Connective tissue

Origin: Embryonic mesenchymal tissue (*Mainly from Mesoderm 中胚层 some connective tissues develop from the ectodermal layer 外胚层 neural crest*)

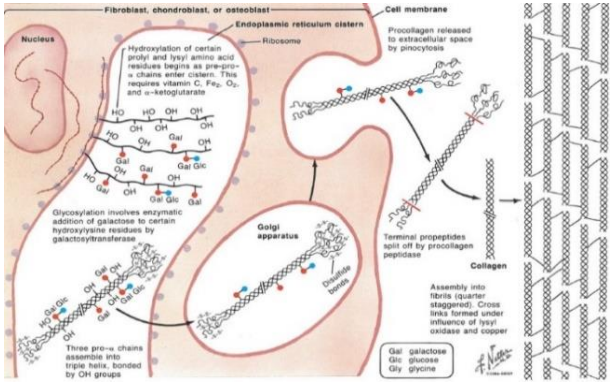
Function: 1) maintenance of *structure integrity*; 2) Immunocompetence, tissue defence, phagocytosis .

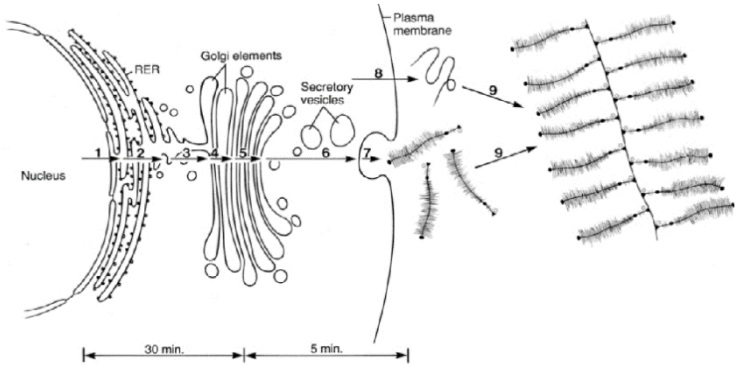
<table>
<tr><td colspan="3">Cells</td><td colspan="2">Extracellular matrix: ground substance</td><td colspan="4">Extracellular matrix: fibres</td></tr>
<tr><td>Cell type</td><td>Produce</td><td>Function</td><td colspan="2">GAGs (glycosaminoglycans)</td><td colspan="4" rowspan="2">3 main connective tissue fibre types
1) Collagen fibre: most abundant mammalian protein (protein collagen)
2) Reticular fibre: much finer, form an extensive network in certain organs (protein collagen)
3) Elastic fibre (protein elastin)
* form an irregular network, allow stretch,
* composed of elastin
* blood vessels, skin, lung, ligaments, joint capsule</td></tr>
<tr><td>Osteoblast
Chondroblast
Fibroblast
Odontoidblast</td><td>Fibre and ground substance</td><td>Structural
Resists deformity</td><td>Sulphated:
Chondroitin sulphate (4 & 6)
keratan sulphate
Heparin</td><td>Non-sulphated
- Chondroiton
- Hyaluronic acid</td></tr>
<tr><td rowspan="2">Plasma cell
Lymphocytes
Eosinophilic</td><td rowspan="2">1.Humoral and cell mediated immunity
2. Phagocytosis of Ag-Ab complexes</td><td rowspan="2">Immunological defence</td><td colspan="2" rowspan="2">Proteoglycan (mucopolysaccharides)
*GAGs + long protein core molecules
* 3 regions of the core protein: 1) HA binding region, 2) KS rich region, 3) CS rich region
* the core protein contains >2000 amino acids.</td><td>Type</td><td>Tissue</td><td>Synthesized by</td><td>Main function</td></tr>
<tr><td>Type I
2 α1+1 α2</td><td>Bone, tendon, ligaments, fascia, skin, annual fibrosis
Cornea, dentin, fibrocartilage, meniscus</td><td>Fibroblast
Osteoblast</td><td>Resistant to tension</td></tr>
<tr><td>Macrophages
Neutrophil</td><td>Phagocytosis of debris, bacteria</td><td>Cellular defence and clean-up</td><td colspan="2">Aggrecans: proteoglycan + hyaluronic acid</td><td>Type II
3 α1</td><td>Cartilage (principal collagen of HAC)
Nucleus pulposus
Vitreous humor of the eye</td><td>Chondroblasts</td><td>Resistant to pressure</td></tr>
<tr><td rowspan="2">Mast cells
Basophilic</td><td rowspan="2">Liberation of inflammatory, other pharmacological substance (histamine)</td><td rowspan="2">Inflammation and repair.</td><td colspan="2" rowspan="2"></td><td>Type III
3 α1</td><td>Wall of blood vessels, internal organ (spleen, liver, kidney), scars of skin, uterus, GI tract</td><td>Fibroblasts, reticular cells</td><td>Structural maintenance</td></tr>
<tr><td>Type IV</td><td>Basal lamina of epithelia, lens capsule</td><td>Epithelial cells, muscle, Schwann cell</td><td>Support (EDS)</td></tr>
<tr><td>Adipose cell</td><td>Fat storage
Insulation
Heat production</td><td>Energy reservoir</td><td colspan="2">Function:
- trap water(H2O +ve dipoles → -ve charged GAGs)</td><td colspan="4">Type V cell surfaces, hair and placenta</td></tr>
</table>

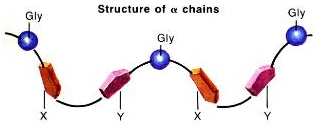
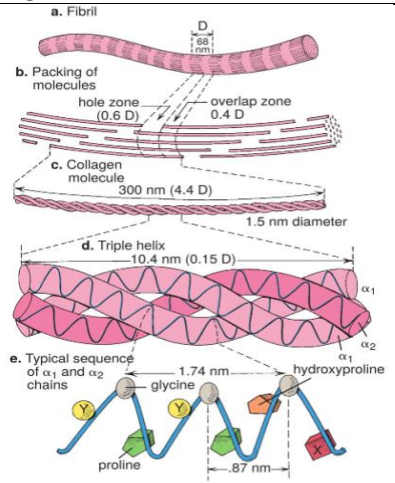
Tissue types: bone, muscle, tendon/ligaments, joints, cartilage, synovium, loose connective tissue, fat, cellular elements, extracellular matrix (ground substance)

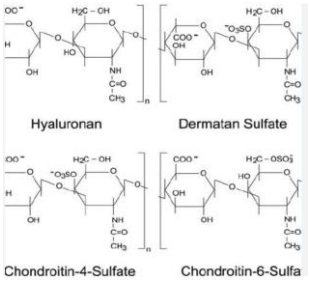
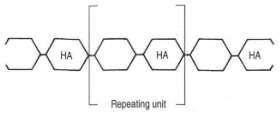
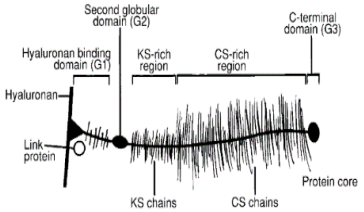
Order of Tissue resists **tension**←→ **compression**: tendon> ligament> fascia> cartilage>bone (collagen←→proteoglycans)

	Loose connective tissue	**Dense** connective tissue
Function	Bulk, padding and storage	Support, protect, connect
Location	Found throughout the body	Throughout the body
Features	Well vascularized and cellular (blood & lymphatic vessels, and nerves) With a high matrix proportion The fibrous component varies in amount, orientation (*depending on the forces and tissue experiences*)	Relatively few cells, little ground substance. **Dense regular** CT: *packed collagen* (orientated in the direction of tensile stress; parallel to each other); **Dense irregular** CT: collagen fibres (*usually elastic F*) are randomly orientated. Coarse & interwoven,
Component	Collagen fibres (resist tension); proteoglycans (resist compression)	Fibrous element,
Example	Subcutaneous tissue	Regular CT: Tendon, joint capsules, ligaments, ligamenta flava (*黄韧带*), cornea Irregular CT: some part of skin, capsules of spleen, liver, lymph nodes, dura mater, nerve sheath





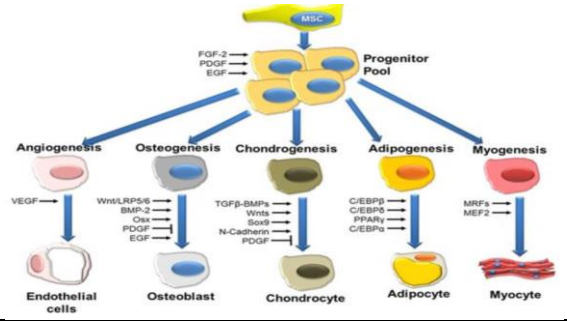
Type	Basic Unit	Higher level structure	Description	Biosynthesis
Collagen (*the rope*)	 Each α chain comprises about 1,000 amino acids. Every third amino acid in chain is glycine, smallest of amino acids. Glycine has no side chains, which thus permits tight coil. X and Y here indicate other amino acids (X often proline; Y often hydroxyproline). Proline and hydroxy-proline, respectively, constitute about 20% and 25% of total amino acids in each α chain Each α chain consists of repetitive primary structure molecules (X-Y-Gly) 1. X often **proline** 20% or total AA 2. Y often **hydroxyproline** 25% 3. **Glycine** * Each chain Comprises about 1000 amino acid	 α chain→ triple helix→collagen molecule→packing of molecules→ fibril	1) **Preprocollagen**: single chain (α) 2) **Procollagen**: triple helix, R-handed twist, bond by OH group. 3) tropocollagen (collagen molecule): procollagen after end cut 4) **Microfibril**: formed by tropocollagen chains 5) **Collagen**: cross linked tropocollagen. (68nm straining *Parallel fibre under microscope*) *at least 12 types of collagens * The most abundant protein in the body * each molecule consists of 3 polypeptide subunits (*α chain*) * 3 α chain form a triple helix. https://www.youtube.com/watch?v=Lk94Vl3EmqI Collagen synthesis & Disorders https://www.youtube.com/watch?v=5BsM8RvgOG4	**Intracellular** 1) **transcription** of mRNA from a collagen gene. 2) **pro-α chains** of procollagen are synthesized on the RER (*rough endoplasmic reticulum*) by translation of mRNA. 3) hydroxylation of **proline** and **lysine** residuals Requires: Vit C, O2, Iron, α ketoglutarate, hydroxylation enzymes (water, lemon) (RER) 4) **Post-translational modifications (**RER**)** - Glycosylation of C-terminal propeptide (sweets) - formation of disulphide bonds - Formation of the triple helix in the RER. 5) **Exocytosis:** Transportation of the procollagen from the RER to the Golgi apparatus. (Guests leave the home) **Extracellular** 1) the C-terminal and N-terminal propeptides are **cleaved** by *procollagen peptidase* c and N 2) procollagen → tropocollagen→ microfibril. 3) collagen fibre is formed 4) collagen is stabilized by **cross linking** btw lysine or hydroxylysine residuals
Aggrecan	1) **Disaccharide unit**: *Repeated sequence of 2 molecules* -- **HA**: *Hexose Amine* (*6 carbon glucosamine molecule*)	2) **GAGs** (*Glycosaminoglycans*) - long chains of repeating disaccharide. - **Main GAGs**: CS 6 (*Chondroitin Sulphate)*, CS 4, KS (*Keratan sulfate*), DS (*Dermatan sulphate*) **CS the most prevalent in cartilage (55-90%)* * GAGs are *highly charged* and contribute to the osmotic pressure effect that holds water. -- COOH---Acid terminals - CH_2OSO_3H—sulphate terminal - **Sulphated** GAGs attract water more strongly	**Proteoglycans** - are large complex macromolecules - GAGs + core protein *- CS composed of **25-30** repeating Units* *- KS chains are smaller; less amount than chondroitin, vary with age and disease.* - CS= 2x KS water binding capacity→- water binding capacity dependent on CS total -Consists of a linear protein core with 3 globular regions: G1, G2. G3	**Proteoglycan Aggrecan:** - GAGs + core protein + hyaluronic acid→extremely large molecule - GAG side extensions are potentially ionizable→ gives the aggregates ability to trap water. **Water trapping** 1) **GAGs** chains are highly polar and negatively charged, thus is the main force of GAG holding water (*positive water dipoles (H+)*. 2) Thermodyniamic effect of the proteoglycan aggrecan physically trap water within the matrix .

	-- **Sugar molecule**   	Disaccharide unit→GAGs→Proteoglycans→ Aggrecan	 	**Age changes** 1) aging or disease→ CS segment breaks off → aggregate size decreases → physical trapping ↓ 2) aging→ **KS:CS ratio** increases (KS ↑ CS↓) → electrostatic binding capacity↓ → water binding capacity ↓

Immunocompetent cells: Tissue specific cell origins

	Macrophages	**Neutrophil**	**Eosinophil**	Lymphocytes	**Plasma Cells**
Origin (*Derived fr*)	Monocytes in the blood	Mostly in blood, Attracted to cytokines from macrophages	Little time in the circulation	Prevalent in the gut.	From B lymphocytes
Function	-Phagocytosis *(ingest dead cell, debris*) -Defence against infection (*ingest bacteria*, *secrete mediators: nitric oxide*) -process and present antigens to lymphocytes	Assist in destroying bacteria - gather at the site of infection - Stick to capillary walls, migrate through	- Moderate the severity of allergic reaction (degrading histamine) - Responsive to parasite infection - contact dependent cytotoxicity	Principle agents of the immune system - process antigens presented by macrophages - produce antibodies	1) Major *producers* of humoral antibodies 2) Produce immunoglobulins
Types	Fix or free (presents different phases- resident, elicited, and activated type)			**T cells** Cell mediated immunity. T stands for the thymus gland Subset: *Helper, cytotoxic, memory, regulatory, natural killer, gamma-delta T cell* **B cells** Humoral immune response Essential of adaptive immune system. Form antibodies Perform function of Antibody presenting Cell (APC) Memory B cell *remember specific antigens, respond quickly in the future.*	Large nucleus, rough endoplasmic reticulum (RER)
Examples	Monocytes: in blood stream Osteoclast: in bone Type A cell: in synovium Alveolar macrophage: in lungs Histocytes: in skin Kuppfer cells: in liver	**Mast cell** Largest cells in CT (*Only found in tissues)* Contains basophilic granules **Contains**: Heparin, histamine, proteases, Eosinophilic chemotactic factor * histamin is released by compound exocytosis after antigen attaches to IgE. **Function**: mediate inflammation (*hay fever, asthma, anaphylaxis*)			
	Cytokins: - Interleukin 1. 6 - TNF - Interferon - Erythropoetin - PDGF (*platelet derived growth factory*) - FGF (*fibroblast growth factor*) - TFG (*transforming growth factor*)				

Stem cells	Definition	Phenotypic expression.	

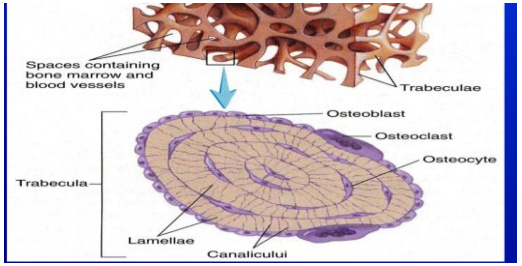
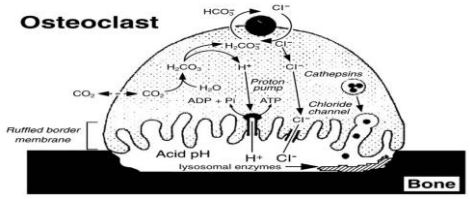
	- Cells of most MSK tissues are derived from - mesenchymal stem cells (*multipotent cells*) - They can differentiate into bone, cartilage, fibrous tissues	- genotype: refers to the genes present in its genome - Phenotype: the array of genes expressed and their relative levels of expression. -cell differentiation: Only a fraction of the genes is expressed A specific profile of gene expression →sets the cell apart from other cells → determining its structure and function * **cell proliferation** and **differentiation** are inversely related. * *Contact inhibition*: cell-cell contact prevents non-specific differentiation.	

Bone formation/ embryology

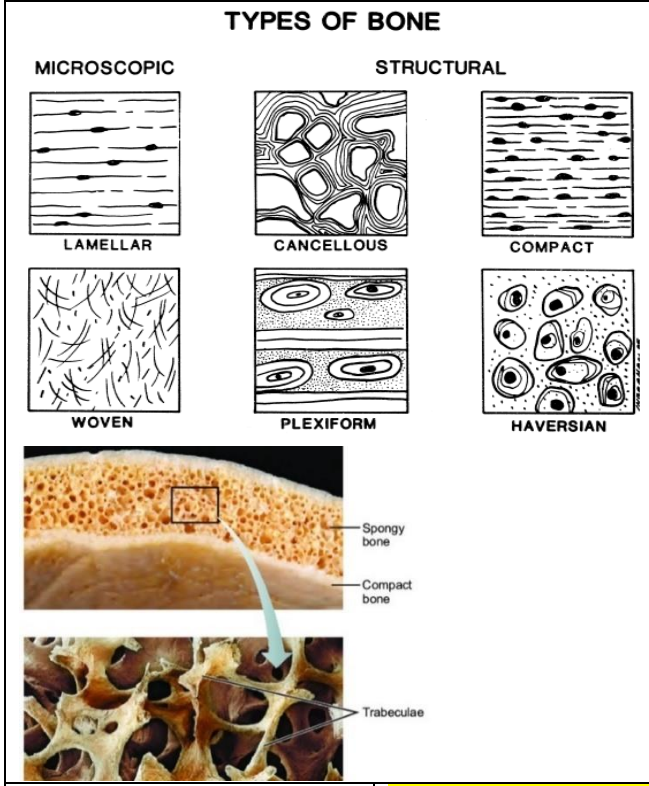
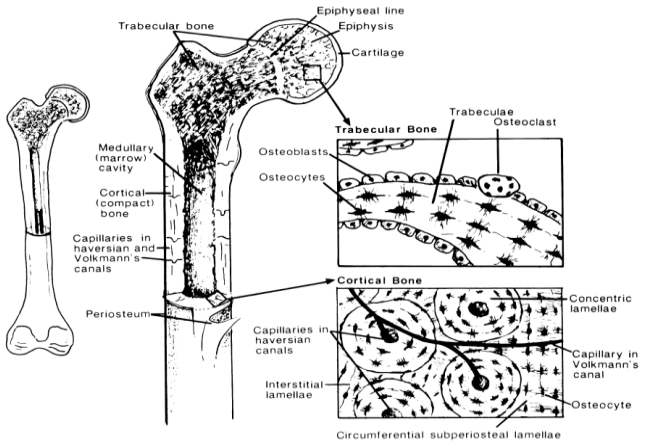
3 derivatives of skeleton 1) **Cranial neural crest cells**: Form flat bones of the skull, clavicle, cranial bone 2) **Somites** : forms the remainder of the axial skeleton. 3) **Lateral plate mesoderm**: form the long bone https://www.youtube.com/watch?v=WmlbqVyhMts&list=PLTF9h-T1TcJiUxgs0dqyDCaS-glauXcsL&index=9 Embryology development of skeletal system.	**Ectoderm** 外胚层: Mesoderm 中胚层: Endoderm 内胚层: Notochord 脊索： release GF, SHH,	**Mesoderm:** **A. Paraxial mesoderm** 轴旁中胚层 —》**somite** 体节 (*contains somatocoele*) 1) Dermatome: → meninges, **skin** 2) myotome→ muscle (epiaxial muscle, hypaxial muscles) 3) Sclerotome→ vertebrae, IVD, ribs	**B** Intermediate mesoderm 侧旁中胚层 (renal system, ureters; Testes , epididymis, overies, fallopian tubes) **C Lateral plate mesoderm: (LPM)** -3a: **Somatic layer of LPM:** 1) sternum 2) **Limb buds**: bones, cartilages -3b: **visceral layer of LPM**: adrenal cortex, spleen, smooth muscle of GI, CVS,
Limbs * A limb bud comprises **mesoderm** (中胚叶) covered by **ectoderm** * The **LPM** forms the **bone** and **connective tissue** of the growing **limb bud** * the **muscle** of the growing limb bud are formed by the somatic mesodermal plate	**Axial** * The axial skeleton is derived from the **sclerotome** of the **somites** * **Mesoderm** flanking the **notochord** begins to locally condense from 3rd wks of gestation.		**Neurocranium**: derived from the **neural crest**, brachial arches
Position of limb buds 1) HOX genes 2) TBX4. TBX5 genes 3) FGF-10 **AP** (anteroposterior: digits): HOX, Shh **PD** (Proximodistal): AER/AEMF, HOX **DV** (Dorsoventral): Growth factors	* The homeobox (HOX) gene controls **mass** and local growth of the limb bud in the distal direction of the condensing mesenchyme * The sonic hedgehog genes (Shh)direct development in the AP direction * The apical ectodermal ridge (AER) and zone of polarizing activity (ZPA) regulate the proximal distal and posterior-anterior axes of development and the function of the mesenchymal **progress zone (PZ)** cell		**Apical ectodermal ridge** (AER): → stimulate FGF-4, FGF-8 . **Progress Zone** (PZ): *proliferating zone*. Allow from proximal→ distal G.

Bone

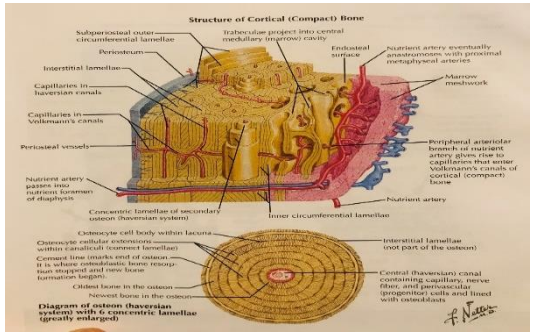
Bone	**Osteoblast**	**Osteocytes**	**Osteoclasts**
Definition	Cells that form bone tissue(osteoid, or bone matrix) Derived from osteoprogenitor cell	Fully differentiated osteoblasts that are encased in secreted bone matrix (*mature bone cells*) Represent 90% of all bone cells	- Large **multinucleated** cells, formed by fusion of **monocytes** - Derived from **monocytic precursor (**bone marrow-derived macrophage-monocyte line**)** - Share some characteristics with monocytes and macrophages
Function	1. Produce **ECM** (**Osteoid** *类骨质*) **(when** mineralised with *crystalline hydroxyapatite*→ bone) 2. Produce **type 1 collagen** 3 Produce **regulatory protein** (growth factor) 4 Produce **non-collagenous proteins** * *osteonectin,* * *osteocalcin,*	1) **Regulate Calcium exchange** Canaliculi: channels through which the osteocytes processes pass Oriented in a radial fashion round the central Haversion canal Connexins: Osteocytes have cell-cell connections 2) **Regulators of osteoblast and osteoclast activity**:	**Resorption of bone** 1. Carbonic anhydrase is expressed & generates intracellular protons (H+) 2. **Proton pump** pumps H+ into the matrix-cell space (→ acidifying) 3. Acid dissolves the hydroxyapatite

	* *osteopointin,* * *sialoprotein,* * *Dentin*	Respond to the development of surface changes under bone loading	4. aided by lysosomal enzymes (acid-activated hydrolases(cathepsins) that degrade the matrix collagen 5. Glycosylated lysosomal enzymes are left in the matrix surface to attract more osteoclasts. 6. PTH stimulates function.
Features	-When active, they have rounded, oval, polyhedral form, nucleus at the end (*shows intense staining with basophilic stain*)) - When not actively formed, OB elongated and flat, quiescent metabolically - Line the surface of bone, follow osteoclasts in cutting cones. -abundant **Rough endoplasmic reticulum** (*produce type I collagen*) **- ALP** distributed over the outer surface of the cell **Express** mRNA for a1 procollagen, ALP and bone forming proteins such as osteopontin and osteocalcin **Receptors**: PTH (parathyroid hormones), Vitamin D, Glucosteroids, Oestrogen, PGs. ILs https://www.youtube.com/watch?v=LC80hvjpHWo Bone cells and bone formation.	-Numerous long cell processes that extend throughout the matrix (**through the canaliculi**)and contact other osteocytes - Osteocytes express CD44, osteocalcin and galectin 2. -higher nucleus-to cytoplasm ratio, -Contains fewer **organelles** -lie in lacunae, **Receptors**: **PTH** (release calcium) **Calcitonion** (do not release calcium)  	-The surface on the bone matrix contains multiple invaginations known as the **ruffled border**. - Attach to bone surfaces via a receptor: integrin - Move along the bone surface by **pseudopodia** (like *amoebae*) - Average life span is 10-14 days. - Large size 20-100μm - Osteoclasts **proliferation** is stimulated by TNF-α - **Proinflammatory cytokins** are also involved in tumour bone resorption, infection, and prosthetic loosening **Receptors:** calcitonion, estrogen, IL-1, RANK L, Inhibited by bisphosphonates 
Stimulation	*Weight-bearing activity* Growth Fluoride Intermittent PTH/PTHrP (*PTH release hormon*) Ultrasound		Lack of weight-bearing activity Hyperparathyroidism(high PTH) Hypercortisolism Hyperthyroidism Oestrogen deficiency Testosterone deficiency
			Acidocis Myeloma Lymphoma Inadequate Ca intake Normal aging
Inhibition	Lack of weight bearing activity Alcoholism Chronic disease Normal aging Hypercortisolism		Weight bearing activity Estrogen Testosterone Bisphosphonate Calcitonin
			Adequate Vit D intake Adequate Ca intake

Bone function	**Bone forms**	Microscopic bone types	Structural bone types
1.serves as **attachment** sites for muscles 2.**protection** for organs (*cranium, ribs)* 3.**reservoir for minerals** in the body: 99% of body's calcium stored as hydroxyapatite crystals 4. Hematopoiesis site.	**Long bones:** 1. form by **enchondral ossification** (except clavicle): primary (in shaft) secondary growth centres 2. have physes (growth plates) at each end where it grows in length (metacarpals, metatarsals, and phalanges of hand and feet typically have only one physis **3. 3 parts of long bone:** * **Diaphysis**: shaft, made of thick cortical bone, filled with bone marrow	**Lamellar** （板层骨） - **Mature bone**: (*begins to form 1m after birth, by 4y.o most normal bone is lamellar)* - A thin plate of bone, highly organized with stress orientation (*collagen fibres in parallel*)	**Cortical** (compact) （密质骨） - strong, dense outer coating of bone (80% of the skeleton) - composed of multiple **osteons** (Haversion systems) with intervening interstitial lamellae. - has 4 times the mass of trabecular bone, but metabolic turnover of trabecular bone is 8 times greater (*due to extraordinarily high surface area for cellular activity*) - remodelling 50% first 2 years declining to 2-5% per year in elderly. *- e.g. found in the diaphysis of long bones*

	* **Metaphysis**: widening of bone near the end, typically made of cancellous bone * **Epiphysis**: end (usually articular) of bone, forms from secondary ossification centres. **Flat bones:** Form by intramembranous ossification (e.g. pelvis, scapula)	*cortical and cancellous bone are both made up of lamellar bone. **Woven:** （编制骨） - **Immature** or pathologic bone - **weak**, poorly organized, not stress oriented. - Often hypercellular, and darker staining - **Higher** rates of bone formation - **isotropic** (等方向性) - replaced by lamellar bone at a later date. - e.g. Immature: bones in **embryo**, **infants**, fracture callus (hard); Pathologic: tumours, Paget's disease, osteogenesis imperfecta.	**Cancellous** （松质骨） (spongy/trabecular *骨小梁*) 1. Crossed lattice structure, inner honey-comb web (20% of the skeleton) 2. High bone turnover rate. Bone is resorbed by osteoclasts in Howship's lacunae and formed on the opposite site of the trabeculae by osteoblasts 3. Osteoporosis is common in cancellous bone, making it susceptible to fractures 4. commonly found in the 1) ***metaphysis*** *and* ***epiphysis*** *of long bones (femoral neck, distal radius, tibial plateau)*. 2) ***vertebral bodies***
			
Bone composition	Mineral (*60% of bone weight*)	Water (5%)	Organic (*35% of bone weight*)

Bone is composed of multiple components: - organic phase, - inorganic, - water	**1) Calcium hydroxyapatite** ($Ca_{10}(PO_4)_6(OH)_2$): *羟磷灰石* primary mineral in bone. Add **compressive** strength. *Plate-like crystal, 20-80nm long, 2-5nm thick*. **2) Osteocalcium phosphate**: Is a secondary/minor mineral in bone 3) Small amounts of: Mg, Na, K, Fluoride, Chloride.	Approximately 5% of bone weight (varies with age and location)	1) Collagen: *Type 1* collagen is the main collagen in bone - gives tensile strength (90%). - **Mineralization** occurs at ends (hole zones) and along sides (pores) of the collagen fibres **2) Proteoglycans**: Gives bone compressive strength. 3) Noncollagen proteins: -Osteocalcin # 1, is indicator of increased bone turnover (e.g. Paget's disease). - Osteonectin, - osteopontin. 4) Cells(2%) Osteoblasts, osteocytes, osteoclasts

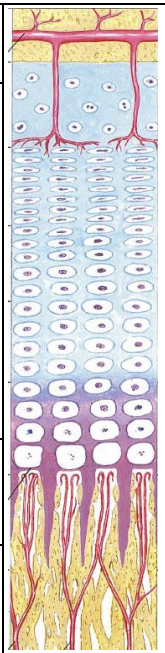
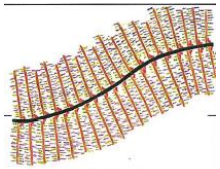
Blood supply: 3 main groups	**Lymphatics**	**Osteon**（骨单位）	Types of lamellae
1. **Nutrient vessels** (*enters diaphysis of a long bone within medullary cavity → ascending and descending branches*) 2. Arteries to **metaphyseal** and **epiphyseal** regions 3. **Periosteal arteries**:	Difficult to demonstrate. Probably runs with *periosteal blood vessels* **Innervation** Periosteum, cortex, trabecular bone all innervated.	**the fundamental functional unit of cortical bone** *– Oriented in the **long bone axis** of the bone* *- It is an irregular, branching, and anastomosing **cylinder** composed of a more or less centrally placed **neurovascular canal** (Haversian canal)surrounded by cell-permeated layers of bone matrix (lamellar plate)* ***Haversian canal***: centrally at each osteon, contains *blood vessels, nerves* (central canal) ***Volkmann's canals***: perforating at right angle to central ***Lacunae***: house osteocytes ***Canaliculi*:** connect lacunae; orientated in a radial fashion; contains processes of osteocytes; **Cement lines**: distinct, basophilic regions visible on H& E staining, indicating where resorption was completed, and bone formation began. **Resting lines**: Linear area of basophilla where osteogenesis is thought to recommence after a period of local quiescence. **Sharpey's fibre**: Section of decalcified bone shows attachment of periosteum to bone by perforating fibres called Sharpey's fibre.	- concentric lamellar (*around the central canal of each osteon*) - interstitial lamella - Inner or outer circumferential lamellae (*wrap around the entire bone*) https://www.youtube.com/watch?v=H1LakKZjD6o Osteon OxyMMBS 
Clinical relevance 1) Osteomyelitis: nonviable cortical or cancellous bone as the focus for bacterial adherence. 2) Posttraumatic osteonecrosis: acute disruption of the arterial blood supply, when epiphyseal arteries cannot rapidly be recanalized, produces trabecular weakening and microfracture. 3) Prosthetic joint devices/external fixation devices/ bone plates affect both the endosteal supply, and the periosteal surface 4) Fracture of bone (esp. high-energy trauma)→ ischemic fragments -→ susceptible to infection.	**Anatomy of the physis** - The physis provides longitudinal growth in long bones - 4 zones 1) Reserve zone 2) Proliferative zone 3) Hypertrophic zone 4) Metaphysis 5) Other *Periosteum: thin membrane covers outer surface of shaft,* *endosteum: walls of marrow cavity covered by the membrane*		

Growth plate histology (Physis)

* The physis provides longitudinal growth in long bones.

* There is another physis in each epiphysis (similar organization). Responsible for epiphyseal growth (not longitudinal).

Zone structure	Histology	Function	Cells feature	Other features	Proteoglycans in matrix	Examplary disease
Secondary bone epiphysis						
Reserve zone (**superficial zone**)		Matrix production, Storage metabolites	Vessels passing through but does not supply it; Chondrocytes do not proliferate	Loosely organized cell produce		Diastrophic dwarfism Pseudoachondroplasia Kneist syndrome
Proliferative Z. 生发层		Matrix production Cellular proliferation	-Cells are flattened and -aligned in longitudinal columns; - Chondrocytes actively divide,	Cells in column		Achondroplasia
Maturation zone 成熟区			Cells are spheric and greatly enlarged.			

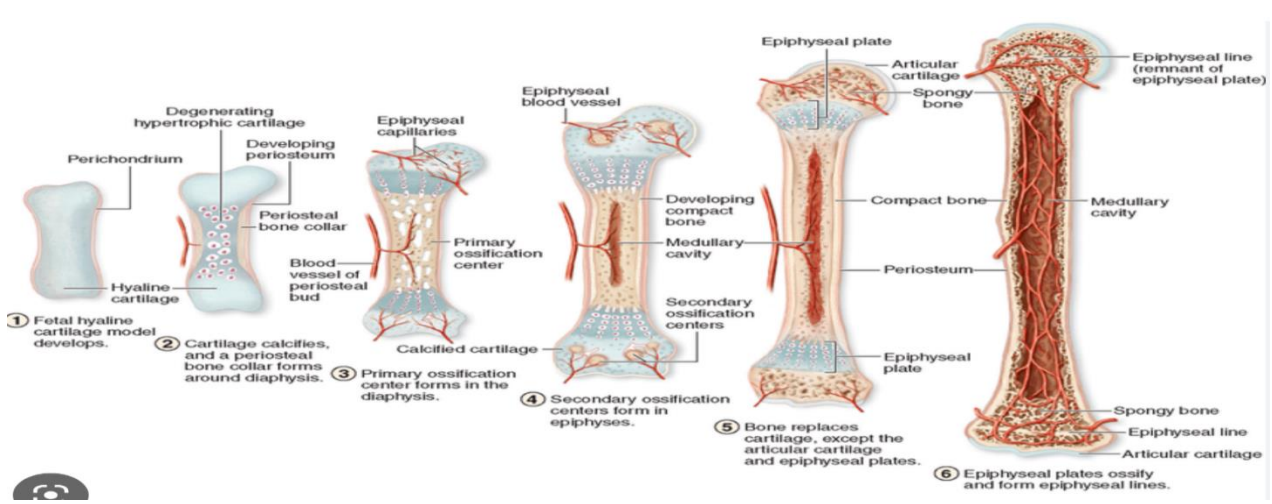
	Degenerative zone 退化区		Preparation of matrix for calcification				
	Zone of provisional calcification		Calcification of matrix	- Cells are bigger - Cell become vacuolated (*有空泡的*) and undergo apoptosis	- Undergo calcification Radiographically dense zone		Rickets, osteomalacia
Metaphysis 干骺端	Primary spongiosa		Vascular invasion and resorption of transverse septa; Bone formation	-heterogeneous mix of calcified matrix, osteoid and immature bone	Osteoblasts make immature (woven)bone on the calcified cartilage		Metaphyseal chondrodysplasia Acute hematogenous osteomyelitis
	Secondary spongiosa		Remodelling— Internal: External:	Remodelling replaces primary spongiosa with mature lamellar trabecular bone	Osteoclasts remove cartilage & immature bonoe		Osteopetrosis Osteogenesis imperfecta Scurvy Metaphyseal dysplasia

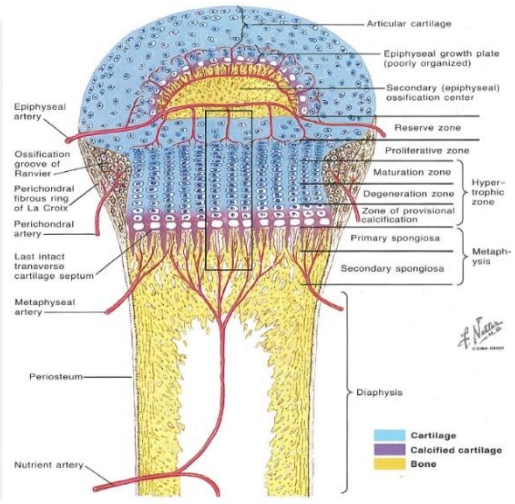
Bone formation

4 situations that bones form: 1) Embryological and foetal development 2) Bone growth. 3) Bone remodelling, 4) Fracture healing

bone formation	**Endochondral** (软骨内成骨)	**Intramembranous** （膜内成骨）	**Appositional growth**
Definition	Bone formation from a pre-existing hyaline cartilage model * typical in long bones (except clavicle) ***Cartilage precursors** formation in the 6th wks of IU life ***Primary centres** of ossification formation in week 8. * **Secondary centres** of ossification formation: after birth	Bone formation without an intervening cartilaginous step (*Osteoblasts lay down bone directly into fibrous tissue, with no cartilage precursor*) * In utero before 8th weeks	Growth in the thickness of long bones where bone is formed at the periosteum Surface by osteoblast, and bone resorbed by osteoclasts at the inner layer of a bone
Mechanism	**Mineralization front (MF):** - osteoblasts produce ***osteoid***→ mineralises ~10y later. - a basophilic linear line - Substances that bind at the MF may cause pathological states *(e.g. aluminium induced osteomalacia in pts on dialysis*) *or iron induced osteomalacia in hyperchromatosis* -fluoride binds at MF and makes bone less susceptible to resorption	**Mesenchymal** cell 间叶细胞 differentiate into osteoblasts, which produce bone	-Occurs via perichondrium -A cuff of tissue characterized by mesenchymal cell growth and differentiation.
Marker	Cbfa1, osteocalcin, osteopontin, bone sialoprotein		
Steps	1) Cartilage enlarges, then chondrocytes die (*先增大再死亡*) 2) Blood vessels grow into perichondrium, cells convert to osteoblasts, shaft becomes covered with **periosteal collar** 3) More blood supply and osteoblasts produces spongy bone, formation spreads on shaft （先吸收软骨模型再造编织骨） 4) **Osteoclasts** creates medullary cavity, *appositional* growth 5) Epiphysis centres calcify, blood and osteoblasts move in, secondary ossification centres 6) Epiphysis filled with spongy bone; cartilage remain at joints; epiphyseal plate in metaphysis	1) development of ossification centre - cells differentiate into **osteoblasts**→ secretes ECM (collagen fibres) 2) Calcification - Osteoblasts are surrounded by ECM→ deferrentiate into osteocytes→ lacunae 3) Formation of trabeculae - trabeculae start to form. Blood vessels infiltration. 4) Development of periosteum - Fibrous periosteum formed. Red marrow tissue fill spongy bone	

	** The cartilage model is not converted but firstly destroyed by osteoclasts before being replaced by osteoid or new woven bone*	https://www.youtube.com/watch?v=z0ubmKaplo Y Lecturio Nursing	
clinical relevance	*Most bone formation (in length) including growth plates. 1. **Fracture callus**: formed in part by enchondral ossification 2.**Osteochondroma**: cartilaginous cap produces bone via enchondral ossification 3. **Osteophyte**: formed by enchondral ossification 4. **Loose bodies in joints**: one causes is enchondral ossification	1. Growth of skull, scapula, clavicle, ilium bones 2. Developing width of bone 3. Most of periosteal new bone formed in fracture callus 4. Most of the bone formed in response to tumours and infections.	Periosteal-mediated bone diameter (width) growth in long bones.





Bone

mineralization

2 phases 1) formation of initial mineral deposits *at multiple discrete sites* (Initiation) 2) proliferation of additional mineral crystals *on the initial mineral deposits* (growth) https://www.youtube.com/watch?v=Eq9QD9ZWGNw mineralisation	Initial mineralization - increases in the local concentration of **precipitating ions** - Formation or exposure of **mineral nucleator** - removal or modification of mineralisation inhibitors	* Matrix vesicles develop in chondrocytes and osteoblasts (contain calcium and inorganic phosphate ions, *initiate HA formation*) * These matrix vesicles are **extruded** * Sulfated and /or phosphorylated **proteins** act as **stimulators** or nucleators of crystal formation * Matrix vesicles also contain MMPs, responsible for matrix breakdown/turnover.	**paediatric elbow ossification sequence** C: capitellum (2) R: Radial head (4) I: Medial (Internal) epicondyle (6) T: Trochlear (8) O: Olecranon (10) L: lateral epicondyle (External) (12)

Bone healing, remodelling

Fracture healing 5 phases	Bone healing type	Bone modelling and remodelling	Type of remodelling
1. **Haematoma**: bone at fracture surfaces is avascular and dies back 1-2 mm 2.**Inflammatory reaction:** with proliferation of cells begins within 8 hours. Haematoma is absorbed as new capillaries grow into the area 3. **Callus formation**: cells brought in by the new blood vessels differentiate to begin producing a mass of immature (woven) bone and cartilage which bridges the fracture and progressively decreases movement until the fracture unites	**1. Nonstabilised fractures** - Mesenchymal cell condensation - Chondrogenesis with Type II collagen expression - Cbfa1. Osteocalcin, endochondral ossification **2. Stabilised fractures** - No expression of cartilage specific genes - Healing by intramembranous ossification.	**Definition:** The process of bone modelling and remodelling require osteoclastic resorption of bone matrix and deposition of a new matrix by osteoblasts. (*begins early in embryogenesis*) **Bone remodelling units (BMUs):** The (*small, discrete, microscopically identifiable*) unit of **osteoclasts** breaking down bone and **osteoblasts** laying down bone (*coupled bone resorption/formation*) 1) Does not cause net changes in the shape of bone.	**Physiologic remodelling** - Does not change bone shape and consists of bone resorption and deposition in approximately the same location. - This type of bone turnover occurs throughout life and is important for **homeostasis** and **maintenance** of the skeleton. - Surface phenomenon (*occurs on periosteal, endosteal, harversian canal, trabecular surfaces*)

4. **Consolidation**: the woven bone is transformed into mature(lamellar)bone by the action of osteoclasts and osteoblasts forming a solid bridge of mature bone which can take normal loads 5. **Remodelling**: Over *months or years* the bone is remodelled in response to mechanical stress to resemble its original shape, and the medullary canal is reformed.	**Wolff's law** * Galileo observed correlation between **body weight** and **activity** and **bone architecture**. * Bone is a dynamic tissue that modulates its external and internal structure throughout life (sensitive to mechanical and systemic cues) * 2 categories of metabolic processes: formation and resorption (modelling and remodelling)	2) **Bone loss**: endocortical thinning, ↑porosity, trabecular bone loss. 3) 4 stages: *activation, resorption, reversal, formation.* 4) Occurs on **open bone surface** (*periosteal, endocortical, or trabecular*) **BMUs are influenced by** Systemic factors: - **dietary** intake of Ca, and protein - **exercise** (*loading ↑bone mass, decrease loading↓mass*) - **hormones**: *E, Corticosteroids, PTH, Calcitonin, VitD, growth hormone.* Local factors *- Mechanical and electrical stimuli* *- Bone matrix macromolecules* *- Prostaglandins* *- bone growth factors*	- Rate of cortical bone remodeling up to 50%/y in the midshaft of the femur during first 2 yr of life→ 2%-5% per year in healthy elderly **Adaptive remodelling** - is the response of the bone to altered loads and may alter the strength density and shape of the bone. https://www.youtube.com/watch?v=Ei4seya3dOg Bone remodelling and repair: Osmosis from Elsevier

Regulators of bone

Cells		Cellular	Other factors	Non union or delayed union
Osteoblast: secrete IL6 and IL11→stimulate OCs to degrade bone matrix		Mediators of Cell Attachment - Mediators of osteoclast attachment to bone: * Osteopontin, bone sialoprotein - Collagen organisers * **COMP mutations** result in 2 disorders a) EDM1 (Form of multiple epiphyseal dysplsia) b) pseudoachrondroplasia Delta carboxylic acid containing proteins e.g. **osteocalcin** * Made by osteoblasts, not osteoclasts * Metabolised in renal tubule * used as marker for some bone disease *$ Increased in growth spurts, puberty, Pagets* *$ higher in osteoblastic breast mets than in osteolytic breast cancer* * Level rise rapidly in response to calcitriol * Vit K is essential cofactor in synthesis. (*Vit K antagonist in 1st trimester may result in bone defects*)	Osteoconduction: - Process by which the graft acts ass scaffold to promote the orderly laying down of new bone. *E.g. DBM (demineriz ed matrix*) Osteoinduction -Material contains factors that stimulate bone growth and induction of stem cells down a bone-forming lineage - e.g.*BMPS are members of the transforming growth factor b superfamily and are involved in embryogenesis and adult bone repair. BMP2 and BMP7 are most potent* . Osteogenesis - Material directly provides cells that twill produce bone including primitive *mesenchymal stem cells, osteoblasts, and osteocytes*. - *e.g. autograft*. - Mesenchymal stem cells→ differentiate down any cell line - Osteoprogenitor cells→ OB, then OC. * **Cancellous bone** has greater ability than cortical bone to form new bone (*larger surface area*)	* Occurs secondary to imbalance between the catabolic and anabolic responses to bone healing. - Anabolic: forms bone -Catabolic: removes the bone *non/delayed union due to - anabolic deficiency or - catabolic excess * Hypertrophic non union: Results in abundant callus formation but the mechanical environment is not conducive to union due to excessive mobility at the fracture site - *Tx: improve mechanical stability; bone grafting is not required*) * Atrophic non union Occurs secondary to inadequate metabolic response *(e.g. impaired blood supply*) - Treatment: optimizing the biological environment (bone grafting) (combination of **osteo**- conduction, induction, genesis)
Inhibitors of OB - Osteocalcin - Leptin - HoxA2 - TGFb	**Stimulators of OB** -PTH -1,25 Vit D			
Osteoclast: normal fate is apoptosis		MMPs - MMP 9 associated with bone degradation - MMP 1,3,13 associated with arthritis	**Factors that detrimentally affect bone healing**	
F. ↓ bone resorption - oestrogens - Bisphosphonate →osteoclast apoptosis	F ↑ bone resorption→ inhibit OCs apoptosis		- Biological factors Age Nutrition Blood supply Smoking Severity of injury -Mechanical factors Stability Soft-tissue interposition Separation of fragments	

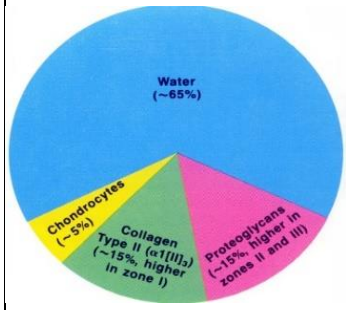
Cartilage

Definition	Character of Cartilage	3 major types of cartilage	Cross section of HAC: 4 zones

- the most abundant mammalian pr.
- a form of **connective tissue**
- Originated from mesenchymal stem cell
- Collagen is formed by the *helical intertwining* of **3 protein chains** (alpha chain)
- **5 major types**:
  a) **Hyaline**
  b) **Elastic**
  c) **Fibrocartilage**
  d) **Growth plate**
  f) **Fibroelastic** (*menisci, intervertebral discs*)

Major component of cartilage

1) Cell (*chondrocytes, chondroblasts*)
2) **ECM** (*95% of volume*)
- **Water**: 65% *deep zones*; 80% surface (*large PG water trapping*)
- **collagen 15%** (*resist tension; Type II most common*)
- **PG** 15% (*weak in shear, heavily hydrated, adapted to bear weight*)



1) Avascular: (*diffusion of substance from blood vessels to maintain viability*)
2) Aneural
3) Alymphataic
4) limited potential for self-repair.
5) Large ratio of GAGs: type II collagen (*to allow above diffusion*)

Mechanical properties *depend on* ***ECM***

HAC is a viscoelastic solid

Aggrecans trap and hold large amount of H2O

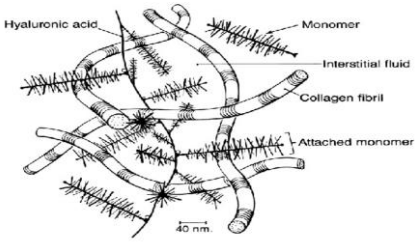
1) swelling pressure is controlled by the *tensile strength* of the collagen network → control the shape and form of the HCA

2) **Permeability** and **compressive stiffness** is controlled by the *water content*

(If lose PG, the H2O content increase→ HAC becomes less stiff & permeable→ more compressible → failure)

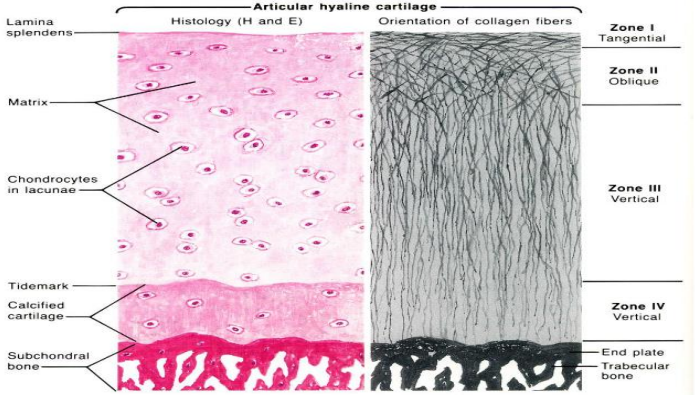
Hyaline	Elastic	Fibrous
Articular c. *Growth plt* *Nose,* *Larynx* *Trachea* *Bronchi* *Costal cart.* *fetal bone*	*Ear(Pinna)* *Epiglottis* *Eustachian T*	*IVD* *Meniscus* *Articular discs in SCJ, TMJ* *Labrum (GH, Hip)* *Pubic symphysis*
Type II	Type II	Type I
1.Transmit load (static, dynamic) 2 Low friction in joint (*Coefficient 0.001*) 3.structural support 4.fetal skeletal	Flexible support	1.Load bearing 2.*Shock absorbing* 3.Attach tendons to bone

** Type I: 2 alpha 1 + 1 alpha 2 chain*
** Type II: 3 alpha1 chain*



The main function of the collagen
-Contribute tensile strength and
- form the articular cartilage

Light microscopy of HCA: smooth and homogeneous
Electron microscopy: Consists of a meshwork of **collagen fibres** and **PG + chondrocytes + water**



https://www.youtube.com/watch?v=9g0TG249BDI Nabil ebraheim.

	Other name	Chondrocytes Cells	Fibres	PG or H2O
Zone I (10-20%)	Superficial z Tangential zone	Elongated and flattened	Type II collagen fibril, parallel to the surface	rich in collagen, H2O, poorer in PG
Zone II (40-60%)	Transitional z Oblique zone	Round	Less organized, oblique orientation	
Zone III (30-40%)	Deep z Vertical zone	Small round, *in short columns perpendicular to surface*	Between columns, perpendicular to joint surface	Rich PG, low H2O
Tidemark:	Heavily calcified line btw Zone III and Zone IV. (blue line with HE stain)			
Zone IV	Calcified z Vertical zone	Small cell. In articular renewal, cell migrate from this zone to joint surface	Calcified matrix,	

Macroscopic anatomy of synovial joints

1) The articular surfaces (AS) are covered with **hyaline cartilage**.
2) Between the AS is a joint cavity filled with **synovial fluid** +/- **articular disc** (*Meniscus*)
3) The joint is surrounded by a ***fibrous articular capsule***, lined by ***synovial membrane*** *(apart from the articular surfaces covered by hyaline cartilage)*
- The membrane is **rich nerve supply**, thus sensitive to stretches, and pain
- The membrane **secretes synovial fluids**→ lubricates the joint and nourishes HCA
4) The capsule is augmented by ligaments, ROM controlled by muscles, ligaments, shape of the articulating bones.

Articular cartilage injury causes

1) Repetitive & prolonged joint overloading
2) Sudden impact forces
3) High sheer stress at the subchondral junction

3 types of injuries

1) Microdamage to cells, matrix
2) Macroscopic disruption to the HAC *(chondral fracture)*
3) Fractures of both HAC & underlying subchondral bone (*osteochondral fractures*)

Response by articular cartilage to these injuries

1)chondrocyte death
2)Loss of chondrocyte regulation of the ECM
-weakening of the collagen structure,
- loss of proteoglycans
- Increase in water content → impairs the normal load carrying capacity of the HCA
→progressive damage and breakdown.

* Mature HAC has limited capacity to intrinsic repair
(due to the avascular, no inflammatory response)

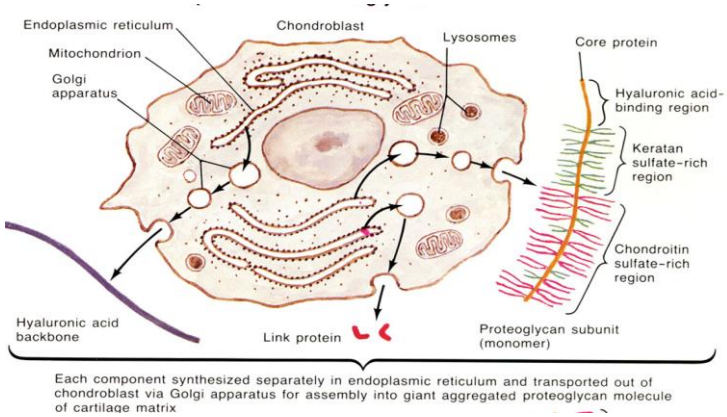
Extrinsic repair of HAC

1) Migration from subchondral bone marrow
2) **Free grafting of**
- non-articular cartilage
- Periosteum
-Perichondrium
- Cultivated chondrocytes+/- biodegradable scaffold(stem cell inj.)

Intrinsic repair

- Recent in vivo investigation (MARS, *medipex all resolution system*): cartilage has greater capacity for intrinsic repair than traditionally believed.
- variable and is person specific
- better in younger males and female >65.

Cartilage cells

	Chondrocyte	Chondroblast	Extracellular cartilage matrix
Definition	Arise from undifferentiated mesenchymal stem cell		Maintenance of ECM depends on chondrocytes balancing - synthesis of matrix components - Their incorporation into the matrix - the component's degradation and release from the cartilage Controlling factors include - Soluble mediators (Growth factors, interleukins) - matrix composition - Mechanical loads - Hydrostatic pressure changes - Electric field changes
Function	1) Cartilage production 2) Type II collagen production 3) Proteoglycan synthesis		
Features	Produce ECM: *2 major pathways* - Endochondral calcification pathway (*cells undergo maturation, hypertrophy and matrix calcification*) - Non endochondral calcification: *cells are relatively quiescent and carry out load bearing and structural function* Chondrocyte metabolism - Chondrocytes have high metabolic rates - Principally on anaerobic pathways for metabolism		

Synovial Membrane

	Synovium	Type A cell (M cell)	Type B cell (F cell)
Definition	Is a vascular mesenchymal tissue lining all diarthrodial joints	Originate from monocytes with prominent lysosomes	Probably derived from fibroblasts
Function	Produces synovial joint fluid (secrete hyaluronic acid and protein) Supplier of nutrition Remover of debris	Resembling a macrophage: phagocytic	Resembling a fibroblast: Secretory Secrete prostaglandins, collagenase and hyaluronic acid
Features	1)It contains **multiple villi** that increases the effective surface area of the tissue **2) The internal surface** is lined by 2 parallel lines of cells **3) The deeper layer** consists of loose fatty CT (with varying fibrous elements) 4) There is a **rich supply of blood** vessels and **lymphatics** 5) Unmyelinated nerve (nociceptive) fibres extend into the adventria of the blood vessels only	Lie closest to the joint lining	Rich in rough endoplasmic reticular

	Meniscus	Synovial fluid	Lubrication of synovial joints	Type of lubrication: 1) Boundary 2) Fluid film
Features	Majority of Type I **Circumferential**: Majority; resist compressive force **Radial fibres**: only in superficial 25%; resist shear forces Fluid filled clefts: seen in inner meniscus is normal.	- an ultra filtrate from plasma - **high viscosity** (variable but generally high) - Clear colourless /straw colored low volume (<3.5ml in knee) - **Composition:** HLA, lubricin, proteases, collagenase, <200 wbc/mm3, <25% plolys and phagocytes	3 components 1) Lubricin 2) Surface active phospholipids 3) Hyaluronic acid	1) **Boundary**: - *achieved by the shearing of surface molecules e.g.lubricin, absorbed onto the cartilage surface* - Occurs when the *opposing articular surfaces come into contact creating contact asperities*; Or *when the fluid film is depleted under severe loading conditions*. - *low joint loads* 2) **Fluid-Film** lubrication (*high joint loads*) (by the interposition of a viscous fluid between the bone end) - Hydrodynamic (non-// surfaces) - **Squeeze-film** (⊥ surfaces): 2 surfaces don't slide, lubricant squeezes laterally. - elastohydrodynamic
Function/ Others	**Joint stiffness** is Measured in terms - frictional resistance, -viscous drag of synovial fluid, - - elastic forces from tissue elasticity - Inertial stiffness - Plastic or visco-elastic stiffness	1) Reduction of friction by lubricating the articular surfaces 2) Shock absorption (rapidly increasing its viscosity when load applied) 3) Nutrient and waste transportation	**Lubricin** - the superficial zone protein - Is a proteoglycan synthesized by superficial layer chondrocytes and B cells of synovium - contributes to boundary lubrication by facilitating low friction levels	

	Contribution: - Joint capsule 46% - Muscles 41% -tendons 10% - Skin 2% *↑with age, M>F, cold temp. with wide spread damage to the articular cartilage.	4) Phagocytosis of microbes and debris from wear and tear 5) Molecular sieving	- Has **chondroprotective** properties - Regulated by cytokines and growth factors	3) **Mixed lubrication** - Boundary- Fluid-film - Boosted

Muscle

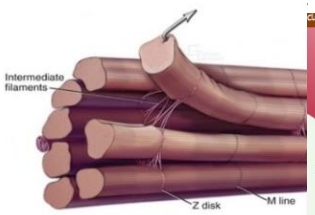
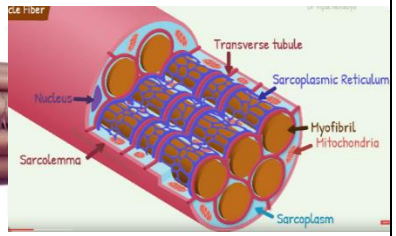
Muscle characteristics: 1) Excitable, 2) Contractile. 3) Extensible(stretchable) 4) Elastic.

Muscle function: 1) Producing movement. 2) Posture. 3) Stabilize joints. 4) Produce or generate heat.

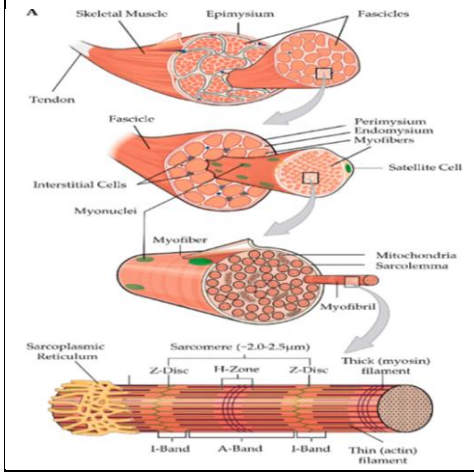
***Smooth muscle**:1) lack of cross-striated banding pattern; neither troponin nor T tubules. Neither myofibrils nor sarcomeres. Innervated by nerve derived from the autonomic nervous system (contract spontaneously);*

***Cardiac muscle**: Much shorter fibres. Long refractory period (avoid tetanus in heart).*

Structure and biomechanics

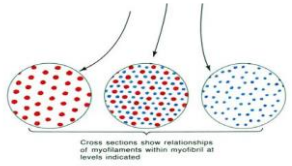
Level 1	**Skeletal Muscle** * *Mesodermal origin*	**Epimysium** (肌外膜): Surrounds the muscle- sheath fuses with the tendon; *Dense irregular CT*.
Level 2	**Fascicle** （肌束） * *the smallest unit of structure visible to the naked eye*.	**Perimysium** (肌束膜) surrounds a **bundle of cells;** *Dense, irregular CT*
Level 3	**Myofiber** /cell（肌纤维） * *Multinucleated cells* * *Derived from embryonic fusion of myoblasts* * Mature cells are known as **myotubes** or muscle fibres * vary in size and length btw sexes, muscle groups * Individual fibres span the full length of the muscle they form.	**Endomysium** (肌内膜) surround a single cell (muscle cell) (*muscle cells are the largest cells in the human body*) - *areola connective tissue (less tough, less collagen)* - Contains capillaries and nerves - Aids in providing an appropriate chemical environment for the exchange of Ca. Na, K **Sarcolemma** (肌纤维膜) Or myolemma. *Underneath endomysium*. Is the phospholipid bilayer *cell membrane* surrounding a skeletal muscle fibre (The site of the defect in Duchenne Muscle dystrophy)
Level 4	**Myofibril** (肌原纤维) * the contractile apparatus - 1 µm diameter - A string of **sarcomeres** arranges in series (*Striated*) - Muscle fibre grows is to *increase the number* of myofibrils - each myofibril is interconnected with one another by intermediate filaments - each myofibril span the entire muscle length.	 
vel 5	**Sarcomere** (肌小节) The fundamental contractile units 2-2.5 µm in length, 1 µm in dimeter Visible under electron microscopy Variation along the length of the myofibril (shorter at MTJ)	**Sarcoplasmic reticulum** (endoplasmic reticulum) *- Degeneration, rebuilding of the myofibrils occur in sarcomere units* *- e.g. adjustment of the length of a muscle immobilised in a shortened condition: by the dissolution of a number of sarcomeres, and their replacement by a smaller number*

* **Sarcolemma** (*细胞膜*): cell membrane.
* **Sarcoplasmic reticulum** （*肌浆网*）: endoplasmic reticulum
* **Sarcoplasm** （*细胞质*）: cytoplasm
* **Sarcosomes** （*线粒体*）: mitochondria
* Sarcomere (肌小节)
* Terminal cisternae （*终末池*）



Sarcomere cross section:

* Each **thick filament** is surrounded by 6 **thin filaments** .
* Each thin filament is equidistant to 3 thick filaments.



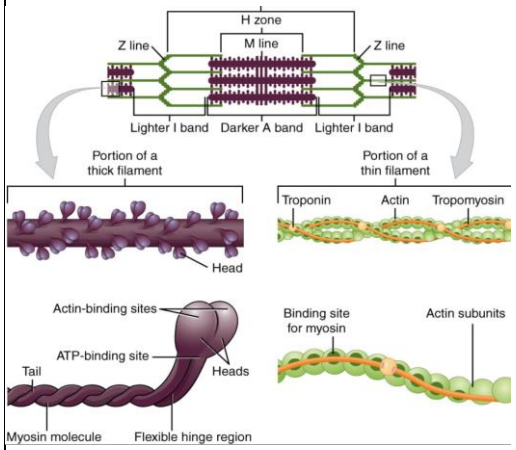
Myofilament structural protein

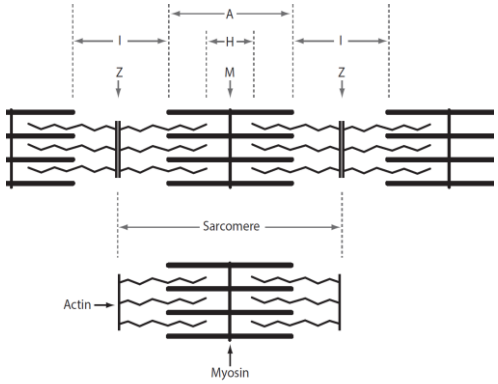
Alpha-actin: links actin filaments to the z-band
Myomesin: in the M line, links titin to the M line
C protein: in the H band, links myosin together
Titin: anchored to the M line by myomesin
Nebulin: anchoring & regulating thin filament length

Sarcomere: (z line – z line)
Component: **Actin** (thin filament); isotropic
Myosin (thick filament), anisotropic
Titin (Elastic filament)

Structures:

Name	feature	Filament	protein
A band	* Anisotropic Haematoxylin-stain ** Does not shorten*	**Thick**	Myocin (inc. overlapping z.)
I band	* Isotropic * Shorten with contraction.	Thin	actin
H band	* Shorten with contraction	**Thick**	Myocin *(exc. Overlapping zone)*
M line	Mid line		
Z line	Margin.		



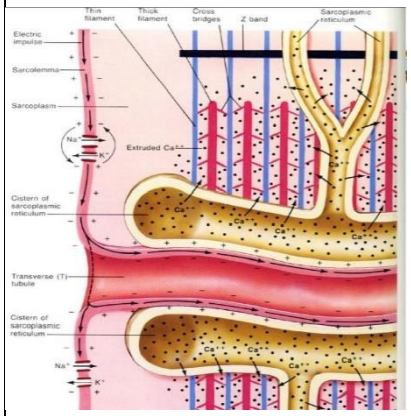


I- and H bands shorten
A-band remains unchanged

Sarcoplasmic reticulum (肌浆网):

1) **Definition:** a network of longitudinal channels (longitudinal tubules) and sad-like horizontal storage areas rich in calcium (Terminal cisternae) surrounding each myofibril.

3) Function: regulation of Ca2+ ion concentration (*storage, release and reuptake*)



Triad junction= SR+T-tubule+ SR.

https://www.youtube.com/watch?v=dCcsk_LV9CY (Skeletal Muscle Fiber: Nonstop Neuro)

The T tubule system *(transverse tubules)*

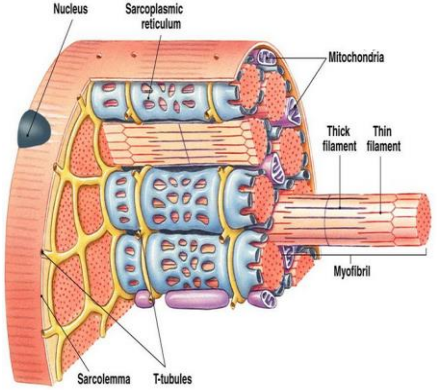
1. Definition: The sarcolemma forms regular invaginations (*内陷*) at the ***junctions of A- and I bands***, which insert between **myofibrils**.

2. Function: Carry the **surface depolarisation** to the terminal cisternae.

3. Depolarisation of the sarcolemma: by a Na+/K+ gated pump

4. The depolarisation potential reaches the SR by T tubules

5. 2 systems of T tubules from every sarcomere (each one in contact with 2 cisternae of the SR)



Calcium

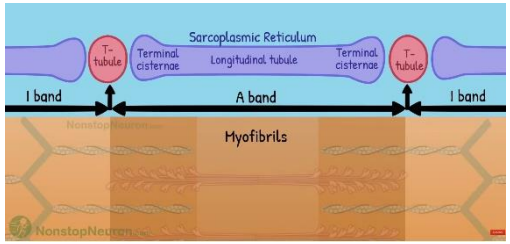
Ca2+ : the chemical stimulus to contraction of the myofibrils.

Ca2+ storage:

- Ca2+ is stored in **Sarcoplasmic reticulum**
- A neuronal impulse releases Acetylcholine → excites the **muscle fibre cell membrane** (Sarcolemma)
  → Ca2+ influx into the **Sarcoplasm** (*immediate trigger to contraction*) → contraction (10x increase in concentration)

Calcium pump

- **SR** contain Ca^{2+} pump (maintains high concentration of Ca2+ in the SR, low in sarcoplasm)
- The energy for the Ca^{2+} pump is supplied by the cleavage of ATP by the enzyme Ca-Mg ATPase.
  (One cleavage transports 2 Ca2+ molecules)
- The Ca2+ in the SR is partially maintained by the Ca2+ binding protein Calquestrin.



Maintenance of ATP

- **ATP** replenished from **ADP + P** (*oxidating metabolism*) (in mitochondria in the sarcoplasm)
- The mitochondria are clustered round the sarcolemma and its oxygen rick capillaris.

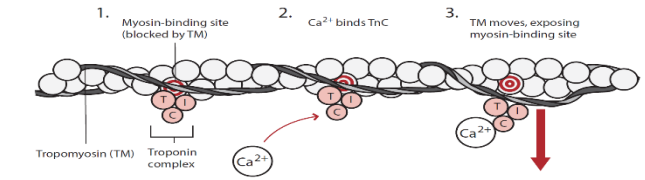
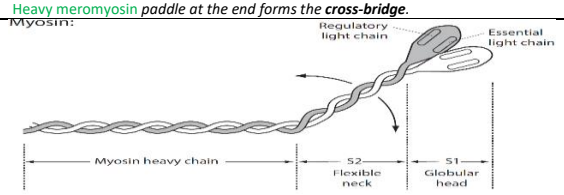
Mitochondria:

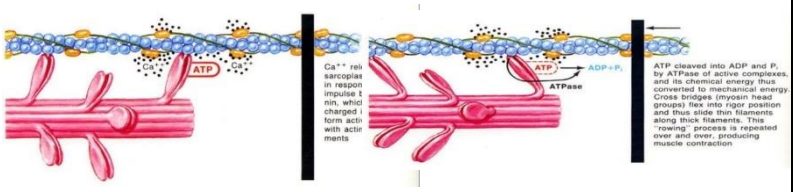
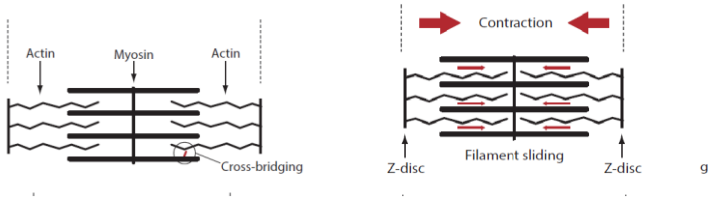
3D network generating energy (*by synthesizing ATP by oxidating metabolism)*, utilizing oxygen.

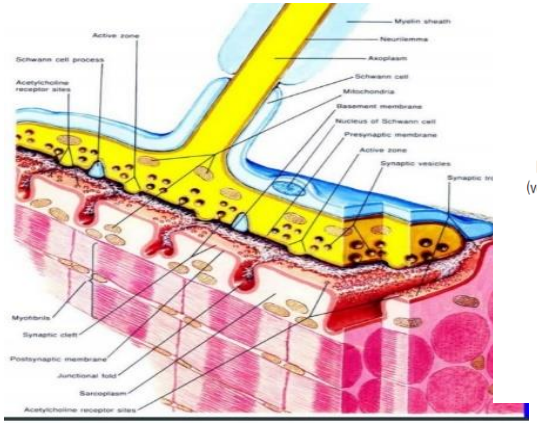
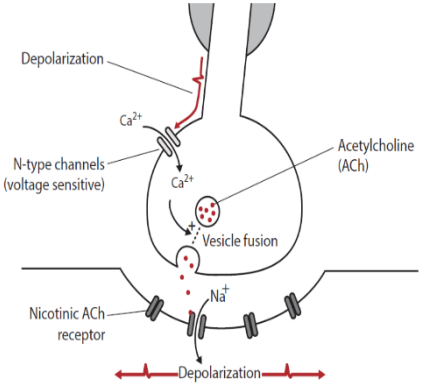
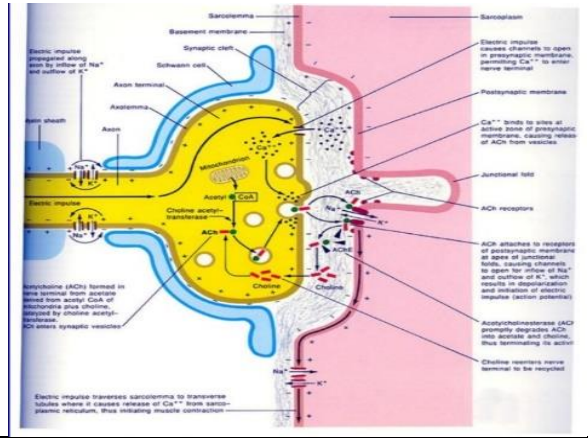
- **Anaerobic metabolism** is possible in muscle from the breakdown in stored glycogen.
- Myoglobin: The oxygen carrier. Muscle capillaries Filling only on relaxation
- Creatine kinase: the enzyme that is involved in intermediate stage in the production of ATP. Serum levels of CK are elevated in muscle disease.

https://www.unm.edu/~jimmy/muscle2_notes.htm https://www.youtube.com/watch?v=JIhCukkphWM https://www.youtube.com/watch?v=UKgbfxPTn_s

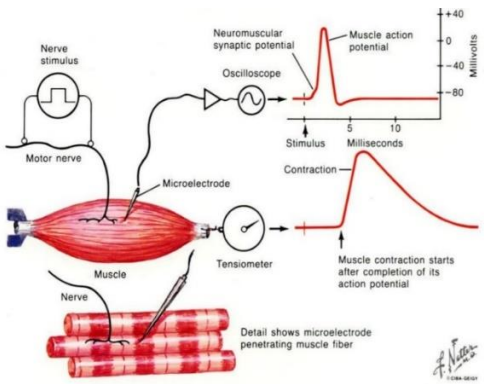
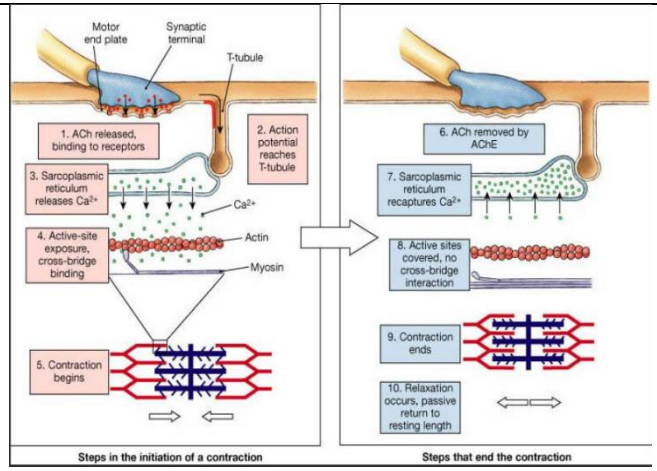
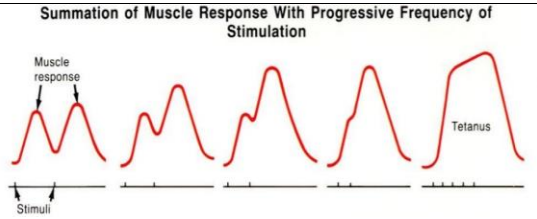
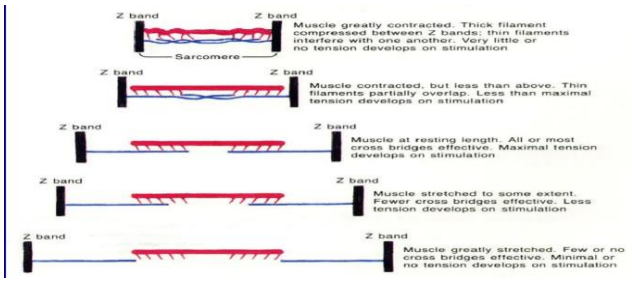
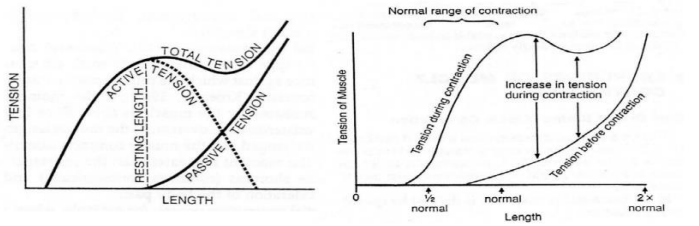
Contractile protein

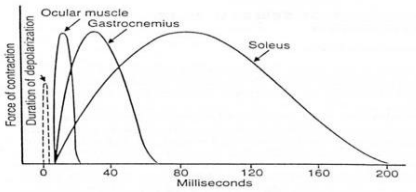
	Thin filaments	**Thick filaments**
component	Actin (*Filamentous actin*)	Myosin
Molecules & weight	G-actin: (globular protein) MW 40,000, 1 μm long total Troponin: MW 70,000, Lies in the grove formed by the double helix linked by thin tropomyosin molecules. - Trop I: affinity for actin; (*Inhibits contraction)* - Trop T: affinity for Tropomyosiin - Trop C: affinity for calcium ions Tropomyosin: thin molecule rod-shaped protein, spiralling around actin to stabilise it. Blocking the binding sites of the myosin head. Double helix linear structure	500,000 - 2 heavy chains S1 segment (globular head) S2 segment (flexible neck) -4 light chains. Essential light chain Regulatory light chain.
Structure	Double helix rod	2 filaments in alpha-helix formed by Light meromyosin 酶解肌球蛋白 Heavy meromyosin *paddle at the end forms the* ***cross-bridge***.
Picture		
Cross bridge	**Cross-bridge theory:** Huxley (1957) 1. Calcium ions are released from the SR into sarcoplasm and bind to the Troponin **C** subunits 2. *Tropomysin* changes configuration (displaces troponin I from the actin and expose *myosin binding sites on actin*) 3. Cross bridges form when **ATP** binds to the ***myosin head*** groups 4. The resultant charged unit then binds to an *actin* subunit under the influence of calcium ion 5. Movement occurs when the **myosin head units** *bend backwards* (pulls thin F to M line)	https://www.youtube.com/watch?v=nTZnBdeIb5c sliding filament theory of muscle contraction https://www.youtube.com/watch?v=7_LZFmfeCuk Sliding filament theory Dr Matt & Dr Mike

	6. The energy for this is supplied by the hydrolysis of ATP into ADP+P 7. **ADP** then dissociates from the myosin heads 8. As the process is repeated, the thin filaments are pulled past the thick filaments so producing contraction of the myofibrils 	

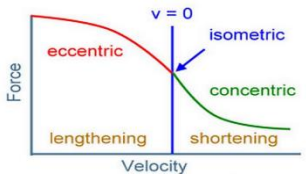
Neuromuscular junction (NMJ)	The connection between a **motor neuron** and a **muscle fibre** is called NMJ. This is a chemical synapse between a **motor axion terminal** (*presynaptic terminal*) and the **motor endplate** (*post-synaptic membrane*) of a muscle fibre. *https://www.youtube.com/watch?v=zbo0i1r1pXA Alila medical media*		
Neuromuscular junction	**Motor axons terminals** (presynaptic terminal) 1. **Motor axons** are large and myelinated 2. The Terminals are covered by a Schwann cell with finger-like projections between the membranes 3. The terminal lies in a trough in the muscle **sarcolemma** 4. Terminals are rich in mitochondrial and synaptic vesicles full of Acetylcholine (Ach) 5. Vesicles are clustered round nipple shaped **active zones**  	**Active Zones** 1. **Sarcolemma** is *invaginated* opposite each active zone 2. Synapse is 50nm wide 3. Postsynaptic membrane has granular structure because of Ach receptor grouping 4. Connective tissue basement membrane continues into **synaptic cleft** 5. This contains most of the **acetylcholinesterase** 
Neuromuscular junction nerve conduction	Physiology of NMJ nerve conduction * Nerve impulse propagated by inward flux of Na+ ion and repolarized by efflux of K+ ions ** depolarization channels located at nodes of Ranvier* * Na+/ K+ pumps located closely together.	Nerve terminal 1. Contains fewer Na+ channels, different types of K+ channels, and **voltage dependent calcium channels** 2. When the impulse arrives, the Ca++ channels open and calcium influxes into the terminal 3. This Ca++ is then pumped into intracellular organelles (ER and Micochondria) 4. The rise in Ca++ causes release of Ach into the intermembranous space by *Exocytosis*.	The synapse 1. Once in the synapse, Ach binds to receptor molecules opening sodium and potassium channels so depolarizing the **muscle membrane** (Depolarization is dependent on the rate of release of Ach into the cleft) 2. Ach is then rapidly hydrolysed to **Acetate** and **Choline** by *acetylcholinesterase* 3. Choline is retransported back into the terminal and converted to acetylcholine by the action of choline acetyltransferase.

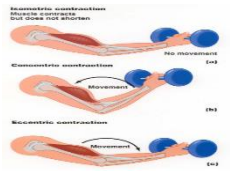
Muscle contraction

Muscle response to stimulation	**Transmitter Release** 1. The amount of transmitter (Ach) released at the **end plate** is sufficient to produce a muscle *action potential* 2. The action potential will be initiated within the muscle fibre by activation of voltage-gated Na+ channels 3. This propagates through sarcolemma deep into the fibre via the T tubules 4. **Calcium** ions are released synchronously to produce a ***'twitch'*** (*The tension of the twitch can be measured*).		
Twitch tension	1. Single twitch is a *constant property* 2. If a second twitch is generated before the first has relaxed, the achieved tension is *increased* 3. If the muscle is activated at a sufficient frequency, a *sustained contraction* (tetany) result.		
Muscle length	**Effect of muscle length** * Maximum tension is generated at "normal "muscle length (Sarcomere 2 μm) * When stretched prior to contraction, it contains a log of resting tension due to elastic forces in tissues. * active tension decreases as the muscle is stretched beyond its normal length.	**Length-Tension relationship curve** * The curve has a similar overall shape. * Final tension generated is related to the final length of muscle achieved. - Maximum tension occurs when all the cross bridges are activated (*at the normal resting length*) - If the muscle is too contracted, the thin filaments overlap - if it is too stretched, the thin filaments cannot access all of the myosin head groups	
ATP	Role of ATP: 1. Supply energy (*actuates the walk-along action of the myosin on the actin*) 2. Supply energy (*maintain Ca 2+ pump at sarcoplasm/ sarcoplasmic reticulum*) 3. Supply energy (*maintain the Na+/K+ pump at the muscle membrane*) * {ATP} of 4mmol can maintain contraction for 1-2 seconds	**The Source of ATP** * Generated by glycolysis and oxidative metabolism of **carbohydrate** and **fat**. * ATP is regenerated at multiple points along these metabolic pathways. * ATP is regenerated very quickly from ADP. ***Glycolysis*** *1. Glucose 6 phosphate (G6P) is derived from the **phosphorylation of glucose*** *2. This is broken down to two molecules of Acetyl coenzyme A- A(CoA)* *3. During this process, 3 molecules of ATP are generated*	**Kreb's Cycle** 1. A(CoA) enters the *citric acid (Kreb's) cycle* in the mitochondria （线粒体） 2. This involves the reduction of **oxygen** to **water** 3. Under *anaerobic* conditions only 3 molecules are generated by this system 4. Under ***Aerobic*** conditions 35 molecules of ATP are formed 5. The *whole system is 'buffered 'by* Creatinine phosphate which can quickly donate a P to ADP

Efficiency	The efficiency of any 'engine' is calculated as the **percentage of energy** put into the system that is **converted to work** versus the **amount converted to heat**. * Maximum efficiency occurs at moderate velocity - At no velocity heat is generated without movement - At high velocity energy is required to overcome friction	*Efficiency= W/E^{total}*	With **muscle** this is less than 20-25% - *Half the energy in food is lost during the formation of ATP* - *Only 45% of the energy in ATP can be converted into work*
Isometric contraction	**Isometric contraction** 1. Most often used for measuring functional characteristics of different muscle types 2.This because purely force generated is measured 3. During contraction the elastic components of the system are stretched - *Tendons* - *Tendon attachments* - *Hinged arms of cross bridges* 4. Muscle has to shorten an extra 3-5% to make up for this		**Duration of Isometric Twitches** 1. Fibre size varies greatly -range 10-80 µm 2. Energetics vary from one muscle to another 3. Illustration shows the characteristic duration of contraction of 3 very different muscles - Ocular muscle required to move very rapidly - Gastrocnemius required to contract moderately rapidly to walk and run - Soleus contracts slowly against gravity for body support

	Eccentric contraction	Isometric	Concentric contraction
Definition	is the motion of an active muscle while it lengthens under load .	muscle under load but does not lengthen or shorten	are used to generate motion. Shortening contractions
Force	High	Medium	Low
Muscle length	Lengthening	No change	Shortening
Risk of muscle injury	High		Low



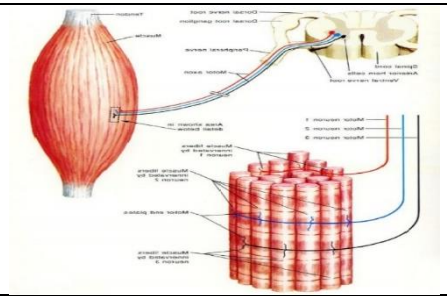
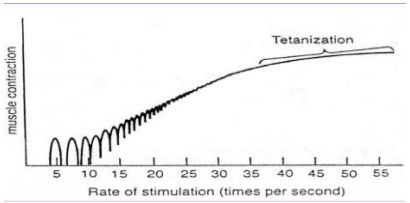
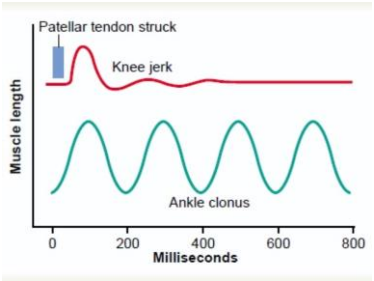


Muscle fibre types: https://www.youtube.com/watch?v=EH_Eem-VBZg

	Type I (S. S. R. Mito, Aero, weak, FR)	Type II A (F. L. P. FR, aero & Anae)	Type II X (F. L. W. Anae. Fatig)
Other name	Red, slow twitch, Slow oxidative (SO)	**fast twitch**, fast oxidative glycolytic (**FOG**)	**Fast twitch**, Fast glycolytic (**FG**)
Structural	* **Small** muscle fibre diameter, **Smaller** nerves, **fewer** muscle spindle * **High capillary** density→ large amount of **myoglobin** (red) * Large number of mitochondria * low in glycolytic enzymes, high in oxidative enzymes	* larger fibre diameter * Red fibres	* Largest diameter fibre; More muscle spindles * Less extensive blood supply (White fibers) * Rich in **glycolytic enzymes** (*for rapid energy release*) * Fewer mitochondria. * Extensive sarcoplasmic reticulum for rapid release of Ca2+
Metabolic - speed - fatigue - power - storage	* Aerobic cellular respiration (*Krebs's; oxidative phosphorylation*). * **Slow** contractive speed (↓ *myosin ATPase* → ↓*hydrolysis*) * **Fatigue resistant** (more energy efficient) * **Not very strong** (low power) * Triglyceride	Intermediate (aerobic & anaerobic) Fast Intermediate	* Anaerobic (glycolysis) * Fastest *(high glycolytic enzymes)* * Most fatigable (inefficient energy use) * **Strong** (*high power output over a short period of time*). * Glycogen, creatine phosphate
Function	* Run marathons (*endurance sports*) * Antigravity muscle (posture muscles)		* Sprinting or weightlifting: *quick, powerful movement*
Motor unit	S (slow) Slim	FR (fast fatigue resistant)	FF (*Fast fatigable*) Bulky muscle

* Hennemari's size principle: as force production requirements increase, motor units are recruited in order: Type I, Type II A, and Type II X.
* **speed** of contraction correlates with extent of development of **sarcoplasmic reticulum**
* **Tolerance to fatigue** and **oxidative capacity** correlates with **mitochondrial content**.
* A muscle fibril may express simultaneously more than one type of myosin heavy chain.

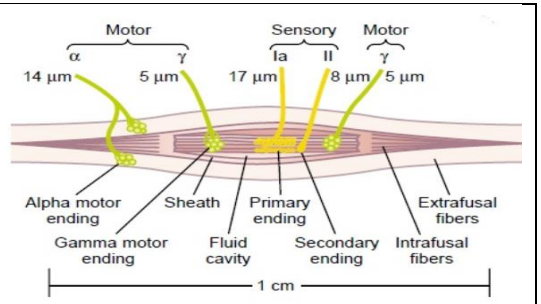
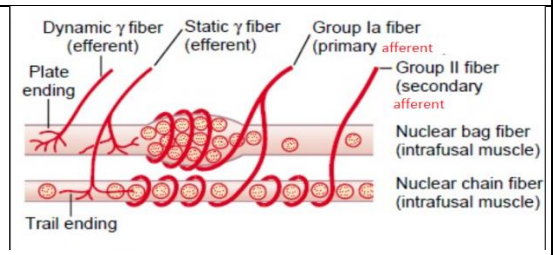
Motor units	**One axon + all the fibres** - **neuronal cell bodies** lie in the anterior horn - **nerve fibres** enter the muscle at the motor end plate zone. - The motor axon branches and splits many times - Each muscle fibre is innervated by only one motor axon. -all muscle fibres in the **same motor unit** have the same contractile and metabolic properties.	**Power** vs **control** * **Strength of contraction:** dependent on the number of fibres activated by 1 axon (*e.g. in large powerful muscles, a motor unit may be up to 2,000 fibres in size*) * **Fine control**: (*e.g. muscles requiring fine control may have <10 fibres*). * Small motor neurons: activate *small motor unites*, initiate *movements* **Diameter** vs **length** of a muscle fibre	

	- the number of muscle fibres within a motor unit is highly variable. * Muscle fibres next to each other are not usually innervated by the same parent motor neuron. ** Initially each developing muscle fibre is multiply innervated by several axons.* ** Later only one axons remains the synaptic connection with the fibre*	* **Diameter** determines its strength (*altered fibre diameter in mature muscle → level of muscle use has changed*). * **Fibre length** influence fibre contraction velocity, distance over which the fibre can shorten. **All-or non-phenomenon** * a single contraction of an individual fibre is an all-or-non * Activity of a **motor neuron** → activation of the whole MU * Contraction of a **whole muscle** is dependent on the number of MU activated, and the size of those motor MU.	
Summation	* The adding together of individual twitch contractions to increase the intensity of overall contraction. 	**Multiple fibre summation** (*increases the no. of motor unites firing*) 1. Weak nerve signals stimulate *small* motor units first 2. Larger units are excited as the signal becomes stronger 3. These can be up to *50 x stronger* than the smallest units 4. This allows the **gradation of muscle force** in very small steps 5. Small units are driven by smaller nerve fibres and smaller neurons in the cord are more excitable and fire first 6. Also different motor units are driven *asynchronously* by the cord .	**Frequency Summation** (increase the frequency of contraction) 1. Low frequency of stimulation produces individual twitches 2. As frequency increases each new contraction occurs a little before the previous one has finished 3. After a critical level they fuse together to form one smooth contraction- *Tetanisation* 4. When contraction reaches its maximum, there is enough calcium in the sarcoplasm to maintain this 5. Maximum force is *3-4 kg per square centimetre* 6. Strength shows a staircase phenomenon over 10-50 twitches
Muscle tone and fatigue	1. Resting muscle tone is a function of **mainly spinal cord intrinsic activity** and **feedback from the muscle spindles** 2. Prolonged contraction leads to fatigue 3. **Fatigue** rises in direct proportion to the depletion of muscle glycogen levels 4. Transmission at the NMJ may also drop off.	Muscle tone is determined by **reflex firing** of motor units on stretching The peripheral receptor for this **monosynaptic reflex**: 1) muscle spindles, 2) Golgi tendon organs The sensitivity of these peripheral receptors is controlled by the gamma motor neuron (→intrafusal fibre contraction) The activity of the gamma efferent fusimotor fibres is controlled by **suprasegmental influences**	
Clonus	* Clonus is **involuntary** and **rhythmic muscle contractions** (*oscillation（震荡）* * Stretch reflex is highly sensitized by *facilitatory impulses)* * Clonus is a sign of certain neurological conditions, particularly associated with UMN lesion. * **examples where** the cord reflexes are highly facilitated: - clonus may be found at the ankle, patella, triceps surae, wrist, jaw, biceps - In *decerebrate animals* *- Cerebral palsy, stroke, multiple sclerosis, hepatic encephalopathy, tonic-clonic seizure, pre-/eclampsia* - in patients with *upper motor neurons lesions*	**Mechanism** 1) hyperactive stretch reflexes 2) central oscillator 3) clonus and spasticity	
Muscle spasm	Reflex muscle spasm often results from **noxious stimulation**	* Muscle spasm following fracture * Abdominal muscle spasm in peritonitis * Psoas muscle spasms from appendicitis * Possibly cramps	
Cramps	-It is a very **painful active contraction** of a muscle in a **spasmodic fashion**. -It begins when the susceptible muscle is in a *shortened position*. -It can usually be interrupted by stretch of the muscle by its antagonists or by external forces - The muscle shows altered excitability and fasciculations for many minutes after resolution of the cramp. * The electrical activity responsible for cramps is *from the nerve*, affecting the motor units (**Not** that individual muscle fibre)	**Causes (Not well understood)** 1. After fatigue, prolonged muscle activity 2. Drug use/abuse 3. night cramps in the elderly (when M is shortened) 4. renal failure 5. Fluid and electrolyte disturbances. 7. Peripheral vascular disease.	e.g. Gastrocnemius, habstrings, abdominal muscles etc.

Delayed muscle soreness	Muscular pain that generally occurs 24-72hours after **intense, prolonged** exercise. * Associated primary with **eccentric exercise** * varies with both the intensity and duration of the exercise * *Different from other pathologies due to muscle fatigues, cramps etc*. * structural damage is repairable.	**Mechanism: connective tissue breakdown** 1) Result of increase in *intramuscular pressure*. 2) **intramuscular damage** to the structural elements of the muscle (confirmed by muscle biopsies and animal models) - **Sarcolemma** damaged accompanied by an influx of Ca2+. - Z-band, A-band disruption, myofibril misalignment - Primarily occur in ***fast-twitch glycolytic*** (type IIB) fibres. -**serology studies:** increased levels of intramuscular enzymes in the serum after exercise (Creatinine kinase, LDH) 3) increased levels of urinary hydroxyproline excretion	**Clinical sign** - Muscle pain several hours- 3 days (*peak at 1 day*)post exercise - reduced activity, strength loss(*up to a 50% loss*) *up to 10d* -firm and swollen muscle

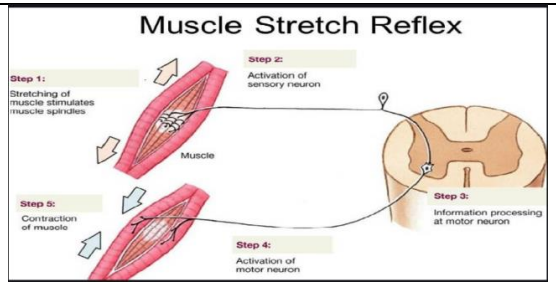
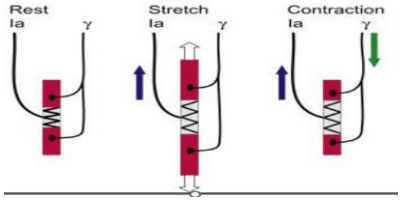
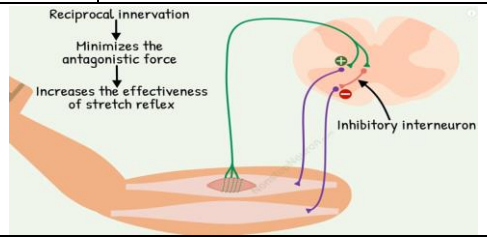
Muscle spindle

https://www.youtube.com/watch?v=zSAdsriRSnE Muscle spindle & stretch reflex: Knee jerk reflex (Nonstop Neuro)
https://www.youtube.com/watch?v=IXV4fRC6nPc Ninja Nerd https://www.youtube.com/watch?v=wwQKSFKyD3U https://www.youtube.com/watch?v=obM1uHucAbM Muscle spindles: basic mechanism

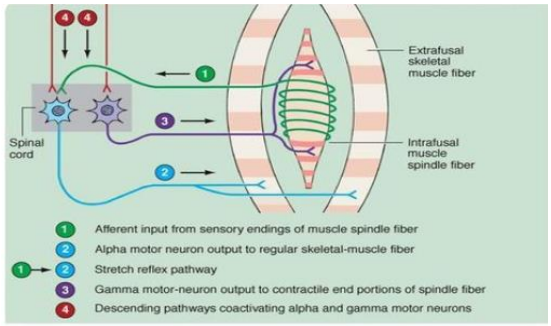
Muscle spindles (MS)	* MS are *stretch-sensitive* **mechanoreceptors** located within skeletal muscle (*through the belly of the muscle*) and monitor the length of the muscle. - *Detect length changes: as little as 25µm. (tonic, slow adapting)* - *Detect velocity of length changes (speed, phasic, rapid adapting)* * Structural Features - Striated, intrafusal muscle fibres (*miniature of skeletal muscle*) - each has a *connective tissue capsule (reduces influence of external factors)* that is built around 3-12 intrafusal fibres - Lies In parallel to the force-producing **extrafusal fibres** - can exceed 10mm length (3-10mm long). - Pointed at their ends, - Attached to the glycocalyx of the surrounding extrafusal fibres - Fewer in number than motor units (*but can still be several hundred in a muscle*).	**Intrafusal fibres** ***Central portion:** - few or no actin or myosin filament (non-contractile) - contains nuclear. - Acts as sensory receptor - Stretch excites central portion fibres a) Lengthening of the **whole muscle** b) Contraction of the **end portions** of the intrafusal fibres (*does not require the muscle length to change*) * **End portion:** - contractile (motor) - activated by small γ efferent fibres(*α efferent fibres innervate extrafusal muscle*) **Extrafusal fibres** - Connect with tendons - Generate movements	 * All **motor neuron**: ***alpha, beta*** *(extrafusal fibre),* ***gamma*** *(intrafusal fibre)* receive input from supraspinal tracts.
MS **sensory endings**	Primary ending (*annulospiral ending*) - In the **centre** of the receptor area a **large sensory fibre** encircles the central portion of each intrafusal fibre - Type Ia fibre of **17µm** diameter, speed 70-120 m/sec (**rapid**) - innervate **both fibre types** (nuclear bag & nuclear chain)	**Secondary ending** (*flower spray ending*) – usually 1-2 but sometimes none - Located to one side of the primary ending (*or both sides*) - Type II fibres of **8 µm** diameter, speed 50m/sec. - Only innervate Chain fibres	
Nuclear bag & Chain fibres	**Nuclear Bag fibres** – Dynamic (bag 1 fibres), static (bag 2 fibres) *- 1-3 per spindle (typically 2- one of each type)* *- Large number of nuclei in expanded central bag* *- sense the onset of the stretch*	**Nuclear Chain fibres** *- 3-9 per spindle, ½ diameter, length of the NBF* *- Nuclei arranged in a chain* *- sense the sustained stretch.*	
Dynamic, static response	**Dynamic response** Response to the **Rate of change** of the receptor length. 1) **Rapid stretch**→↑ MS Length →1° ending (Ia fibre) is stimulated. 2) if MS length shortens→ 1° ending stimulation ↓ 3) When length is not changing, static response starts. * Only primary endings transmit the dynamic response * Nuclear Bag dynamic fibres only have primary ending.	Static response Responsible for **the static response** (*signals about the actual length of the muscle*) * **Continuous static signals/ slow stretch** transmitted by both primary and secondary endings. * The nuclear chain fibres and static nuclear bag fibres are innervated by both 1° and 2° endings. e.g. *posture, maintain muscle tone*.	

Nerve / Muscle	**Ia fibre** 17µm D. 70-120m/s Annulospiral *Dynamic response*	**II fibre** 8µm D. 50m/s Flower spray Static resp.	γ-Static trial ending	γ-Dynamic Plate ending
Nuclear bag - Dynamic	+			+
- Static	+	+	+	
Nuclear chain	+	+	+	

Dynamic response	Rapid lengthening→ 2 reflexes	1) Stretch reflex (*e.g. deep tendon reflex*): - dynamic, static, negative	2) Reciprocal inhibition: *inhibits the antagonist muscle*.

Muscle stretch reflex - afferent -efferent e.g. knee jerk * prevent injury	The monosynaptic pathway Sudden increase of muscle length (*muscle stretched*) → the sensory signal (transmitted by Type *Ia afferent* fibre) enters the *dorsal horn* →One branch passes **directly** to the *anterior horn* motor neurons that send fibres back to the same muscle by γ motor fibre(*This allows a reflex signal to be sent back to the muscle with the shortest possible delay*) →immediate reflex contraction of the muscle (*this opposes sudden changes in muscle length → prevent damage*) Some *Type II* fibres also relay monosynaptically Most *Type II* and many *Ia* collaterals terminate on multiple interneurons in the ***gray matter***		
Static stretch reflex	- Occurs Immediately after the dynamic stretch reflex - Comes from the continuous static receptor signals transmitted by both 1° and 2° endings	1) This *maintains muscle contraction* as long as the muscle continues to be excessively stretched. 2) The overall muscle contraction opposes the forces responsible for the muscle stretch	
Negative stretch reflex	1. When a muscle is suddenly shortened, impulses from Type I and II fibres are inhibited 2. This results in reflex inhibition of muscle contraction 3. The system therefore is important in maintaining overall muscle length		
Reciprocal inhibition	1. The *alpha motor neuron* synapses with the originally stretched skeletal muscle 2. The inhibitory interneuron innervates the antagonistic muscle and causes inhibition 3. This reflex *relaxation* of the *antagonist muscle* in response to contraction of the agonist muscle is *called reciprocal inhibition.*		

Motor neuron

Motor control: **γ, α, β**	**Gamma:** (30% of all motor fibres) * to intrafusal fibres * up to a dozen per muscle spindle * each neuron innervates several muscle spindles * Impulses transmitted through Aγ fibres * average diameter is 5μ (12-30m/sec) Gamma-D (dynamic): * To Nuclear bag; * Plate ending Gamma-S (static): * Nuclear chain; * Trail ending	**Alpha**: * To extrafusal fibres. Muscle contraction * Range 10-20 μ in diameter 960-120 m/sec) * They innervate motor units of 3- 1000 fibres at a time in humans * The impulses cause depolarization of the *sarcolemma* and initiate muscle contraction * Summation depends on the firing rate in the axon	**Beta:** * To extrafusal and intrafusal fibres - similarly to Gamma motor neurons on the intrafusal fibres - stimulate extrafusal fibres directly. * 1-2 per muscle spindle * least investigated and often treated as sub-group of alpha motor neurons
α,γ coactivation	* **Extrafusal** fibres are innervated by **α** motor neuron * **Intrafusal** fibres are innervated by **γ** motor neuron. a) Extrafusal fibres contract (**α fibre fire**) b) intrafusal fibres slack→ *afferent input from **Ia fibre** to spinal cord.* c) Intrafusal fibre contract (**γ fibre fire**) * When motor impulses are transmitted from higher centres, both alpha, and gamma fibres are stimulated simultaneously *(bulboreticular facilitatory system* in the brain stem) → both intra, and extrafusal fibres contract at the same time. → *this keeps the length of the receptor portion of the spindle constant*.		Servo-assistance * muscle contacts against load (isometric): Extrafusal fibres contract less than intrafusal fibre → stretching of the intrafusal fibres provides sensory input→ **extrafusal fibres** to contract even more **Advantages** 1) less brain input contracting against load 2) The length of contraction becomes less load sensitive 3) It compensates for fatigue by eliciting additional muscle contraction when spindles are stretched.

Muscle growth and adaptation

Development
- Arises from mesodermal somite tissue
- **Progenitor**: myoblasts
- **myotubes**: are fusiform cells (*multinucleated cells*)
- Contractile elements: *form at the time of myotube formation*.
-Further differentiation:

Mutability of muscle fibre types
* Fiber type is mutable in adults
* it is dependent on the nerve innervating it.
* innervating it.
*

Growth: in **volume** and **length**
- **Length**: *sarcomere length remains constant*, additional sarcomeres are added in series near the region of the myotendinous junction.
- **Immobilized under stretch**: increases in length (Initially the myofibrils and sarcomeres are lengthened; after a few weeks, additional sarcomeres are added). (*the length-tension curve shifts to produce peak tension at a greater length, to produce less passive force when stretched*)

Aging
1) muscle atrophies
2) muscle function gradually declines
   - decreased force production,
   - contraction velocity,
   - impaired relaxation
3) Sarcopenia: degenerative loss of skeletal muscle.
   * found in 25% of people age 65 to 79 years. 40% of older than 80 years.

Immobilization→ Atrophy quickly
1) reduced **protein synthesis** and
2) reduced hormonal contributions.
→↓ **muscle strength**, ↓**cross-section area**, ↑**fatigability** (*diminished energy stores and metabolic efficiency*)
* more pronounced if NOT stretched.
* If stretched in immobilization
   → *growth in length compensating the loss of strength*.
   →*produces less tension from stretch and maintains its extensibility*

Causes of atrophy:
- decreased muscle stimulation
- systemic illness
- immobilization or bed rest

Mechanism of disuse atrophy:
1) decrease in muscle protein synthesis
2) increase in muscle protein breakdown
3) Denervation

Concurrent training (combine both)
- negative impacts on resistance training but does not affect endurance.
-early phase: strength-endurance
-late phase: strength training.

Training
Adaptations to improve muscle performance.
1) **Motor leaning**:
   - improve the accuracy and performance of motor skills
   →nervous system adaptation: timing and rate of contractions.

2) **Endurance training:** e.g. marathon
   * Aerobic training focuses on
   - Train slow-twitch (type I) fibres; *change type IIX to IIA, or type II to I*
   - ↑mitochondrial number and size,
   - Increases capillary density
   - improve efficiency of oxidative ATP
   - improve cardiac output
   - **AMP kinase pathway**
3) **strength training**: e.g.weight lifting, sprinter.
   *High-force, low-repetition Anaerobic *training*,
   * *training the fast-twitch (type II) fibre*.
   *↑cross-sectional area of the muscle (*hypertrohpy*)(*not hyperplasia inc number or cell*)
   * improved neural activation, motor unit recruitment.
   * **Mammalian target of rapamycin(mTOR) pathway**

Muscle injury
*Causes: ischaemia due to crush/ laceration
Types of skeletal muscle injures
1) acute
2) overuse: chronic or exercise-induced injuries

Types of muscle injury
1) **laceration**: when the *muscle is cut*
2) **contusion**: when the *muscle is compressed*.
3) **degenerative disease** (e.g. Muscular Dystrophies)
4) **Strain**: when muscle fibres cannot withstand *excessive tensile forces*; Generally associated with eccentric muscle action.

Muscle strains
Grade I (mild): small number of fibres tear. DMS.
Grade II (moderate)
Grade III (severe): complete tear/rupture of the muscle

Muscle tendon junction

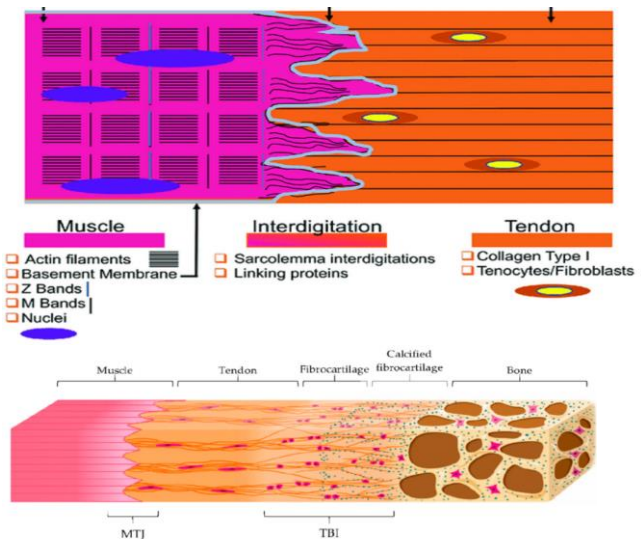
MTJ

* **MTJ** is the interface between muscle and tendon (***Myotendinous unit***: *bone, enthesis, tendon, myotendinous junction and muscle*)
* Is an integrated **mechanical unit** (*transmit force between muscle and tendon*)
* MTJ consists of **subsarcolemmal, transmembrane**, and **extracellular protein complexes**.

Tendinous portion:
- Made up of multidirectional collagen fibres
- The force is longitudinal in tendon, however close to the muscle, the force can be in many directions.
* On the **extracellular side of the MTJ**, the **basement membrane** contains *fibronectin, laminin, and type IV collagen* (have an affinity for the tendon collagen)

Muscle portion
* Stress changed from tensile to shear as folded membranes parallel with axes and fibres of muscles and tendons

*MTJ is a **dynamic structure** (*adapt to mechanical stimuli*).
* **Aging**: Interdigitations shorten
* **Injury**: MTJ failure occurs in the body of the muscle cells just proximal to the MTJ.

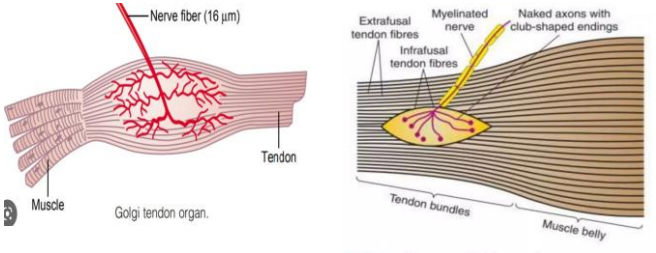
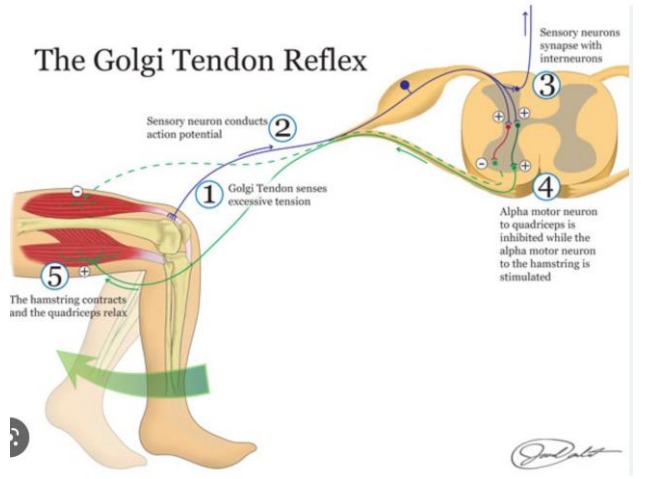
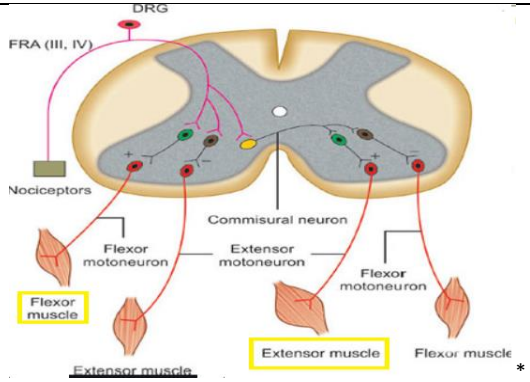


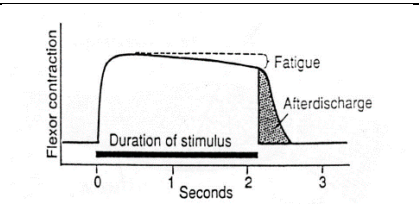
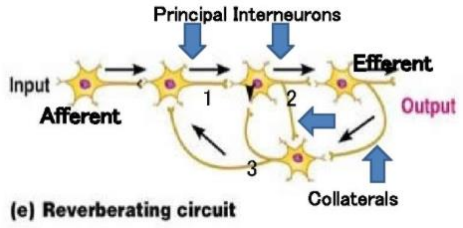
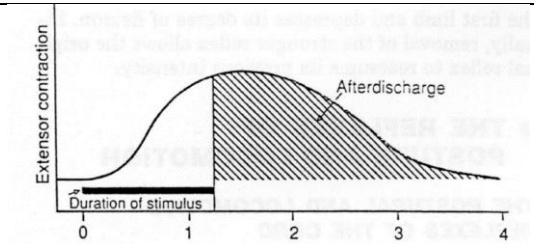
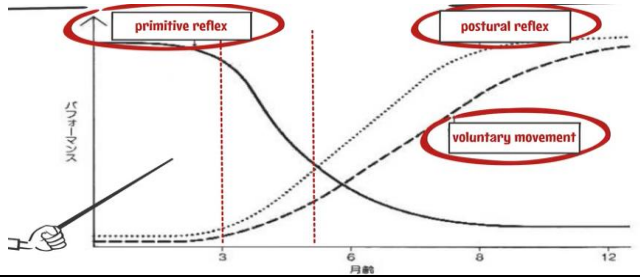
Interdigitation:
* Sarcolemma folded into **finger-like extensions** and invaginations (increases interface area 10-20x →*decreases stress*)

* Actin microfilaments extend from last z-line into the **plasma membrane** to merge with the **tendon tissue**.

Protein complexes
- *Actin-binding proteins* bundle actin filaments together
- Intracellular proteins (vinculin, talin) link the actin to the sarcolemma.
- *Transmembrane protein complexes*: connect the cytoskeletal components to the basement membrane components
- Proteins link the basement membrane to the surrounding collagen-rich matrix

MTJ strength
* Functionally the weakest part of MTU.
* Strains and tears happen more frequently at this level (in the midsubstance of either the muscle or the tendon)
* The muscle fibres just next to the MTJ is stiffer.

Golgi Tendon organs (GTO)	* **This is a Muscle stretch sensory receptors** (Detect tension) * It lies in the **myotendinous junction** (more commonly at the insertion rather than the origin of the muscle) (*connected to **extrafusal** muscle fibres at one end and merging into the tendon proper at the other end*) * 10-15 muscle fibres (*each belonging to a different motor unit*) are connected in series with one GTO * Fibres from multiple motor units → each GTO, * motor unit has fibres attaching to multiple GTOs - The GTO have *neither muscle fibres* nor and *efferent innervation*		**Function of GTO** Equalise the contractile force of different fibres within a muscle - **fibres** exerting **excess tension** are inhibited **insufficient**…….enhanced - This spread muscle load and helps prevent local muscle damage **Nerve supply:** Ib type sensory nerve fibres
Golgi tendon reflex	1. The GTO provides the sensory component of the Golgi Tendon reflex or inverse myotatic reflex 2. It can be activated by **active contraction** or by **very strong stretch** 3. Displays both dynamic and static responses - **Dynamic**: respond to sudden increase muscle tension. - **Static**: a lower level of **steady state firing** that is proportional to the new tension. 1) signals transmitted through a single large myelinated rapidly conducting Type Ib sensory fibre per GTO. (This branches, terminates as spiral endings around the collagen strands) Average 16µm diameter (slightly smaller than *spindle Ia fibres*) 2) Sensory neurons synapse with ***interneurons*** in the spinal cord - **inhibitory interneuron (***via glycine: IPSP's***)**: synapse with α MN back to the same Muscle →*inhibit muscle contraction* Autogenic Inhibition (*Significance: avoid overstretching causing damage*) - **excitatory association interneuron (***via Glytamate: EPSP's***)**: synapse with α MN to antagonist muscle → *stimulate muscle contraction* Reciprocal Activation (*Significance: relaxed muscle fibres can be stretched, improving flexibility*)		**Example of** *Dynamic reflex: (inhibitory)*: 1) Heavy weightlifting: The lengthening response prevents excessive tension causing injury because the muscle "gives out" 2) Resistance training: Acts to increase the maximum weight lifted at least partly by inhibiting the GTO. **Example of** *Static reflex* - Relaxed muscle fibres can be stretched→ improving flexibility. - The cerebellar inputs allow for production of only the necessary amount of tension to complete the movements→ allowing smooth beginnings and endings to a movement.
Withdrawal reflexes (*pain reflex*)	- It is an **automatic response** enacted to withdraw a limb from a *painful stimulus*. - Pain stimulus → flexor reflex → limb withdrawal. - It is a **polysynaptic reflex** (*it uses neurons called interneurons to pass signals from sensory to motor neurons creating multiple synaptic connections*). - **Timing and duration** Onset: milliseconds after stimulation Fatigue: in the next few seconds, the reflex begins to fatigue duration: does not stop immediately after the stimulus is removed due to afterdischarge circuits (*the duration of the after discharge depends on the intensity of the original stimulus*)	**Physiological relevance** 1) allows an injured or irritated part of the body to be withdrawn from the nociceptive source 2) because of afterdischarge, the reflex holds the irritated part away for as long as 1-2 seconds . 3) During this period the rest of the CNS can be organized to move the whole body away as appropriate. (*in decerebrate animals, almost any peripheral stimulation →flexor reflex*) https://www.youtube.com/watch?v=5c8maFAhqIc Pain physiology Armando * 3 basic types of circuits: - diverging circuits: *spread the reflex to the appropriate muscles for withdrawal*. - Reciprocal inhibition circuit: *inhibit the muscles antagonistic to withdrawal*. -Other circuits: *causing a prolonged repetitive afterdischarge following removal of the stimulus*.	 * Painful stimulus to the hand * Signal transmitted to spinal cord, synapse within an interneuron.

	 **Figure 54–9.** Myogram of the flexor reflex, showing rapid onset of the reflex, an interval of fatigue, and finally afterdischarge after the stimulus is over.		* Efferent pathways - flexor (extensor) muscle in the same limb: activated (inhibited) - Flexor (extensor) muscle on opposite side is inhibited (activated)
Reciprocal inhibition	Excitation of one group of muscles is usually accompanied by inhibition of the antagonists	Reciprocal innervation circuits:	
Crossed extension	a) 0.2 to 0.5 seconds after a noxious stimulus causes a flexor reflex in one limb, the opposite limb starts to **extend** b) Sensory nerve input ***crosses to the opposite side*** of the cord via **interneurons** (*The short delay is due to the number of interneurons involved in passing on the signal*) c) after the painful stimulus is removed the crossed extensor reflex continues even longer than the flexor relaxes	This is probably because of enhanced reverberatory circuits in the interneurons	 **Figure 54–10.** Myogram of a crossed extensor reflex, showing slow onset but prolonged afterdischarge.
Postural reflex: 1) The positive supportive reaction 2) Cord righting reflexes 3) Stepping and walking			
Positive supportive reaction	Pressure on the footpad of a decerebrate animal causes the limb to extend against the pressure	Mechanism: Involvement of complex interneuronal circuit	**Significance:** - To allow an animal to stand following spinal cord transection - prevent an animal from falling to one side .
Cord righting reflexes	Spinal animals lain on their side make uncoordinated attempts to right themselves	To help align head and body: e.g. Optical, labyrinthine, neck, body righting reflex	**Optical righting reflex**: Infant tries to keep the head vertical and maintain an upright posture when visual information is available
Stepping and walking			
Higher control	Higher centres receive information at the same time as does the cord.	**Spinocerebellar tracts** carry information from both spindles and GTO to **a)** cerebellum b) **Brainstem c) motor areas of the cerebral cortex**	

Difference between muscle spindle and Golgi tendon organ.

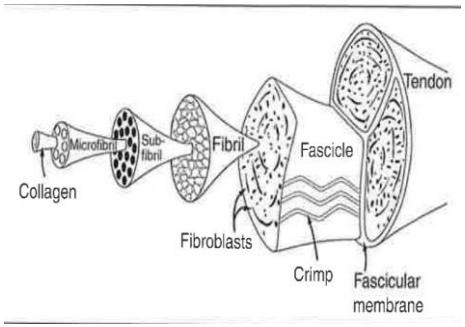
	Definition	Contraction	Sense	Nerve fibre	Protective function	Composed of
Muscle spindle	A small spindle-shaped sensory organ that senses the changes in length of the muscle and the rate of lengthening	Muscle spindles contract	Lengthening of the muscle and the rate of lengthening the muscle	In: Ia & II Out: alpha	Stretch reflex and reciprocal inhibition	Several differentiated muscle fibres that are enclosed in a spindle-shaped connective tissue sac

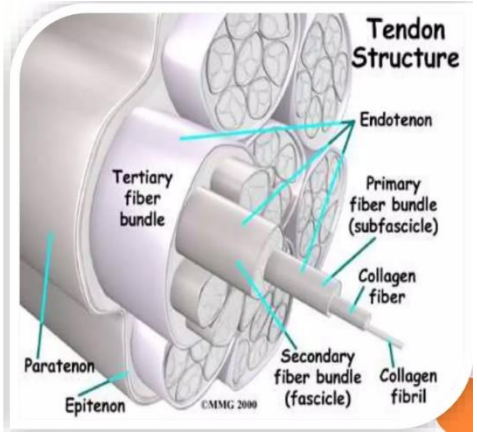
Golgi tendon organ	Is a sensory organ in the muscle tendon unit that senses the changes in the muscle tension	Golgi tendon organs do NOT contract	Tension in the tendon	In: Ib Out: alpha	Autogenic inhibition	Braided strands of collagen which are encapsulated.

Tendon

Basic Anatomy

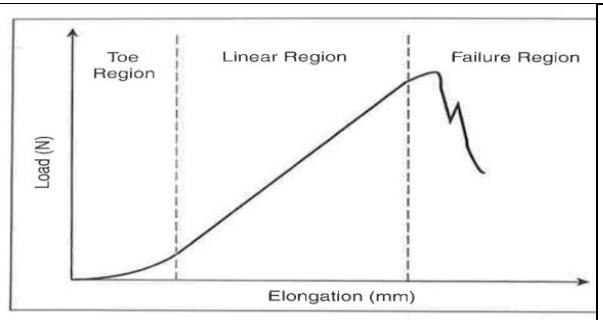
		Paratenon (CT surrounding each tendon, allows smooth gliding against adjacent structure.)
Level 1	Tendon 100-500µm	Epitenon: surrounding bundles of fascicle /whole tendon.
Level 2	Fascicle 20-200 µm	Endotenon: loose CT, surrounding bundles of fibril. - carrying the blood vessels, lymphatic and nerves
Level 3	Fibril 50-200nm Crimp	
Level 4	Subfibril	
Level 5	Microfibril	
Level 6	Collagen molecule	

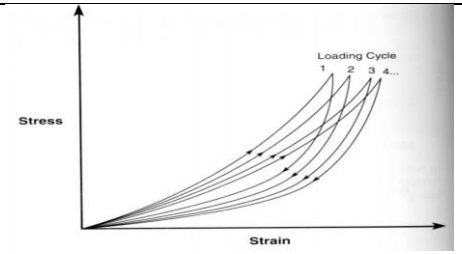




Tendon	A dense regular **connective** tissues, composite material consisting of 1) **Collagen fibrils** (primarily **type I : 95%**):70-80% dry weight; *parallel, viscoelastic, solid and fluid like properties* *- Glycin 35%* *- Proline 15%* *- Hydroxyproline 15% (is unique to collagen*) 2) **proteoglycans** & **Glycoproteins** (1-5% dry weight): *Decorin is the most common proteoglycan in tendon* *Regulate collagen fibrillogenesis and control fibril diameter throughout development and homeostasis.* 3) **Cells** : *Tenocyte and tenoblasts(90-95%)*(main regulator of tendon homeostasis) *mast cells, epithelial cells, chondrocytes,* 4) **water** 55-70% by weight	* Tendons have a **high tensile strength**. * Each muscle has ***two tendons*** to attach each end to bone * Cells are *spindle shaped* and arranged in parallel rows, * In cross section they are **dark star shaped** structures. * They have a **central round nucleus** *Cytoplastic processes extend between collagen bundles **Homeostasis** Tenocyte, tenoblast: main regulator of tendon homeostasis Elastic fibres - make up **1-10%** of tendon dry weight and they are highly elastic, fatigue resistant and able to store energy.	**Function of a tendon** 1) contact bone to muscle 2) support joint 3) store kinetic energy (fibroelastic property) *High tensile strength due to hierarchial structure and local cell population adapting to changes in loading condition*. 4) **Mechanosensitive**: *respond to mechanical loading, modulate ECM by forming and degrading matrix proteins* (**Mechanotransduction**). - *Normal physiological loads necessary for tendon development and maintenance*. - *Abnormal loading inhibits capacity of cell population to maintain homeostasis → injury*. - Reestablishment of mechanotransduction may be key to improving repair following injury
Tendon sheaths and paratenon	1. Where tendons wrap round bony surfaces large compressive forces are produced 2. They tend to assume a local **cartilage-like appearance** 3. Sliding is assisted by synovial fluid secreted from the parietal and visceral (**epitenon**) synovial membrane	**Tendon sheath** 1) Tendons that bend with joint motion are surrounded by a *synovial sheath* (e.g. wrist, ankle); 2) Tendons that do not bend are enclosed in a loose **paratenon**. - many vessels enter at multiple sites - There are watershed area where relative **avascularity** may be a factor in **tendinopathy**.	
Blood supply	1. Blood supply from vessels in the *perimysium*, *periosteal attachment*, *and surrounding tissues* via vessels in the *paratenon* or *mesotenon* 2. Tendons covered by a tendon sheath are relatively **avascular** 3. The **mesotenons** are reduced to *vinicula* which are relatively avascular 4. Tendons reduced vascularity around bony pulleys. 4. Some of the nutrition may therefore come via *diffusion* from the synovia fluid	**Vascularity** Two sources 1) **Intrinsic**: MTJ and OTJ. 2) **Extrinsic**: through paratenon or the synovial sheath.	**Nutrition from** - vessels in **perimysium** - Vessels in **periosteal attachment** - vessels in **paratenon** or mesotenon - Diffusion from synovial fluids.

<table>
<tr>
<td>Stress-strain relationship</td>
<td>1) Initial creep as crimp is taken up
2) Followed by a linear elongation (the slope is the elastic modules due to the tendon's viscoelastic properties before the tendon fails).

* Flexor tendons have greater tensile strength than extensor tendons (2x) No difference at birth
* Exercise increases the tensile strength of tendons,
* immobilisation reduces the tensile strength.
* Tensile overload→ degenerative tendinopathy→ rupture</td>
<td> 
</td>
<td>Tendon injury:
Direct trauma (laceration, contusion)
Tensile overload.

The weakest point: at
- myotendinous junction
- tendon insertion to bone (enthesis)</td>
</tr>
<tr>
<td>Hysteresis
(滞后作用)</td>
<td>With repeated loading and unloading, the stress-strain curve shifts to the right
- Because of viscoelasticity (tendons exhibits stress relaxation, creep, and hysteresis)
- At high strain rates, the onset of permanent stretch is delayed.</td>
<td> 
</td>
<td>Effect on Muscle efficiency
1. Because tendons elongate under repetitive and isometric loading this enhances muscle physiology

2. In an isometric contraction, the tendon gradually elongates
3. Because the muscle tendon unit length remains constant , the muscle is allowed to shorten
4. This increases the efficiency of the muscle contraction, increasing performance and resisting fatigue</td>
</tr>
<tr>
<td>Factors affecting mechanical properties</td>
<td>1. Exercise
1. Exercise training results in a positive increase in stiffness, weight and tensile strength
2. Crimp angle and crimp effect are positively influenced
3. It may also enhance collagen synthesis
4. Exercised tendons have a higher percentage of thick collagen fibrils
5. These contains a higher number of intrafibular covalent cross-links</td>
<td>2. Age
1. Before maturity the linear region is followed by a single yield region in which irreversible elongation and structural damage takes place
2. After maturity the single yield plateau is not as obvious, and there are 2 distinct yield regions
3. The ultimate stress and strain increase with maturation
4. The age-related decrease in the crimp angle decreases the toe region of the stress-strain curve</td>
<td>3. Trauma
a) Direct trauma is especially important in the hands and upper limbs
b) Healing is directly related to the inflammatory response which is related in turn related to vascularity
c) Most tendons can withstand tensile forces greater than can be exerted by the muscles or sustained by the bones .
→ This leads to avulsion fractures and MTJ ruptures</td>
</tr>
<tr>
<td>Tendon healing phases (overlapping)</td>
<td>Initial inflammatory phase (0-7 days)
- Fibrin clot to stabilise site
- Haemostasis
- Migration of neutrophils, macrophages, erythrocytes
- Subsequent neovascularization

https://www.youtube.com/watch?v=zSwwvit00mg physiology of tendon healing</td>
<td>Repair /proliferative phase (3-60days)
Extrinsic stage (up to 4wks):
- Type III collagen production by extrinsic tenocytes (disorganised)
- fibronectin lay down
- vascular network
Intrinsic stage (4wks-6wks)
- intrinsic tenocytes lay down type I collagen</td>
<td>Remodelling and maturation (from 6 weeks)
*Consolidation (6wk-10wks) repair changes from cellular to fibrous
*Maturation (10wks-1 year): increasing synthesis Type I collagen.
1) ECM remodelled and more organised through collagen turnover, realignment, cross-link formation
2) Cell density and vascularity decreases as tissue further repair.</td>
</tr>
<tr>
<td>Collagen and tendon healing stages</td>
<td>1 Synthesis begins as early as 3 days
2 Protein mucopolysaccharide density increases
4. Procollagen Hydroxyproline OH bonds bind with other amino acids ketoamide groups
5. Collagen molecules begin to polymerise into fibrils
6. These progressively accumulate more collagen molecules</td>
<td colspan="2">3days
-Inflammatory cells in the wound
-some fibroblasts

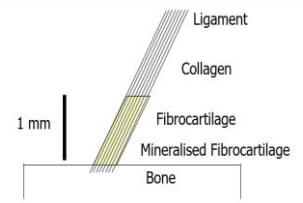
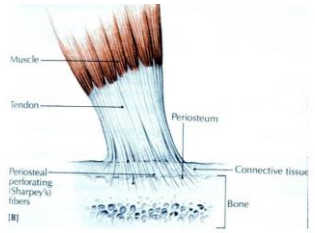
7 days
- increase in fibroblast invasion
- migrating from the paratenon

2 weeks
- tendon stumps fused by a fibrous bridge
- marked increase
Collagen production
Fibroblasts,
vessels
- fibres perpendicular to the wound</td>
<td>21 days
- more collagen in wound
-start of longitudinal fibre
-collagen near the tendon more organised</td>
<td>28days
- increase cellularity
- increased vascularity
-collagen fibres more longitudinally orientated.</td>
</tr>
<tr>
<td>Tendon homeostasis</td>
<td>* Tendon injury often due to excessive or insufficient mechanical loading→ this impairs the ability of the tendon cells the maintain normal tendon function.
- Tendon cells and tendon tissue are mechanosensitive (cells alter the extracellular matrix in response to local load changes)
- Natural tendon healing is insufficient</td>
<td colspan="2">Mechanisms of injury
Internal tensile overloading events (most tendons can withstand tensile forces greater than the muscle can exert or that the bones can sustain→ avulsion fractures, MTJ tears)

* acute: isolated overloading event</td>
<td colspan="2">Mechanisms of chronic injury
- e.g. patellar tendon, Achilles, CEO (ECRB)
- Causes:
1) repetitive motions; overuse leading to microtears.
2) Underuse (loss of homeostatic tension)→ apoptosis.
- Pathology:</td>
</tr>
</table>

	a) Improper collagen fibril diameter formation *b) collagen fibril distribution* *c) overall fibril misalignment*. - Current tendon repair rehab protocols focus on implementing early, well-controlled loading exercises to improve repair outcome. - Tissue engineers look	* **Chronic**: repetitive, excessive loading events * **acute indirect injuries:** often indicative of underlying chronic impairment * **direct trauma**: important in the hands and upper limbs	*1) changes to normal tenocyte morphology, apoptosis* *2) altered collagen fibril distribution profile* *3) Neovascularisation, angiogenesis (hyperaemia on uss)* *If microtears do not repair properly → excessive inflammation* *degeneration, overall weakened structure, risk of rupture*.
Tendinopathy	This is a painful condition of a tendon, exacerbated by activity Most common in the Achilles **Tendonitis**: acute inflammation and injury of a tendon **Tendinosis**: chronic with degenerative cellular changes. No inflammation. **Tenosynovitis**: inflammation of the sheath. Caused by inflammatory diseases, infection or injury. Most commonly in hand/wrist.	**Disrupted homeostasis** Hormonal: Premenopusal have decreased risk of tendinopathy. Postmenopause: equivalent risk HRT: improves tendon structure in active but not sedentary patient DM: Flexor Muscle, increase with ds duration. T2DM impair healing	**Physiological exercise→** ↑*proliferation, collagen production, tenocytic gene expression*. **Overuse/fatigue→** Matrix damage, tenocyte apoptosis **Smoking, obesity, high cholesterol→**promote degeneration
	Clinical presentation of tendinopathy - localised pain. Can be aggravated by dose-dependent tendon load -Negative images is powerful - increased amount of alignment fibrillar structure→ treat the donut - what causes the pain: nerves, cells, biomechanical environment, ion channel expression?	**Treatment** **Goal:** Treat pain, gain strength, improve tissue capacity, motor drive. **Load:** isotonic (concentric, eccentric) or isometric, eccentric **Medications** **Injectables**: PRP, CSI, blood patch, stem cells, prolo, high volume injections **Surgery**: e.g. tendon scraping, paratenonectomy **Braces**, orthoses **Needling**, acupuncture **Adjuncts** eg. ECSWT, laser.	**Loading interventions** 1) reduce pain, improve function 2) Improve extracellular matrix 3) Influence muscle and neural mechanisms 4) Clinical outcomes not dependent on structural changes. **Isometric exercise** *Reduces pain* *Reduces motor inhibition* *Neuroplasticity* *Increases strength*.

Ligaments

Definition and structure * Similar in composition and mechanical behaviour to tendon. * more complex load bearing structures - lower percentage of collagen - Higher percentage of ground substance - More variable collagen fibre directions	**3 main functions** 1) Mechanical stabilizing 2) Viscoelastic behaviour in helping provide joint homeostasis 3) Provide joint proprioception.	**Factors influence the properties of ligaments** 1) biochemistry 2) skeletal maturity 3) age 4) immobilization	**Injuries are classified as** - Partial (grade 1 & 2) - Complex (grade 3) **Healing of ligaments (like tendon)** - Initial inflammatory - proliferative phase - remodelling and maturation
Enthesis The attachment point of the ligament to bone is known as enthesis Tendon → Fibrocartilage → mineralised FC. * This arrangement helps to strengthen the tendon at the critical tendon-bone interface.	 Direct insertion: 4 zones *Zone 1: end of the tendon itself* *Zone II: thin layer of fibre cartilage* *Zone III: mineralized cartilage* *Zone IV: bone*	 Indirect insertion: **Sharpey's fibres**	**Injury** Failure in this region commonly in the soft tissues of the bone adjacent to the junction (avulsion #).

Nerve

Components of the nerve system * **Central NS**: *brain & Spinal cord* * **Peripheral NS**: *cranial(12P), spinal(31P), peripheral nerve* * **Autonomic NS**: *sympathetic, parasympathetic, enteric systems.* **Cells** **Neurons**: sending and receiving signals (*chemically-mediated electrical signals*) **Glial cells**: all nerve cells are surrounded by glial tissue (*support neurons*)	1 **Oligodendrocytes** (CNS) 1) one cell myelinate several different axons 2) average 15 cells--oligodendrocyte 2 **Schwann cells** (PNS) * Arise from the ***neuroectoderm*** * Responsible for **myelination** of PNS - 1 cell myelinates a region of 1 axon - 1 axon →up to 500 Schwann cells * Line up at intervals of 0.1 to 1mm (known as the nodes of Ravnier) * **Multilaminar structure** (Double cell membrane *wrapped round in concentric spirals)* * unmyelinated cells normally have at least one layer of myelin.	**Nodes of Ranvier**: - The gaps between each *Schwann cells* along axon - axon diameter is reduced slightly - Concentration of Na+ channels is high → Facilitates **Saltatory conduction** (AP jumps electrically from one node to the next) **Myelin sheet:** * Formed by **Oligodendrocytes** and **Schwann cells** * Membranous process wrapped concentrically around the anon in a tight spiral (*by 1 schwann cell*) * 70% lipid + 30% protein	**Nerve cells (Neuron)** - **Cell body**: *contains **nucleus, organelles**; <10% T/volume; metabolic centre* - **Dendrites**: *thin processes that branch off the cell body; receiving synaptic input from other nerve cells.* - Axon terminal: - Axolemma: cell membrane - Axoplasm: cytoplasm

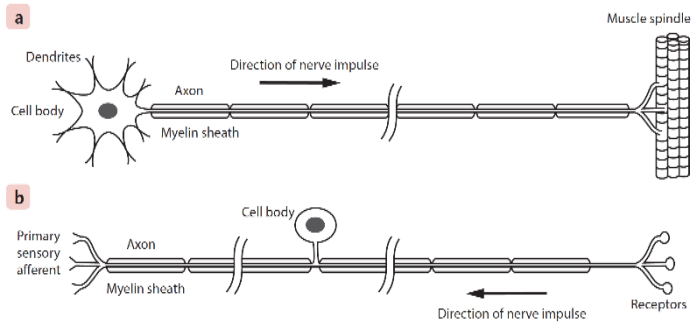
1 **Oligodendrocytes** (CNS)
2 **Schwann cells** (PNS)
3 Astrocytes (*CNS*)
4 **Microglia**

3 Astrocytes (*CNS*)
*1) **supporting** structures.*
2) regulate extracellular K+ concentration
3) synthesis of neurotransmitters
4) removal of neurotransmitters from synaptic cleft
5) Storage and transfer of metabolites (blood → neurons)

4 **Microglia**
* Immune cells
* derived from monocytes (phagocytic role)
* Defending CNS from noxious stimuli while being involved in inflammatory process

* Myelin acts as an insulator (fat).
* if stimulated mid-way, both Orthodromic and antidromic conduction may occur

Demyelination conditions
- e.g. MS, Guillain Barre syndrome.
- Demyelinated regions of the axon have a higher capacitance and a lower membrane resistance→



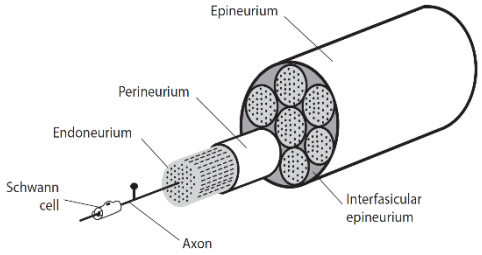
Efferent(motor):
- transmit **somatic** and **autonomic** information
- Brain → periphery.
- Dendrites, cell body, axon, Telodendron

Afferent (sensory):
- *transmit **somatic (voluntary)** and **visceral information***
- periphery → brain.
- Central connections in Dorsal Horn (output), Axon, cell body (*in DRG*), axon, sensory ending (input)
- Sensory receptors:

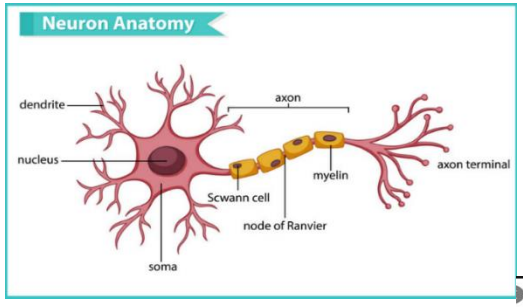
1) **Mechanoreceptors (Aβ):** Merkel cells (slow adapting), Meissner's corpuscles(rapidly adapting mechanical sensitivity), Ruffinis corpuscles (deep lying and important in skin creases), Pacinian corpuscles (rapidly adapting deep receptors), hair follicle receptors.

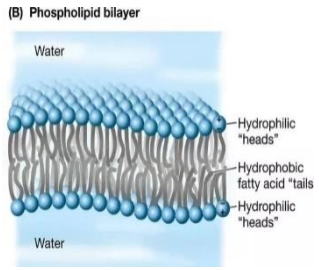
2) **thermoreceptors**: cooling (**C and Aδ**), warming receptors (unmyelinated **C fibre**),

3) **Nociceptors** (Myelinated fast A**δ**, **+** unmyelinated slow C fibre) (found in every organ except the brain). *High threshold for activation*, *polymodal receptors* (*respond to more than one energy form e.g. mechanical, thermal, mechanothermal*)

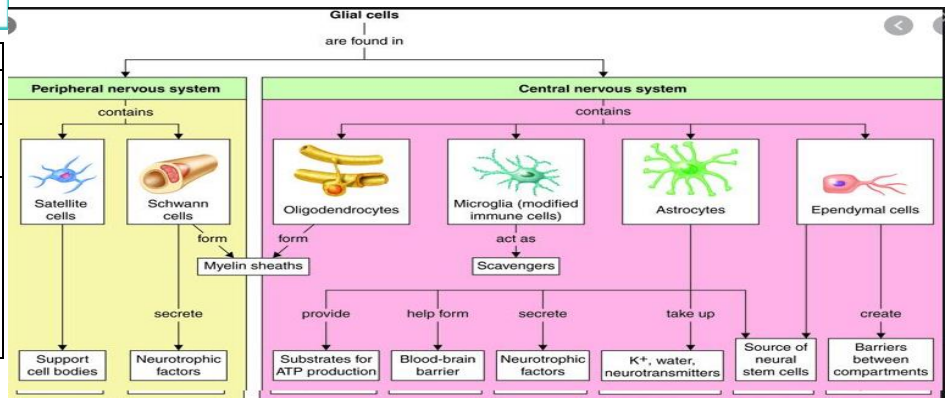


Macrostructure of a nerve





Level 1	nerve	**Epineurium:** a loose meshwork of collagen and elastin fibres surrounding fascicles
Level 2	Fascicle (*bundles*)	**Perineurium**: thin dense connective tissue sheath that surrounds each fascicle
Level 3	Fibre	**Endoneurium**: a loose collagenous matrix that surrounds the individual nerve fibres within the fascicle
Level 4	Neuron *functional unit* can be very long	Axolemma (cell membrane): *phospholipid bilayer* (polarized cell) - Hydrophilic fatty acid: on surface, charged polarised. - Hydrophobic tail: inside. Fatty acyl chains face each other. - **Globular proteins**: full thickness, act as iron channels, pumps Na+. K+, transport metabolites; receptors for hormones and transmitters; structural . Myeline (Schwann cell, oligodendrocytes) -70% lipid, 30% protein



Resting potential-70 mV
* The potential difference of a neuron **at rest**
* due to umbalancd 2K+/3Na+ umbalanced transport with Na/K APTases
  K+ high concentration inside of the cell
  Na+, Cl+ high concentration outside of the cell
* difference maintained by
  1) Lipid membrane prevents the passage of water soluble ions (leaky K+ channels, K+ out)
  2) Selectively permeable ion channels
  3) a metabolically active Na+/K+ exchange pump
  4) Donnan equilibrium

Threshold potential: -55mV
the minimum stimulus intensity needed to produce an AP.

Action potentioal
* Is a property of excitable cells that consists of a rapid **depolarization**, or **upstroke**, followed by **repolarization** of the membrane potential.
* AP have stereotypical size and shape, are propagating, and are all- or -non

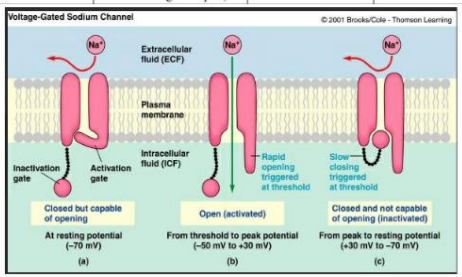
Diffusion potential:
- Is the potential difference across a membrane
- Due to a concentration difference of an ion (*DP can be generated only if the membrane is permeable to the ion*) .
- lipid bilayer membrane can have selective permeabilities based on the size, charge, or hydration of the specific ion.

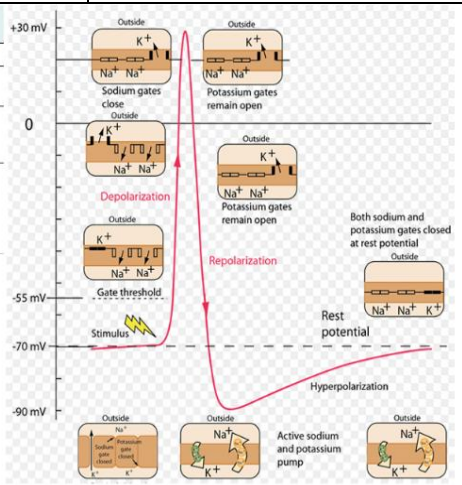
Equilibrium potential: is the diffusion potential that exactly balaced (opposes) the tendency for diffusion caused by a concentration difference
- EP can be calculated using Nernst Equation

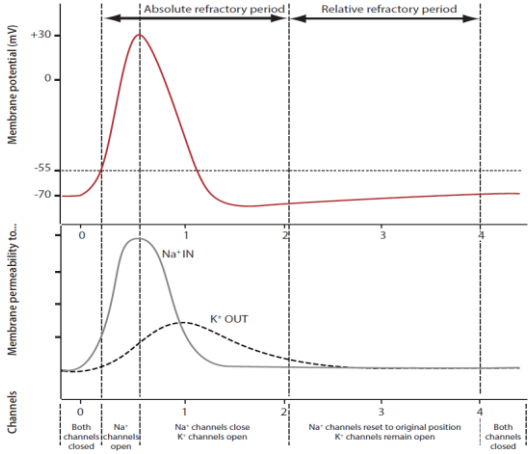
Types of ion channel:
- voltage-gated
- Ligand-gated (open when bound by a specific molecle)
- Mechanically-gated: in responses to physical force.

Steps in sensory transduction
1) Depolarization: *70mV→-55mV→+30mV*
   * makes the **membrane potential** *less negative,* From -70 mV to positive.
   →rapid opening of activation voltage gated Na+ toward the **Na+ equilibrium potential** of +65mV
   Depolarization also closes the inactivation gates of the Na+ channel, opens K+ channels
2) Repolarization: +30mVà-70mV
   makes the membrane potential *less positive* (*slow K+ voltage-gated gate, K+ out*)
3) Hyperpolarization *(0→-90mV)*: make the membrane potential *more negative* *(due to delay in closure of the K+ channels and the time taken for the Na+ channels to convert from an inactive to a resting state)*
4) Refractory period: For a short period after the AP has depolarised a particular section of axon, the mebrane is unable to be further stimulated (*this ensures that AP moves only in one direction*)
   - absolute RP: +30mV to – 55mV
   - relative RP: -55mV to -90mV to -55mV
5) AP is transmitted along the cell membrane (circumduction)

Step	Voltage-gated ion channels	Ion permeability	Action potential curve
Resting state	all channels closed	no ion movement	flat
Depolarization	Na^+ channels open (activation gates)	Na^+ flows into cell	sharp upward spike
Repolarization	Na^+ channels inactivating (inactivation gates) K^+ channels open	K^+ flows out of cell	downward curve
Hyperpolarization	some K^+ channels remain open Na^+ channels reset (activation gates close & inactivation gates open)	some K^+ continues to flow out of cell	slight dip below resting membrane potential



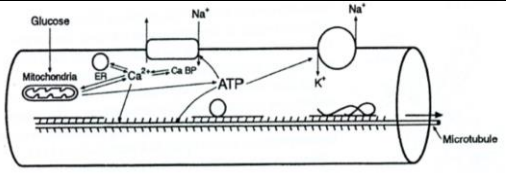
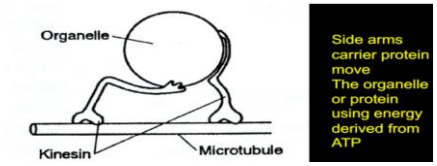




https://www.youtube.com/watch?v=oa6rvUJlg7o Action potential in the neuron
https://www.youtube.com/watch?v=Jk_9IhHVOTk Neurology resting membrane, graded AP. **Ninja Nerd**.

Conduction velocity
* proportional to the diameter of the nerve fibre (myelinated or not)
* The larger→ the faster
* can be measured with a distal recording following a proximal stimulus

Axoplasmic transport

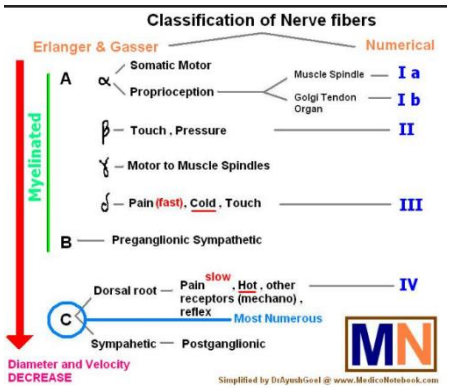
* moving molecules and organelles inside the cell (*long distance between cell bodies and presynaptic terminals*) * proteins can only be made in cell body, *(Transport system delivers molecules to the periphery, return degradation product back for reprocessing)* * 3 transport system: 1) slow anterograde 2) fast anterograde 3) fast retrograde transport	**Energy requirment**: depends on 1) ATP derived from **oxidative metabolism** 2) Ca++ concentration Sequested in mitochondria, Smooth ER Bound to calmodulin (*钙调节蛋白*)	**Microtubule Transport** *Require 1*) *ATP, 2) ATPase, 3) calcium, 4) carrier proteins* * Organelle or protein binds to carrier protein * Carrier protein binds to **microtubule** * Microtubule side arms use ATP (*enables microtubule to move the carrier protein*) * Different carrier proteins are used for different transport rates. * Different speeds are due to different drop off rates	Retrograde Transport 1) Returns material to cell body (e.g. *empty neurotransmitter vesicles*) 2) Delivers **extracellular factors** such as **NGF** to the cell body 3) Deliver **viruses** (*polio, herpes zoster, rabis*), tetanus toxin 4) Dyes can be carried and allow axonal tracking (Materials are packed in large membrane bound organelles)
			

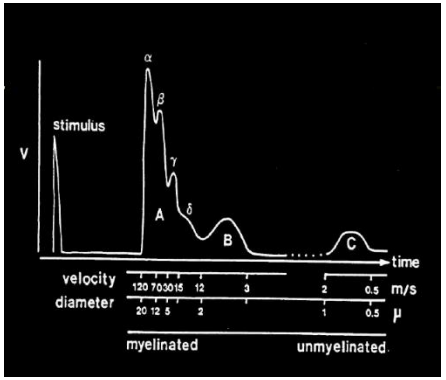
Molecular biology of sensory transduction

Pain: - is a sensory and emotional experience in the brain . - Afferents referred to as nociceptors respond to noxious or potentially tissue-damaging stimuli that are normally perceived as painful. *** Pain fibers**: *- C fibers* (*very small, slow unmyelinated, carry prolonged nociceptive impulse*) ; *mechano-thermal, warm, aching, dull and boring sensations.* *A delta* fibres(*small, myelinated fibre, carry initial response to pain*); *respond to mechanical, cold, sharp pain.* **Sensory transduction**: is conversion of the energy of a stimulus into an electrical signal. - Sensory information arising from the body, referred to as somatosensation.	Mechanical stimuli *when a small amount of pressure is applied, a nonpropagated depolarizing potential resembling an EPSP is recorded * 3 mechanisms underlie the initiation of a generator potential 1) . Na+/ Ca2+: Activation of an ion channel such as transient receptor potential vanilloid 1(TRPV1) with a permeability ratio such that the equilibrium potential for ions following through the channel (E channel) is above the action potential threshold (AP thresh). 2). K+ : closing of a K+ channel such as a two-pore K+ channel 3). Cl+ : activation of a channel that has an equilibrium potential threshold(GABA)	Classification of receptors (type of stimulus / forms of energy converted) 1. mechanoreceptors ==== mechanical touch 2. Chemoreceptors =====chemical smell taste 3. Thermoreceptors =====warmth thermal 4. nociceptors stimuli which are injurious to body tissue example pain 5. Photoreceptors =====Electromagnetic light

Classification of nerves by Erlanger and Gasser

Axon type	Myelination	Diameter (µm)	Conduction velocity(m/s)	Function
Aα (M, S)	M	20	100	Efferent to skeletal muscle Afferent from muscle spindles and tendon stretch organelles
Aβ (S)	M	10	50	Organised sensory receptors, e.g. Merkel, Pacinian, Ruffini, hair follicules
Aγ (M)	M	5	20	Efferent to muscle spindles
Aδ (S)	M	5	20	Fast pain (e.g. knife), crude touch, cold sensation
B	M	3	10	Pre-ganglionic autonomic
C (Pain)	UM	1	2	Post-ganglionic autonomic, slow pain (e.g.nettles), thermoreceptors, reflex responses





Nerve injury and repair

Aetiology of nerve injury	Mechanicism of nerve injury	Classification of injury	
Physical: traction, trauma, injection, thermal Inflammation Infection Ischaemia Pharmacological Tumour Systemic disease Iatrogenic	Open/closed injuries Acute/chronic Single/continuing/repeated Whole/part of a nerve Depth of the lesion Nerve state (healthy/diseased)	**Neurapraxia**: *transient* concussion or crushing of the nerve causes interruption of physical function, and a local conduction block. No Wallerian degeneration (*preserving sympathetic fibres and deep-pressure sensation*); Full recovery is likely. Axonotmesis: degenerative lesion (*a progressive loss of all peripheral function*), with favourable progresis Neuronotmesis: Degenerative lesion with unfavourable prognosis eg. Nerve completely transected; surgery	Wallerian degeneration: Degenerative lesions
Type of neuropathic pain following injury			
1) **post-traumatci neuralgia**: pain after nerve injury with no sympathetic involvement. Spontaneous, worsenedby physical stimulus. Within the teritory of the nerve.	2) **Neurostenalgia**: pain caused by persistent nerve compression/ distortion/ ischaemia or a nerve that is anatomically intact.Pain usually confined to the territory of the nerve	**Causalgia/chronic regional pain syndrome** (type 2) Burning pain with allodynia, hyperpathia, disturbance of skin colour, altered temperature and sweating. This is a rare but severe injury, often seen with partial division of a nerve. Pain is intense, beyond the territory of the damaged nerve. Sympathetic involvement is characteristic.	**Central pain** Caused by root avulsions. - a constant crushing or buring pain felt within the anaesthetic part - a sharp shooting pain within the dermatome of the affected nerve.
Terms used to describe symptoms			
Paraesthesia: Spontaneous abnormal sensation **Dysaesthesia**: Unpleasant spontaneous normal sensation **Allodynia**: pain from stimulation that does not normally cause pain **Hyperalgesia**: increased response to a stimulus that is normally painful **Hypersensitivity**: over-reaction sensitivity of regeneration **Hyperpathia**: deep-seated, poorly localized, fiery pain rediating throughout the limb that is induced by palpation of the muscles		**Double crush syndrome**: * nerve entrapment at two locations of the same nerve, both contributing to symptoms fo the patients. * Proximal compression of a nerve fibre leads to impairments in slow and fast transport→ disruption of axonal transport systems decreases the delivery of cytoskeletal components. E.g.tubulin, actin etc. * a distal impingement of a peripheral neve→ develplment of an entrapment neuropathy at more proximal levels. * e.g. CTS + cervical neuropathy.	