ > than intracellular
- Hormones – **PTH, Vit D, & calcitonin**
- PTH & Vit D increase serum Calcium
- Calcitonin decreases serum Calcium

Daily Ca Nutritional Needs

- **Adolescent** (growth spurts): 500-700mg
- **Early adulthood** (maximum bone mass): 1,300mg
- **Pregnancy:** 1,500mg
- **Lactation:** 2,000mg
- **Healing bone fracture:** 1,500mg
- **Postmenopausal:** 1,500mg
- **Elderly** (2° to decreased enzymatic function- skin & kidney): 1,200mg

(One Daily Equivalent is 250mg = 8oz glass of milk)

12 year old with bilateral hip pain



Age-Related Bone Changes

Youth:

- Rapid **longitudinal** growth
- Limited mineral content increase because of high rate of formation
- **Peak** mineralization in late 20's after growth ceased (Peak Bone Mass)

Age-Related Bone Changes

Late adulthood:

- **5th decade** begins to decline
- **Trabecular:** female > male 2° to estrogen withdrawal, increased rate, 3-6 yrs & self limited, 3x normal "elderly" rate
- **Cortical:** similar rates, constant

Age-Related Bone Changes

Remodeling:

- Formation rates remain **same**/decrease
- Resorption rates **increase**
- **Uncoupling** of osteoclasts & osteoblasts

Components of Articular Cartilage

- Water
- Collagen
- Proteoglycan
- Other
- Chondrocytes

Fig. 10 from Chapter 17 of the AAOS Orthopaedic Basic Science

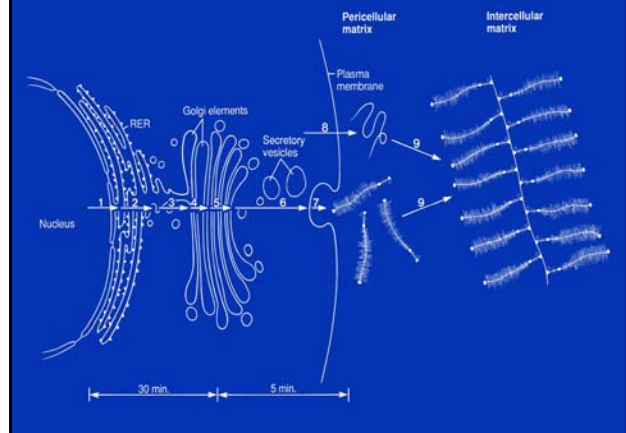
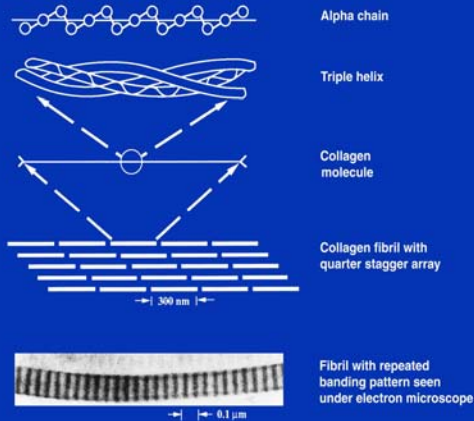


Fig. 5 from Chapter 17 of the AAOS Orthopaedic Basic Science



Mow et al. Structure and function of articular cartilage and meniscus. Basic Ortho. Biomech., 1991

The class 1 (long triple-helix) Collagens of Hyaline Cartilage

- Type II
 - 90-95% of total
 - Covalently cross-linked fibrils
- Type XI
 - Thin fibrils
 - Links to other XI fibrils
 - Possible framework for type II deposition

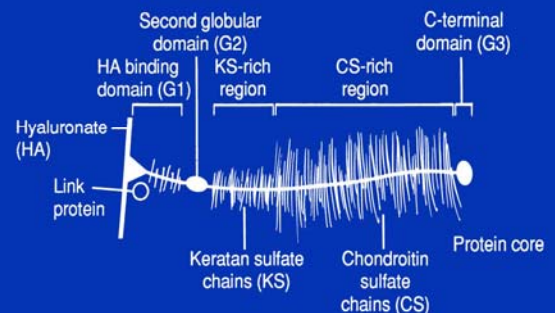
The class 3 (short chain +/- globular domains) Collagens of Hyaline Cartilage

- Type IX
 - Interrupted triple helix
 - Cross-links type II
- Type VI
 - Less than half triple-helix → beaded microfibrils
 - Limited to pericellular region
- Type X
 - Fine fibrous network
 - Limited to calcified zone (Possible role in calcification)

Although not confirmed yet, this point is tested on examinations

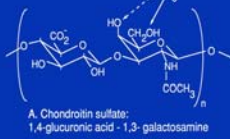
Fig. 6 from Chapter 17 of the AAOS Orthopaedic Basic Science

Proteoglycan Aggregate



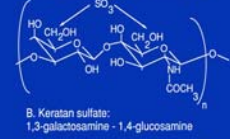
Drawings from Fig. 7 from Chapter 17 of the AAOS Orthopaedic Basic Science

25-30 CS units
in each chain off
protein core
15-20 kD



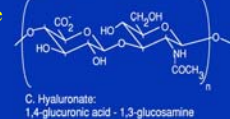
55-90% of total

10-15 KS units
in each chain off
protein core
5-10 kD



↑ with age
↓ in Osteoarthritis

Not on Protein Core
Not Sulfated
Unbranched chains
>1,000,000 kD



Wright et al. Proteoglycans:
Structure and function. Cell
Bio. Of ECM, 1991

Fig. 10 from Chapter 17 of the AAOS Orthopaedic Basic Science

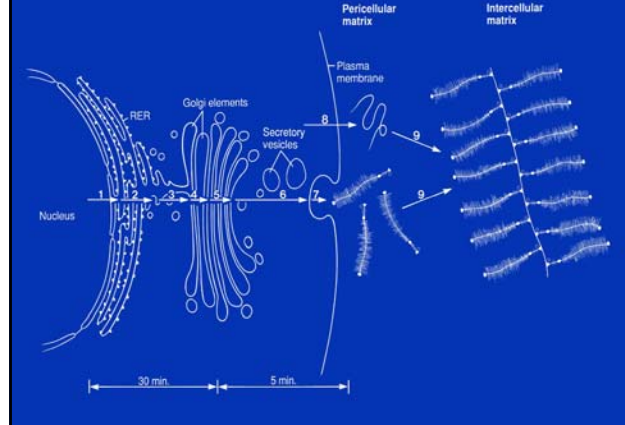


Fig. 8A from Chapter 17 of the AAOS Orthopaedic Basic Science

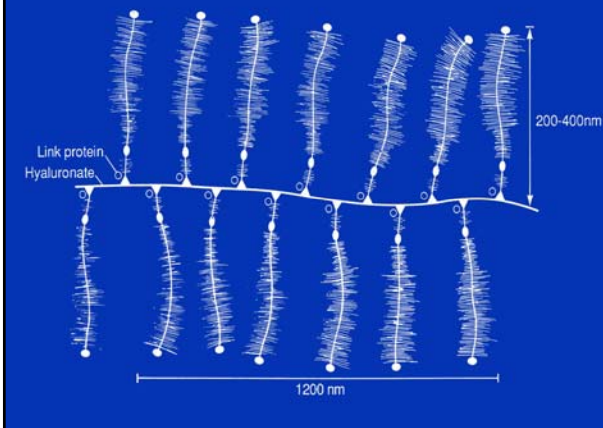
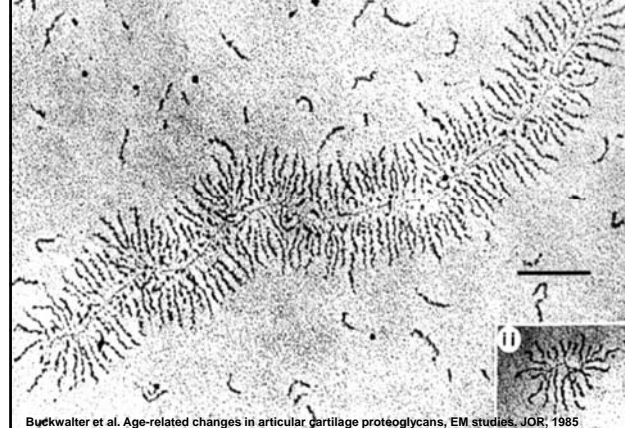


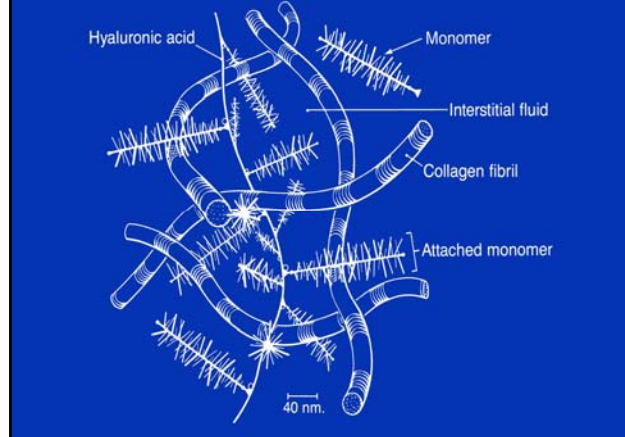
Fig. 8B from Chapter 17 of the AAOS Orthopaedic Basic Science



Proteoglycans in Hyaline Cartilage

- Aggrecans
 - 80-90% of total mass (~300 per hyaluronate)
 - Largest → up to 100 CS and 50 KS on each
- Biglycan -small
- Decorin -small - on the surface of collagen
- Fibromodulin -small -contains KS
- Type IX collagen -carries a KS chain

Fig. 9 from Chapter 17 of the AAOS Orthopaedic Basic Science



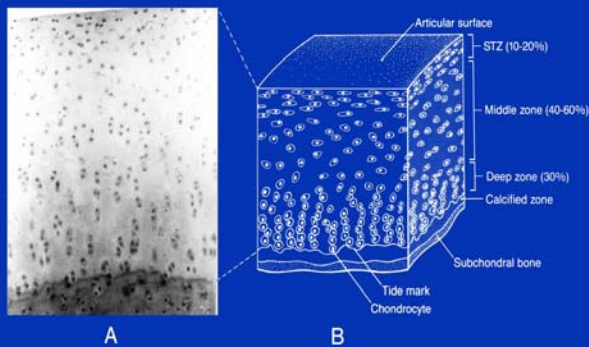
The Non-collagenous Proteins of Hyaline Cartilage

- Anchorin II
 - Binds to Chondrocytes
 - In pericellular zone
- Cartilage Oligomeric Protein (COMP)
 - Binds to Chondrocytes
- Fibronectin
- Tenascin

Chondrocytes

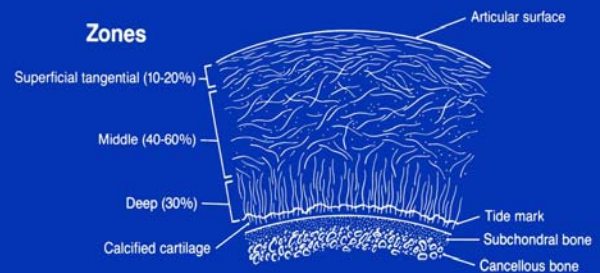
- Of Mesenchymal origin
- Less than 10% of Mature Hyaline Cartilage
- Maintain ECM
 - Perform analogous functions of Osteoblast, -clast, & -cyte for bone ECM
- Largely anaerobic metabolism

Fig. 1 from Chapter 17 of the AAOS Orthopaedic Basic Science



Mow et al. Basic Biomechanics of the Musculoskeletal Sys. 1989.

Fig. 4A from Chapter 17 of the AAOS Orthopaedic Basic Science



Functions of Hyaline Cartilage

- Reduce friction & lubricate diarthrodial joints
- Absorb and spread shocks and stresses
- Reduce wear on bones

Cartilage bears load as a biphasic material

A collagen-proteoglycan solid matrix

&

Fluid flow against a high frictional resistance.

Factors Drawing Water into the Cartilaginous Matrix

- Donnan Osmotic Pressure
 - Electrostatic repulsion of fixed negative charges on proteoglycan (COO⁻ and SO₄⁻ groups)
 - Water brings hydrogen bonds and physiologic cations to neutralize these charges
- Entropic Tendency of Proteoglycan
 - In free solution, proteoglycan conformations fill 5X the space they receive in Cartilage

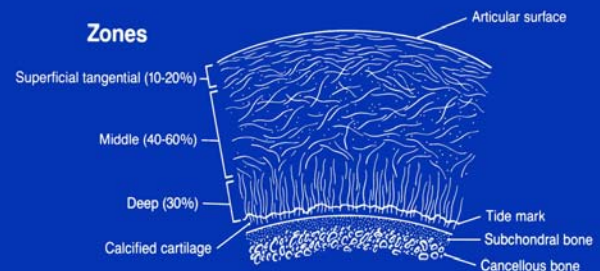
One Factor Limits Water Influx into Cartilage

- The collagen-proteoglycan network limits the potential expansion space, thus maintaining water avidity

Stress shielding:

90-95% of compressive stress on Hyaline Cartilage is borne by hydrostatic pressure rather than the solid matrix itself

Fig. 4A from Chapter 17 of the AAOS Orthopaedic Basic Science



Factors of Biological Control

- PDGF – mitogenic
- bFGF – mitogenic with insulin; stimulates repair
- TGF- β – potentiates bFGF, EGF, IGF-1
 - Increased PG synthesis and decreases col II syn
 - Increases TIMP and PAI-1 production
- IGF-1 – maintains proteoglycan synthesis
 - Competes with IGF-2 and insulin

Important points to remember

- Nutrition through diffusion (low oxygen tension, 1-2%)
- Energy through glycolysis
- Transforming growth factor beta
 - Chondroprotective effect
 - Smad3 which is transcription factor activated by TGF-B also is chondroprotective
- Insulin like growth factor – increases collagen and proteoglycan synthesis
- Bone morphogenetic proteins 2 and 7 – increase proteoglycan synthesis and maintain chondrocyte phenotype (BMP 2,7)

Important points to remember

- Interleukin-1
 - Inhibits proteoglycan synthesis
 - Stimulates metalloproteinase activity (catabolic enzymes)
- Tumor necrosis factor alpha
 - Inhibits collagen synthesis
 - Stimulates metalloproteinase activity (catabolic enzymes)
- Other catabolic enzymes
 - Cyclooxygenase (COX-2)
 - Nitric oxide synthetase

Chondroprotective (anabolic)

- 1) Transforming growth factor beta
- 2) Smad3
- 3) Insulin like growth factor
- 4) Bone morphogenetic protein 2
- 5) Bone morphogenetic protein 7

Chondroablative (catabolic)

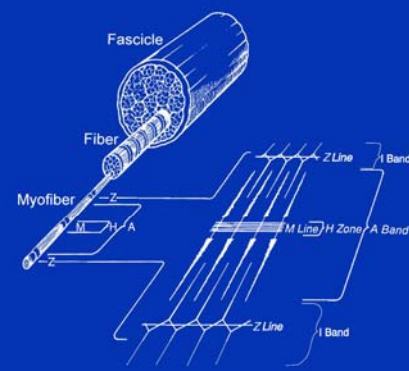
- 1) Interleukin 1
- 2) Tumor necrosis factor alpha
- 3) Cyclooxygenase (COX2)
- 4) Nitric oxide synthetase

Collagen

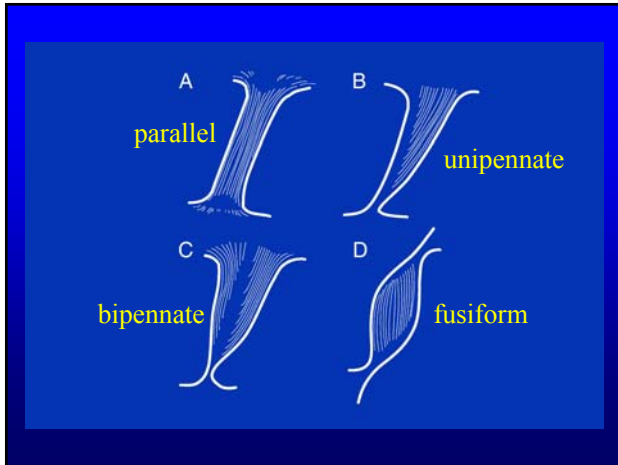
- Type II collagen
 - 90-95% of the total collagen
 - highly cross linked and interconnected
- Type IX
 - Forms cross links with Type II
- XI
 - Regulates the Type II fibril diameter

Muscle

- Skeletal Muscle
 - ➔ 40-45% of body weight
 - ➔ organization
 - muscle cells
 - Nerves
 - Blood vessels
 - Extra-cellular connective tissue matrix



Muscle fiber – single long cell



Endomysium - delicate connective tissue surrounding individual fibers

Perimysium - connective tissue surrounding the fascicles

Epimysium - connective tissue surrounding the entire muscle

Maximal force production is proportional to *physiologic cross-sectional area (PCSA)*

Type I red, slow twitch (ST), slow oxidative (SO)	
Speed of contraction	slow
Strength	low
Fatiguability	low
Aerobic capacity	high
Anaerobic capacity	low
Motor unit size	small

Type IIA- white, fast twitch (FT), fast oxidative glycolytic (FOG)	
Speed of contraction	fast
Strength	high
Fatiguability	high
Aerobic capacity	medium
Anaerobic capacity	medium
Motor unit size	larger

Type IIB fast glycolytic (FG)	
Speed of contraction	fast
Strength of contraction	high
Fatiguability	highest
Aerobic capacity	low
Anaerobic capacity	high
Motor unit size	largest

Sprinters	Type II
Long distance runners	Type I

Mutability – the entire motor unit is capable of adaptation: muscle fiber, neuro-muscular junction, and alpha motorneuron

- In humans, the percentage of Type I and Type II fibers is determined genetically and probably can not be changed
- Within the Type II fibers there can be Conversion into and from Types IIA and IIB

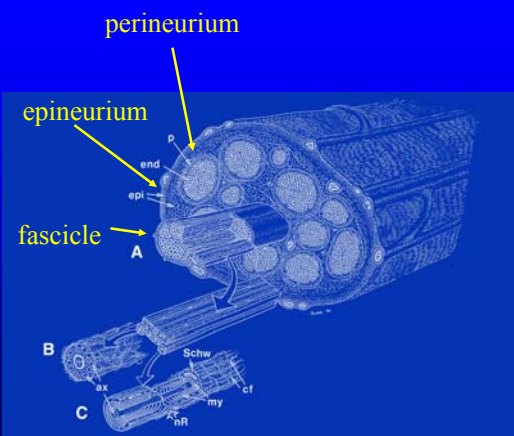
Muscle strength training

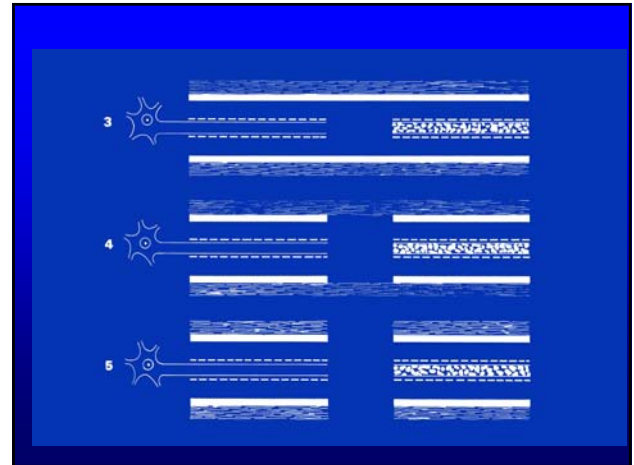
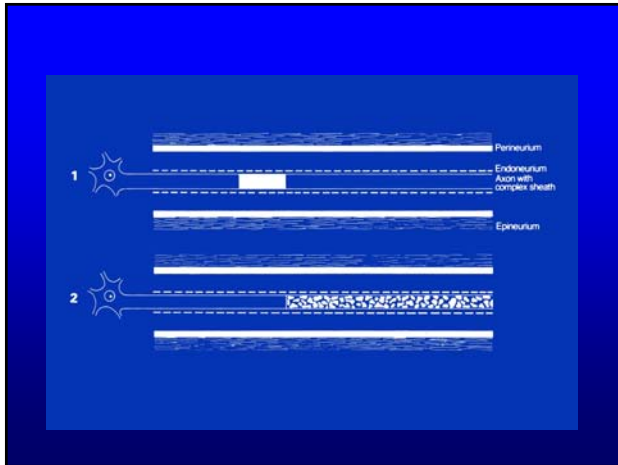
- Muscle increase is size by hypertrophy
- Neurologic component
 - ➔ poorly conditioned – 60% simultaneous firing
 - ➔ better conditioned – 90% simultaneous firing
- Type II fibers greater ability to hypertrophy

Endurance training

- Increase in stroke volume and ventricle size
- Increased number of muscle capillaries
- Increased mitochondrial size and number
- Carbohydrate load
 - ➔ high carbohydrate, low fat
 - ➔ increases muscle and liver glycogen

Nerve Anatomy and Injury





- First degree (neuropraxia) – local conduction block
 - axon continuity is intact
 - no Wallerian degeneration
 - completely reversible
- Motor nerves are more susceptible
- Order of loss:** motor, proprioceptor, touch, temperature, and pain

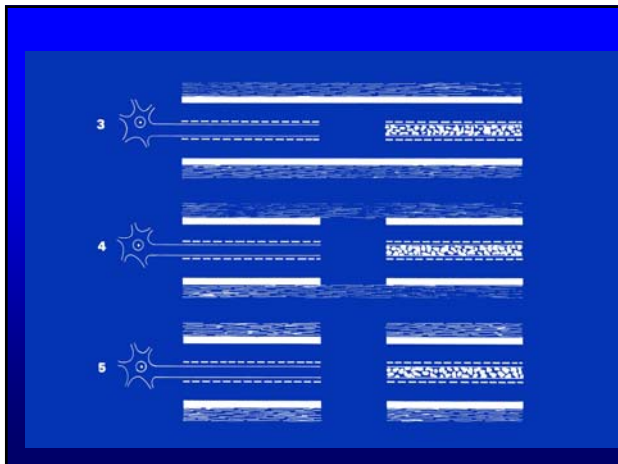
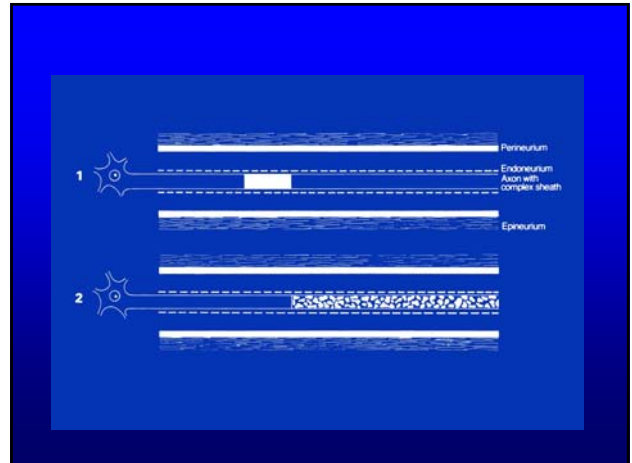
- ### Nerve injury
- Second degree (axonotmesis)
 - severe damage or severance of axon
 - Wallerian degeneration
 - Schwann cell layer is maintained
 - ❖ usually full recovery
 - ❖ fibrillation
 - ❖ denervation potentials and muscle atrophy

- ### Nerve Injury
- Third degree
 - loss of endoneurial tube continuity
 - perineurium is intact (arrangement of individual fascicles is preserved)
 - Wallerian degeneration
 - ❖ Variable recovery, misdirected axons
 - ❖ The more proximal the injury, the worse the recovery

- ### Nerve Injury
- Fourth degree
 - nerve trunk in continuity but fascicles disrupted and disorganized
 - Wallerian degeneration
 - more severe proximal neuronal injury
 - ❖ Limited recovery, usually requires surgical repair

Nerve injury

- Fifth degree
 - loss of continuity of the nerve trunk
 - proximal – neuroma
 - distal Wallerian degeneration
- ❖ requires surgical repair



Wallerian degeneration

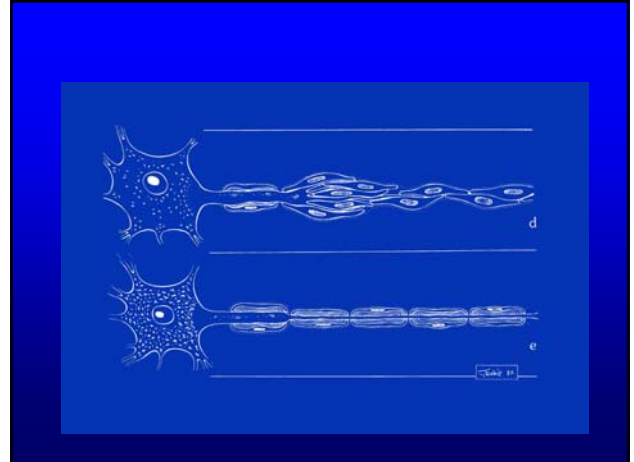
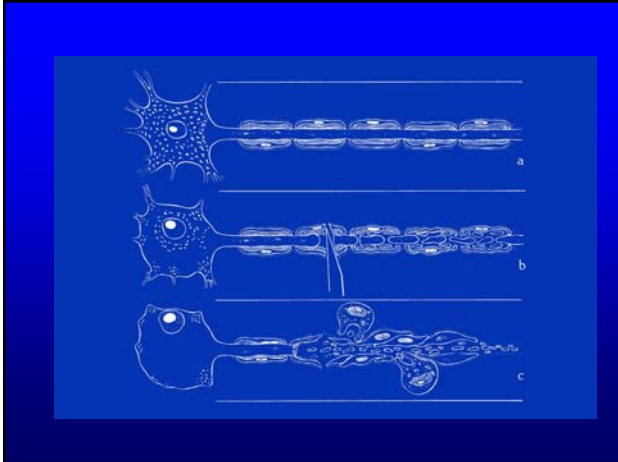
- Axon degeneration
 - disintegration of axoplasmic microtubules
 - myelin breakdown
 - interior of the nerve – amorphous mass of axon and myelin debris

Wallerian degeneration

- Schwann cell response
 - Schwann cell proliferation
 - more Schwann cell proliferation and the cells line up bands of Bungner
- Macrophage response – interleukin-1 expression which stimulates nerve growth factor

Wallerian degeneration

- Nerve Cell body response
 - production of proteins for axon repair



Motor and sensory nerves fail sequentially

first, then: motor
 proprioceptor
 touch
 temperature
 pain

❖ opposite for recovery:

➢ pain, temperature, touch,
 proprioceptor, and motor

Pharmacology

- Antibiotics
- Anticoagulation
- Inhibitors of Bone Resorption
- Corticosteroids
- Non-steroidal anti-inflammatories
- Desensitizing Agents

Antibiotics

Defn – chemical substances produced by micro-organisms that suppress the growth of other micro-organisms

Classified by mechanism of action:

- 1) Inhibition of cell wall synthesis
- 2) Increase cell membrane permeability
- 3) Ribosomal inhibition
- 4) Interference with DNA metabolism
- 5) Anti-metabolite action

Cell wall synthesis inhibition

- penicillins
- cephalosporins
- vancomycin
- bacitracin
- imipenem
- aztreonam



Penicillins:

- ❖ penicillins and cephalosporins block the transpeptidase enzyme

Penicillin G - inactivated by enzyme beta-lactamase

Synthetic penicillin's (methacillin, oxacillin) are active against most beta-lactamase producing *S. aureus*



Cephalosporins

1st Generation - primarily anti-staphylococcal, some gram negative

2nd, 3rd Generation - increased negative with diminished gram positive



Vancomycin

- ❖ bacteriocidal for gram positive organisms
- ❖ effective for methicillin-resistant *S. Aureus* and *S. epidermidis*
- ❖ effective for patients with penicillin/cephalosporin hypersensitivity



Imipenem:

- ❖ structurally related to beta lactamase resistant drugs
- ❖ broadest antibacterial spectrum of all antibiotics
- used for superinfection from resistant organisms



Inhibition of ribosomes:

- reversible inhibition of protein synthesis and prevention of bacterial multiplication

- tetracycline
- chloramphenicol
- erythromycin
- clindamycin



Erythromycin effective against *S. aureus*

Clindamycin active against all anaerobes and most gram positive cocci enterococci



Bacteriocidal ribosomal inhibitors

aminoglycosides

- gentamycin
- streptomycin
- tobramycin
- amikacin
- neomycin

❖ *Bind to 30S subunit, mRNA is misread, formation of abnormal proteins leading to cell death*

Aminoglycosides:

- ❖ used against gram negatives
- ❖ toxic to kidneys, auditory and vestibular apparatus

Interfere with transcription and translation of bacterial DNA:

quinolones
rifampin
metronidazole

Fluorinated quinolones:

- ❖ ciprofloxacin
 - active against gram positives and negatives
 - effective orally and intravenously
- ❖ **Achilles tendon ruptures may occur**

- ❖ inhibition of cell wall synthesis
 - beta-lactams (penicillins, cephalosporin, etc)
 - carbapenems (imipenem)
 - glycopeptides (vancomycin)
- ❖ inhibition of protein synthesis
 - macrolides – (erythromycin)
 - aminoglycosides (gentamicin)
 - lincosamides (clindamycin)
 - tetracyclines
- ❖ inhibition of RNA synthesis
 - rifampin
- ❖ inhibition of DNA synthesis
 - fluoroquinolones (ciprofloxacin, levofloxacin, gatifloxacin)

Protein Inhibition at the 70S subunit of the ribosome

- macrolides (erythromycin) – 50S sub unit
- aminoglycosides (gentamycin) - 30S sub unit
- lincosamides (clindamycin) - 50S sub unit
- tetracyclines - 30S sub unit

Sequence of events after traumatic nerve injury

Electrophysiologic abnormality	Timing of onset
Conduction block across injury site	Immediate
Reduced amplitudes on distal stimulation	>7 days
Denervation changes on EMG	2-5 weeks
Reinnervation on EMG	> 6-8 weeks

Musculoskeletal Disorders and Genetic Defects

Achondroplasia	FGF receptor 3
Osteogenesis imperfecta	Type I collagen
Pseudoachondroplasia	Cartilage oligomeric matrix protein (COMP)
Marfan's syndrome	Fibrillin
Spondyloepiphyseal dysplasia	Type II collagen

Musculoskeletal Disorders and Genetic Defects

Multiple epiphyseal Dysplasia	COMP or Type IX collagen (COL9A2)
Thanatropic dysplasia	FGF receptor 3
Diatrophic dysplasia	sulfate transporter
Duchenne muscular dystrophy	Dystrophin

Musculoskeletal Disorders and Genetic Defects

X-linked hypophosphatemic Rickets	PEX (cellular endopeptidase)
Osteopetrosis	Carbonic anhydrase Type II, proton pump
Fibrous dysplasia	G s alpha (receptor coupled signaling protein)
Schmid metaphyseal dysplasia	Type X collagen

Musculoskeletal Disorders and Genetic Defects

Jansen metaphyseal Chondrodysplasia	PTH/PTHrP receptor
Multiple hereditary Exotoses	EXT1, EXT2 genes
Hypochondroplasia	FGF receptor 3

Thank You