Sensory & Pain Receptors

Receptor	Receptor Type	Sensation	Neuron Type
Ruffini's End Organs	Tonic (very slow adapting)	Continuous touch Pressure	Aβ
Merkel's Disks	Tonic	Light touch	Aβ
Meisner's Corpuscles	Phasic	Touch (texture)	Aβ
Hair End Organs	Phasic (rapid adaptation)	Light touch	Aβ
Pacinian Corpuscles	Phasic (very rapid adaptation)	Deep pressure Vibration Proprioception	Aβ

http://faculty.stcc.edu/AandP/AP/AP2pages/Units14to17/unit15/sensory.htm

http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=neurosci.section.676

Free Nerve Endings	Tonic (little - no adaptation)	Pain / Pressure / Touch Itch / Joint movement	Aδ (fast) C (slow)

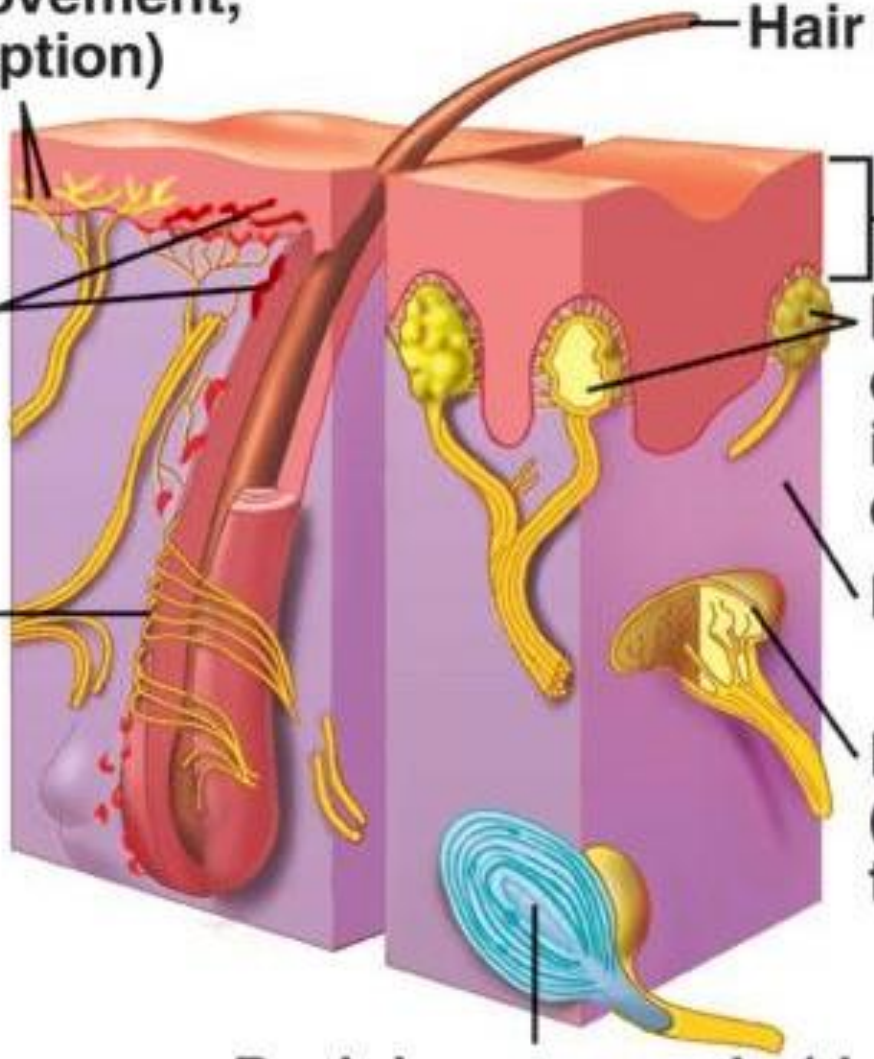
- Widespread in: skin, periosteum, arterial wall, joint surfaces, cranium
- Most deep tissues are not extensively supplied with free nerve endings

- "Sharp" or "Electric" pain that is usually felt within .1 seconds — Aδ
- Neurotransmitter example: Glutimate (exists for only milliseconds)

- "Aching" "Throbbing" "Burning" pain (tissue destruction) — C
- Neurotransmitter example: Substance P (exists for seconds to minutes)

Cold Receptors	Tonic (incomplete adaptation)	cold / cold pain	Aδ
Warmth Receptors	Tonic (incomplete adaptation)	heat / heat pain	C

Sensory & Pain Receptor Locations in the Skin



Free nerve endings (respond to painful stimuli, temperature, itch, joint movement, or proprioception)

Hair

Merkel's disks (detect light touch and superficial pressure)

Epidermis

Meissner's corpuscles (touch: involved in two-point discrimination)

Hair follicle receptor (detects light touch)

Dermis

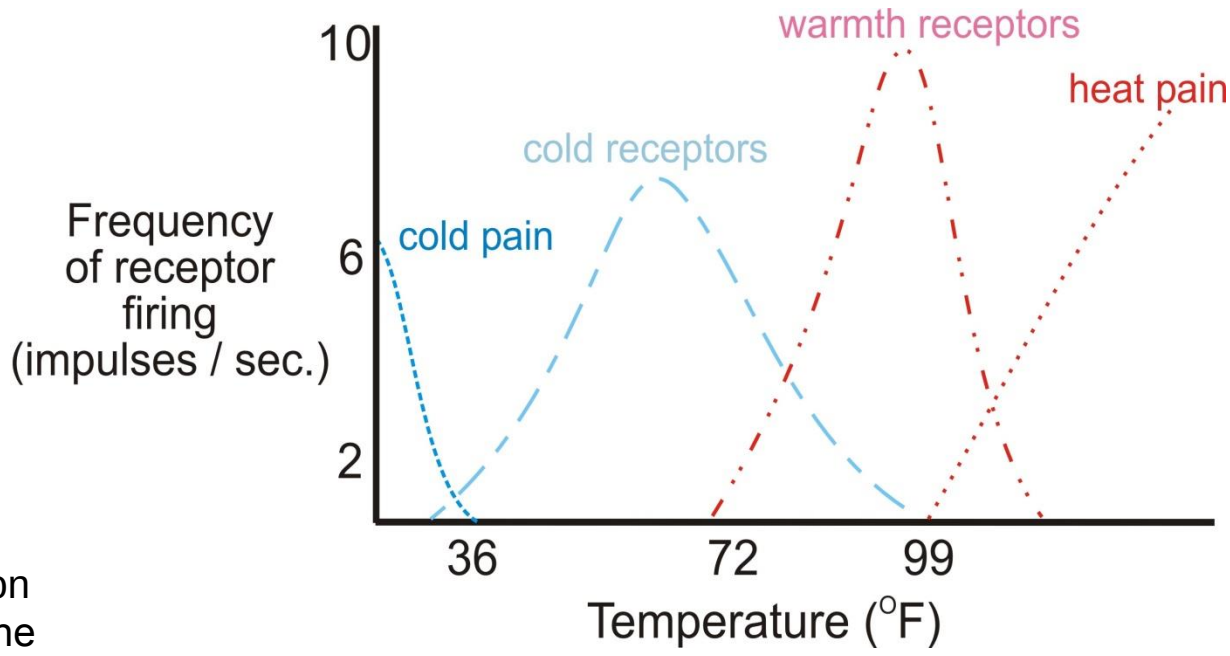
Ruffini's end organ (detects continuous touch or pressure)

Pacinian corpuscle (detects deep pressure, vibration, and proprioception)

Temperature Sensation & Spatial Resolution

Temperature Sensation

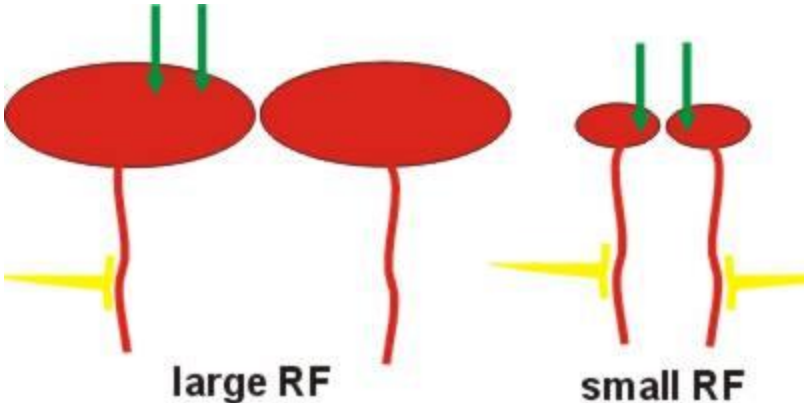
- Not well understood
- Mostly transmitted through free nerve endings (thermoreceptors)
- Thermoreceptor adaptation occurs (think of hot tub, cool bath, etc.)
- Hot Flashes
  - Hormone signal malfunction "tells" hypothalamus that the body is too hot
  - Body responds with temperature reduction mechanisms (sweat, etc.)



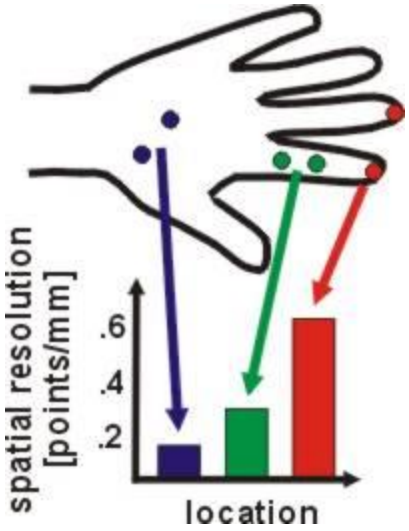
http://paincenter.wustl.edu/c/BasicResearch/documents/ThermoTRPsNatureRevNeurosci2003.pdf

Temperature Sensation & Spatial Resolution

- **Spatial Resolution** - the minimum physical distance between stimuli that results in a two point stimulus being perceived as a two point stimulus.
  - Is a function of:
    - Sensory “field” size (Receptor Field Size)
  - Spatial resolution smallest for tongue: 2 mm
  - Spatial resolution for finger tips: 4 mm
  - Spatial resolution largest for back: 40 mm



The **Receptive Field size** determines **spatial resolution** (the number of points that can be detected in a given skin area)



Tactile resolution (receptive field size) varies for different areas of the body surface: finger tips are better than palm of the hand, etc...

Pain (Nociception) & Sensation Theories and Principles

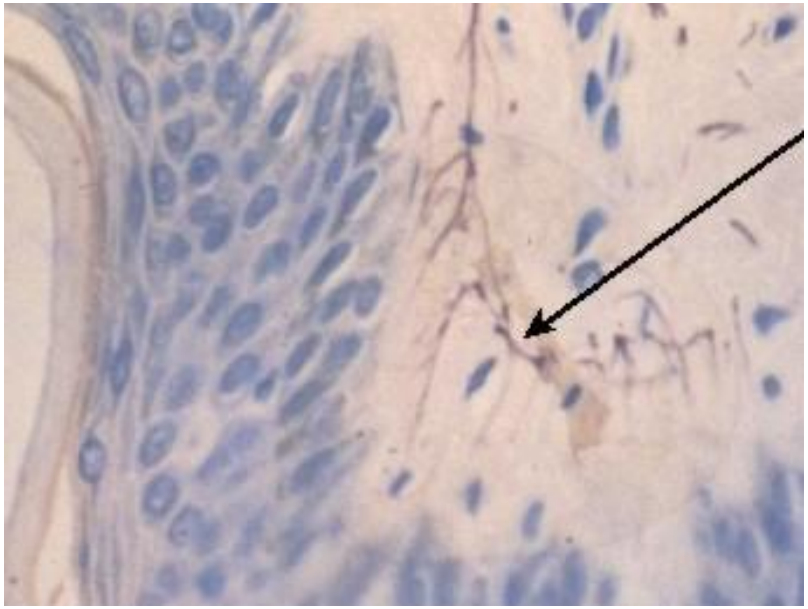
Pain: An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage **(IASP)***

- **Pain is the most subjective of our senses and is influenced by:**
  - Past experiences and sleep disturbances
  - Emotion (anxiety, depression, fear, isolation, previous pain experience)
  - Individual variation and culture – chronic pain sufferers form a sub-culture
    - A lifelong worker feels useless after retirement → ↑ depression → ↑ pain
    - Loss of social rank or status
  - Pain threshold lowered by: anger, anxiety, depression, isolation, chronic pain
  - Pain threshold raised by: rage, diversion, empathy, rest, sympathy, medication

http://www.nursingtimes.net/nursing-practice/1860931.article

Activation of nociceptors is often associated with a variety of reflexes:

- ↑ Heart rate
- ↑ Blood pressure
- ↑ Respiratory rate
- ↑ Sweating
- ↑ Pain site blood flow
- Dilated pupils
- Spasm of nearby muscles



Pain Receptors (free nerve endings)

*** IASP: International Association for the study of Pain**

The Problem with End-of-Life Pain in our Medical Culture

- Pain management is not taught at all or not extensively taught in US medical schools
- Less than 10% of people die suddenly, most die after a long painful illness
- **Only ½ of all chronic pain patients say their chronic pain is under control**
- Patients dying from the following diseases experience severe pain:
  - CHF (Congestive Heart Failure)
  - COPD (Chronic Obstructive Pulmonary Disease – Emphysema, etc.)
  - ESRD (End Stage Renal Disease)
  - ALS (Amyotrophic Lateral Sclerosis - Lou Gherig's disease)
  - MS

" Pain is often undertreated, even when prevalence rates and syndromes are well understood and the means of relief are within all practitioners' capabilities to provide, directly or through consultation. With careful assessment and a comprehensive plan of care that addresses the various aspects of the patient's needs, pain can be controlled in the vast majority of cases. It is the professional and ethical responsibility of clinicians to focus on and attend to adequate pain relief for their patients and to properly educate patients and their caregivers about analgesic therapies."

Perry G. Fine, M.D., Professor of Anesthesiology, University of Utah, Salt Lake City; Attending Physician, Pain Management Center, University of Utah, Salt Lake City; Vice President, Medical Affairs, National Hospice and Palliative Care Organization (NHPCO)

Consequences of Unresolved Pain

- **Significant evidence exists that inadequate pain relief hastens death by:**
  - Increasing psychological stress (depression, anxiety, & spiritual despair)
  - Diminishing immune function (↑ chance of pneumonia & other infections)
  - Reducing mobility and other physical capability → ↑ psychological stress
  - Increasing chances of thromboembolism (stroke or MI)
  - Increasing the work of breathing and myocardial oxygen requirements
  - Causing sleep disturbance
  - Causing a decline in recreational, social, & family activity → ↑ stress
  - Causing malnutrition

What about a world without physical pain ??

Consider 5 year old Ashlyn Blocker of Patterson Georgia

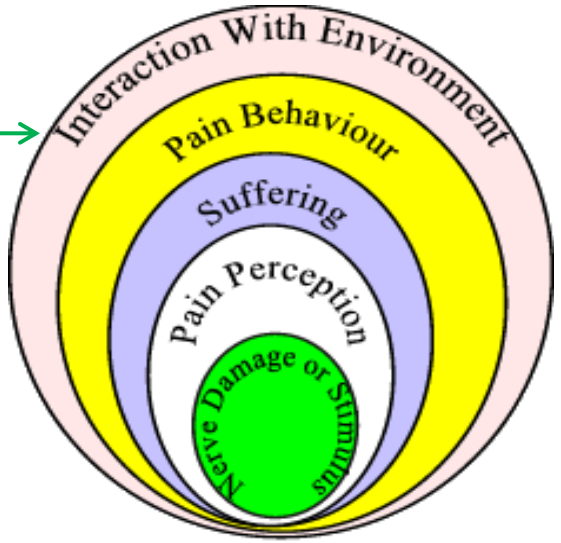
- **She has Congenital Insensitivity to Pain with Anhidrosis (CIPA)**
  - **Unable to feel pain or sense heat and cold.**
  - **Very rare: only 34 current cases in the United States (2004)**

- Her teachers and parents have to put ice in her hot food or she will eat it and scald her mouth and throat.
- Her teachers have to keep her off the "jungle gym" on playgrounds because if she falls and cuts, bruises herself, or fractures a bone, she won't realize it.
- In the future she cannot feel pain related warning signs of such serious diseases as ovarian cancer, colorectal cancer, urinary tract infections,…….
- Such patients often die before the age of 25 from some sort of infection (appendicitis, blood poisoning). They can't even feel a heart attack.
- She rubbed her eyes so hard as to blind one and only see 20/300 out of the other.

Pain (Nociception) & Sensation Theories and Principles

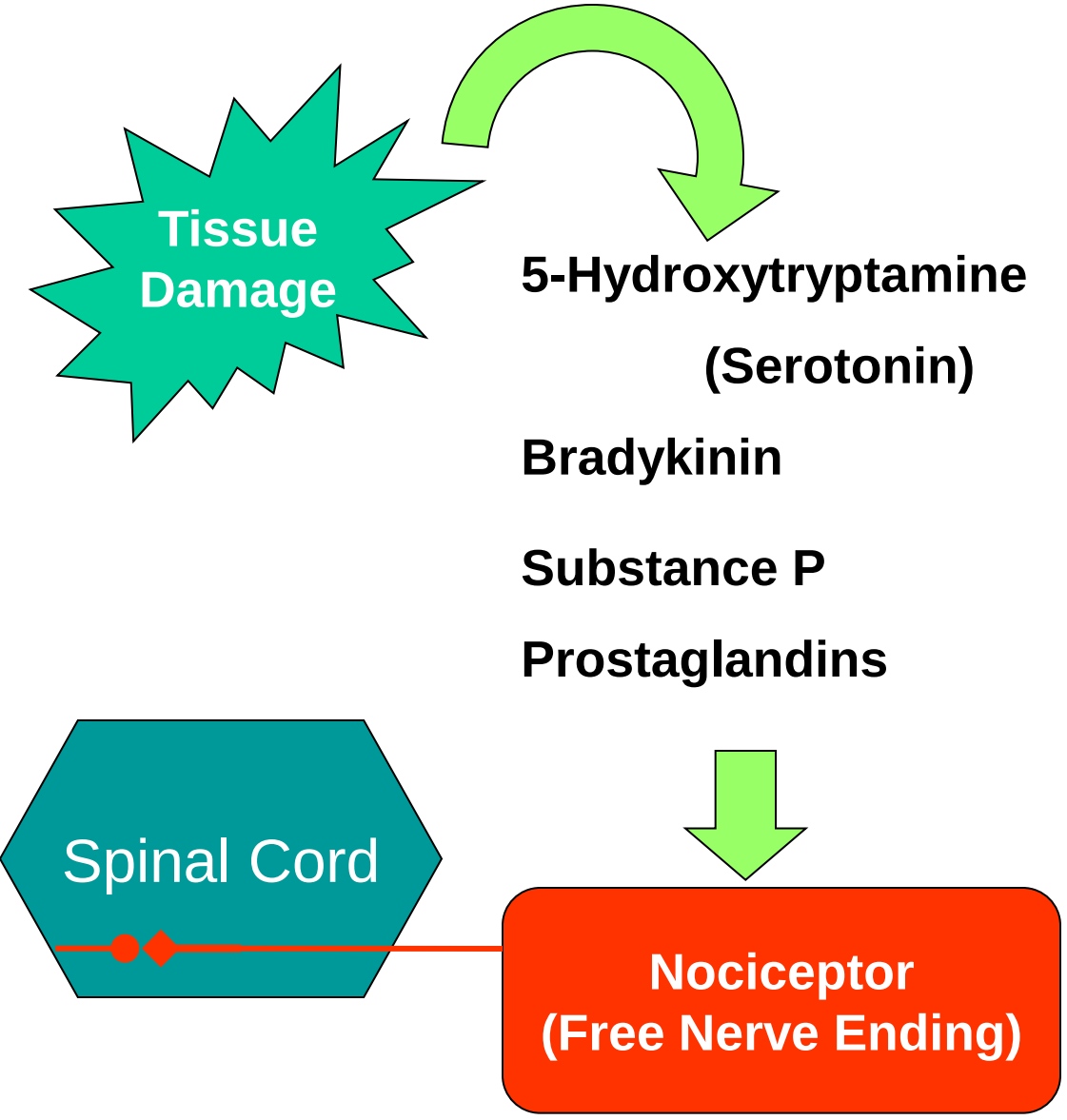
- **Gated Control Theory (Melzack & Wall 1962)**
  - Pain shares transducers and neural pathways with other sensations
    - light pressure - low sensory organ firing frequency - “touch” sensation
    - heavy pressure - high rate of sensory organ firing - “pain” sensation
  - Transmission of all impulses is “gated” (regulated) at the spinal cord level

- **Loesser’s Onion Theory**
  - Pain mechanisms are “layered” like an onion
    - 1st layer: tissue damage and receptor function
    - 2nd layer: perception of pain
    - 3rd layer: suffering
    - 4th layer: pain behavior
    - 5th layer: interaction with environment
    - Only the 4th & 5th layer can be observed



- **Contemporary theory: a combination of the two theories above**
  - **Summed up by likening the pain pathway to stereo amplifiers at 3 levels:**
    - **Pain can be “amplified” or “dampened” at all three levels**
      - **Periphery (pain sensors and surrounding influences)**
      - **Spinal cord (gate mechanism)**
      - **Brain (emotions, experiences, culture, etc.)**

Simple Peripheral Pain Transmission And Common Pain Neurotransmitters



Pain Receptors (Free Nerve Endings)

- Most FNE's located in skin, arterial endothelium, bone periosteum, joint surfaces
- No FNE's in Brain or Alveoli
- 3 different types of stimuli excite pain receptors:
  - Mechanical, Thermal, Chemical (neurotransmitters)

Other Pain Receptor Stimulators and Neurotransmitters

- Histamine
- K^+
- Acetylcholine
- Proteolytic enzymes
- Norepinephrine……..

Prostaglandins - enhance the sensitivity of pain receptors

- Recent studies suggest that they may also activate the receptor

Different Ways to Classify Pain

- **Somatic** – originating in joints, muscles, skin, or ligaments **(responds well to NSAID's)**
  - Described as "aching", "throbbing", "stabbing", or "pressure"
- **Visceral** – originates in internal organs or smooth muscle **(usually requires narcotics)**
- **Superficial**– originates in skin or mucous membranes
- **Cancer** – pressure from tumor on organs or nerves, fractures, muscle spasms
- **Psychogenic** - real to the patient but originates from psychological factors
- **Referred** – pain occurs at an area different from tissue origin

Different Ways to Classify Pain

- **Vascular**– originates from vascular pathology (inflammation ➞ change in blood flow)

Migraine headaches – severe throbbing unilateral pain lasting 4 – 72 hours

- Affects 24 million Americans

http://www.webmd.com/migraines-headaches/guide/migraines-headaches-overview

- Cause is not completely clear – affects women more than men

Triggers: barometric pressure change, estrogen cycle, hunger, insomnia…

Therapy: 1. Prophylactic: β–blockers & Ca^{++} channel blockers, antidepressents, anticonvulsants **TOPOMAX (Topiramate)**

2. Abortive: various NSAID's are effective for some people

5-Hydroxytriptamine (Serotonin) agonist - best abortive drug

IMITREX (Sumatriptan) RELPAX (Eletriptan)

FROVA (Frovatriptan Succinate)

- Binds to 5HT receptors ➞ ⬆ blood vessel constriction

- ⬇ release of inflammatory & pain neuro-peptides

- Cost about $35 per 100mg pill

MIGRANAL 5-HT agonist + α adrenergic agonist

Different Ways to Classify Pain

- **Fast pain:** Aδ fibers – usually travels a direct route to higher neurocenters
  - Acute Pain - Warning system….**Pain is a symptom**….most often very treatable
    - Localized pain lasting only as long a receptor is stimulated
- **Slow pain:** C fibers – usually travels a multisynaptic route to higher neurocenters
  - Usually from visceral sources (examples: smooth muscle pain, stomach ache)
- **Chronic Pain:** Continual firing of non-adapting nociceptors for weeks, months, or years
    - 86 million Americans suffer from chronic pain (about 9% to 11% of the population)
      - More women than men suffer chronic pain
      - Cost: > $100 billion annually (lost work time + medical expenses)
      - Only about 8000 doctors in the U.S. are chronic pain specialists
  - Pain has no biological value and lasts more than 3-6 months
  - Usually originates in deep tissues and organs
  - **Pain is a disease**….very difficult to treat
  - ***Chronic pain's terrible triad: suffering, sleeplessness, sadness***
  - May result from:
    - Displacement of tissues causing ischemia, inflammation & tissue destruction
    - An initial injury or pathology that is not "resolved" or "cured"
      - Back spasm, ruptured disk in back, unresolved infection, arthritis…..)
    - Damage or malfunction in the nervous system

Different Ways to Classify Pain

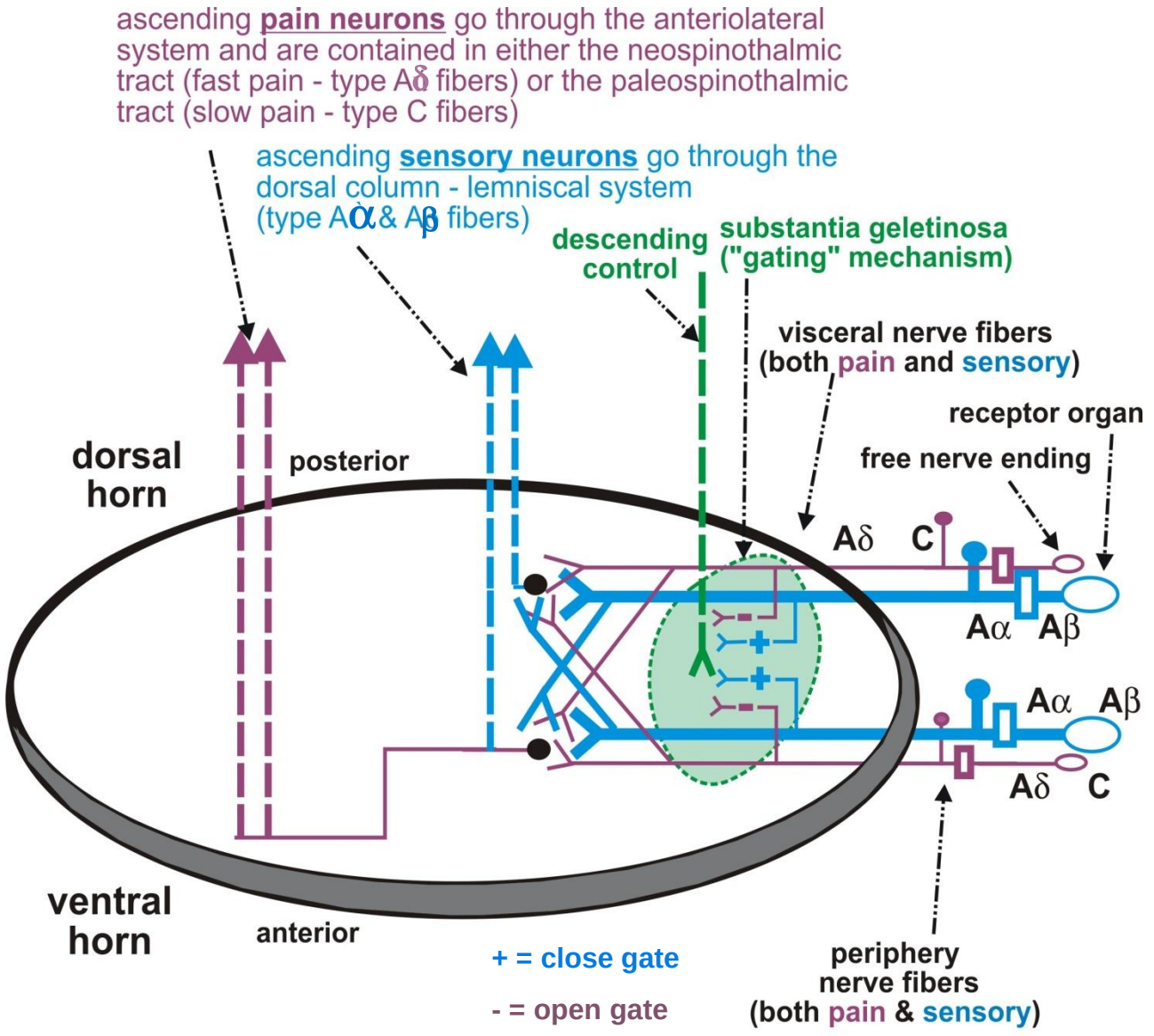
- **Chronic pain (continued)**
  - Unlike acute pain, it passes through hypothalamus & limbic system before reaching brain
    - Hypothalamus releases stress hormones (cortisol)
    - Limbic system is connected to emotional centers
  - **Neuropathic pain** – results from damage to CNS fibers or periphery nerve fibers
    - Often triggered by past pain or disease, but hard to pinpoint exact cause
    - May result from cell content spillage or unresolved inflammation
    - Described as “tingling”, “burning”, “searing” “sharp and shooting sensations”
    - **Allodynia:** pain resulting from non-painful stimuli (common in neuropathic pain)
  - **Phantom pain** – pain in a limb no longer present – may dissipate over time
    - 50% - 80% of amputees experience phantom pain
    - **Theories as to the cause:**
      - Remaining proximal neurons activated by sensory/pain neurons close by
      - Parts of the thalamus continues to send signals to sensory cortex
      - Loss of sensory input from amputated limb causes “crosswiring” in cortex

Sensory & Pain Pathways

Referred Pain **pain in a region of the body where that part of the body is not the source of the pain stimulus (example: angina)**

Peripheral and central afferent neurons converge on the same ascending neurons at the spinal level, therefore higher brain centers cannot distinguish exactly where the pain comes from.

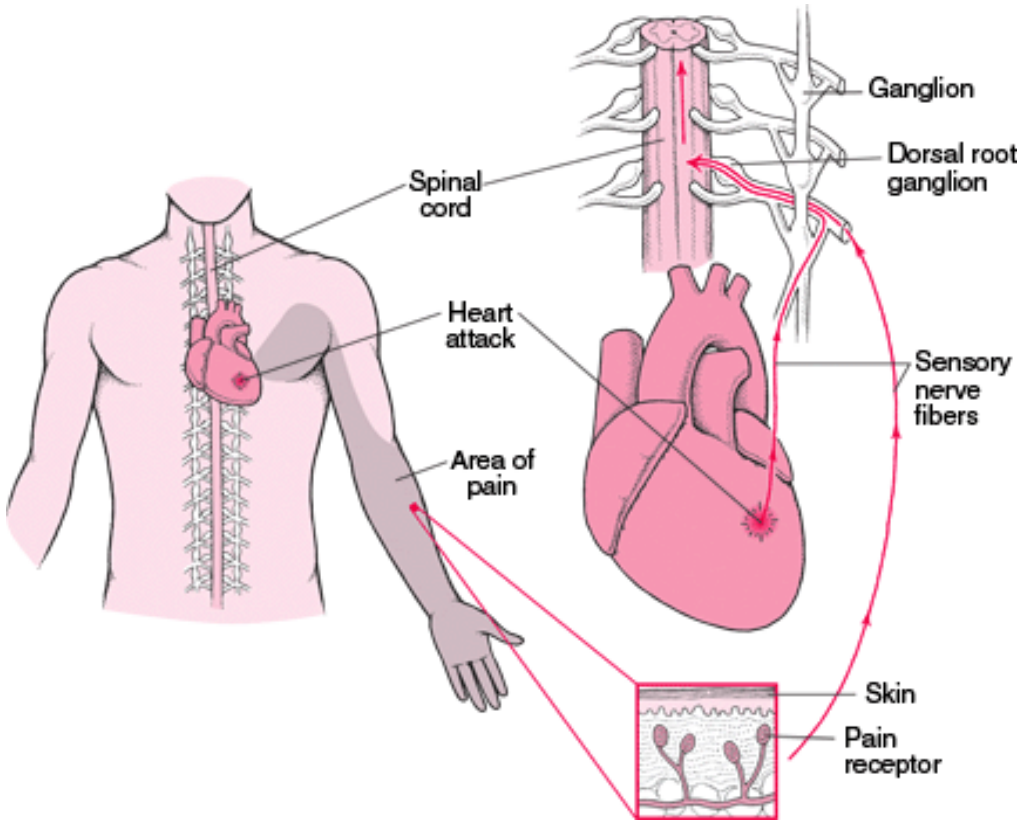
Principle of Counter-irritation **the "crowding out" of pain signals by overloading sensory input and closing (+) the gate**



Cross Section of Spinal Cord

Pain (Nociception) & Sensation Theories and Principles

- **Examples of Referred Pain**
  - Angina – heart pathology may produce pain in the left side of chest & left arm
    - Does the heart have pain receptors or free nerve endings?????
  - Gall bladder pathology may produce pain in the right shoulder
  - Pathology of the throat or teeth may be referred to the ear
  - Kidney pathology may produce pain in the groin area
  - Intestinal pathology may produce pain in the mid or lower back

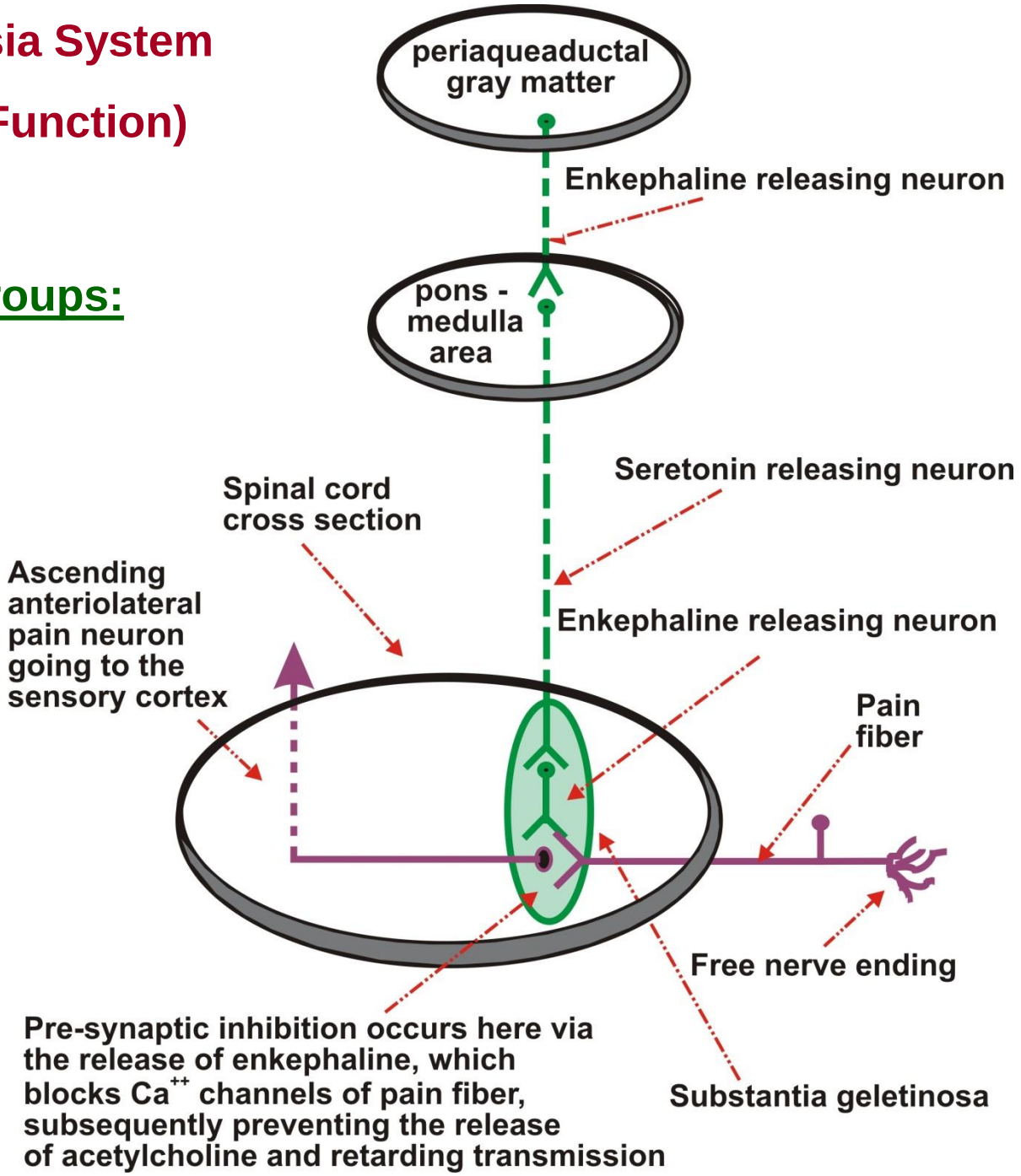


The Descending Analgesia System

(Endogenous Opiate Function)

Endogenous Opiate Groups:

- Enkephalins
- Endorphins
- Dynorphins
- Endomorphines
- Nociceptins



Neuropathic Pain (Neuralgia)

Neuropathic Pain – Damage to somatic sensory nerves or other nerve axons in the periphery or the CNS, recall: sensory fibers connect with pain fibers in the dorsal horn

- ➡ Loss of sensation, numbness, tingling
- ➡ Pain that ranges from slight discomfort to excruciating (worse at night)

- Damage done by: trauma, diabetes (diabetic neuropathy), amputation (mastectomy), herpes zoster (shingles), demylenation (MS), stroke
- To the patient and physician, the pain may seems to have no cause
  - Cause is difficult to determine
- Affects about 1.5% of the general population
  - **45% - 80% of nursing home residents have untreated neuropathic pain**
- Pain may be triggered by light touch (pulling the sheets over you, air movement)
  - Called **Allodynia**
- Pain sensitivity to a relatively mild painful stimuli may be enhanced
  - Called **Hyperalgesia**
- This type of chronic pain is difficult to manage
- It usually does not respond to standard analgesic interventions including opioids
  - This non-response implies damage or malfunction of pain fibers / pathways

"Non Traditional" Pain Treatments & Associated Mechanisms

- **Capsaicin:** – (Topical) chili pepper derivative – may take weeks to see results
  - Application produces counter-irritation effect
- **Tricyclic antidepressants:** **Amitriptyline (ELAVIL), Imipramine (TOFRANIL)**
  - Seems to have a sodium channel blocking effect on pain neurons
- **Anticonvulsants:** **Carbamazepine (TEGRETOL), Gabapentin (NEURONTIN), lamotrigine (LAMICTAL), Pregabalin (LYRICA) - new anti-seizure drug**
  - Various mechanisms for each drug include sodium channel blockade
  - **Baclofen (LIORESAL):**
    - Block spinal cord GABA receptors & may inhibit substance P
    - Anti-convulsant used to treat MS spacticity & associated pain
- **Ketamine (DIPRIVAN):** N-methyl-D-aspartic acid (NMDA) receptor antagonist
- **Administration of membrane stabilizers** – **Lidocaine, Novacaine**
  - Nerve block by injection: in many cases accompanied by a corticosteroid
  - **IV Lidocaine & Mexiletene** has been shown to be useful is some cases
- **Radiofreqeuncy ablation** – CT scan guided radio waves heat & destroy nerves

"Traditional" Pain Medications & Associated Mechanisms

- **Exogenous Opioids** (**Codene, Hydrocodone, OXYCONTIN**, **VICADIN, DEMEROL, Fentanyl**)
  - Bind to opoid receptors located in brain, spinal cord, & various nerve plexuses
  - Receptor stimulation → ↑ K^+ conductance → cell hyperpolarization → ↓ transmission
  - Receptor stimulation → ↓ Ca^{++} entrance into terminal bouton → ↓ neurotrans. release
  - Binding to gastrointestinal - urogenital receptors → ↓ peristalsis & ↓ bladder contraction
  - Binding to respiratory control centers → antitussive effect (↓ coughing)
  - Addiction rate for chronic users: 5% - 19%
- **Local Anesthetics (Lidocaine)**
  - Inhibits influx of Na+ into the nerve cell during depolarization (↓ action potential firing)
- **Corticosteroids** (**Prednisone dosepack [systemic]**), (**Cortisone injections [local]**)
  - Corticosteroid (hydrocortisone) similar to the endogenous hormone **cortisol**
    - **Cortisol: secreted during stress → ↑ BP, ↑ blood glucose, ↓ immune response**
  - ↓ Cell membrane phospholipase activity → ↓ production of arachadonic acid
  - 70% ↓ in lymphocyte function and availability
    - **May ↓ immune function if administered systemically over a long period of time**
  - Inhibit the cytokines Interluken 1 (IL1) and Tumor Necrosis Factor (TNF)
  - Should never be injected inside the actual tendon (in the tendon sheath only)
  - Should be limited to 3 injections - danger of degenerative changes & tissue rupture
  - Loss of bone mineral density with long term systemic dosages

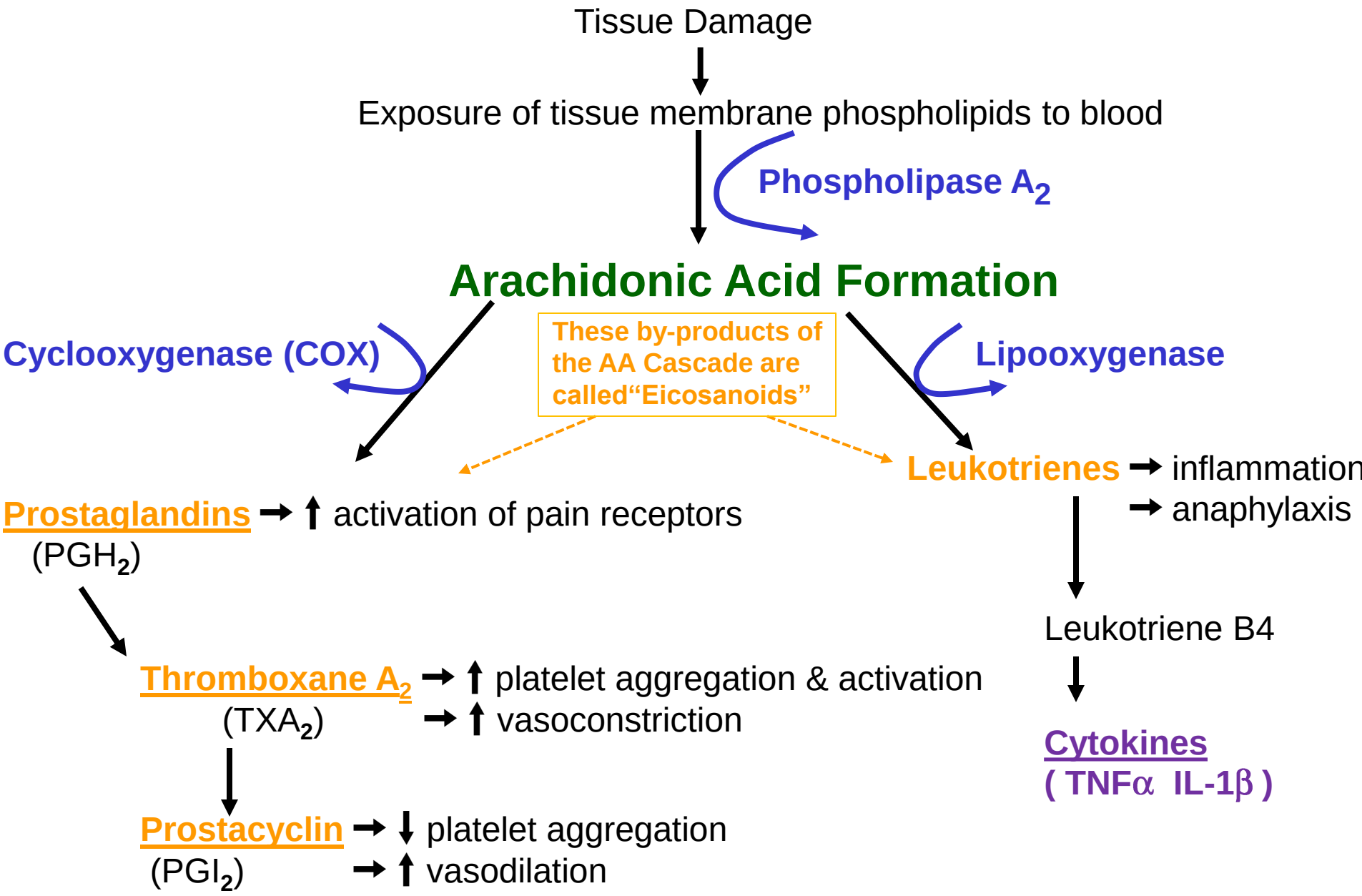
"Traditional" Pain Medications & Associated Mechanisms

- **Non-Steroidal Anti-Inflammatory Drugs (NSAID's)**
  - Block the breakdown of arachidonic acid into prostaglandins
  - May slow healing, especially in fractures, due to ↓ in a specific type of prostaglandin
  - Blocks bradykinin synthesis in the blood
  - Many inhibit the COX1 enzyme which is also necessary for gastric mucous formation (necessary for protection from stomach acid – COX 1 inhibitors → GI upset & ulcers)
    - Acetylsalicylic acid: **(Aspirin)** blocks formation of Thromboxane A_2 →↓ platelet aggregation
      - May also inhibit the synthesis of prothrombin →↓ coagulation
    - Acetic acid: **Indomethacin (INDOCIN)**
    - Proprionic acids: **Naproxin (ANAPROX NAPROSYN ALEVE) Ibuprofin (ADVIL)**
    - Enolic acids: **Piroxicam (FELDENE)**
    - Prostaglandin synthetase inhibitors: **Ketorolac (TORADOL MOBIC DAYPRO)**
    - COX 2 inhibitors: **Celecoxib (CELEBREX), Rofecoxib (VIOXX)**

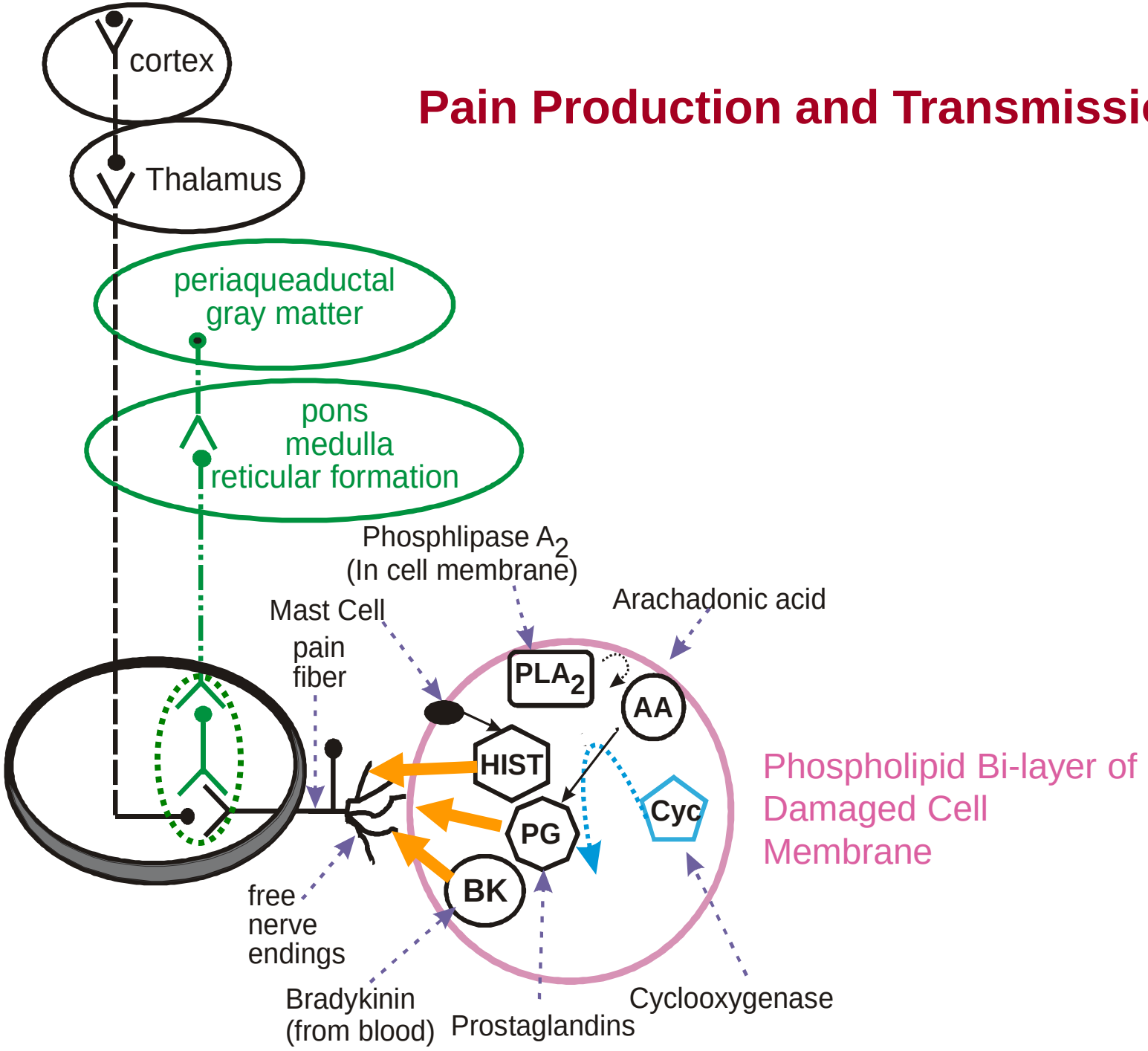
      COX 2 NSAIDS linked to ↑ risk for MI, stroke, thrombolic events, severe GI bleeding, anaphylaxis

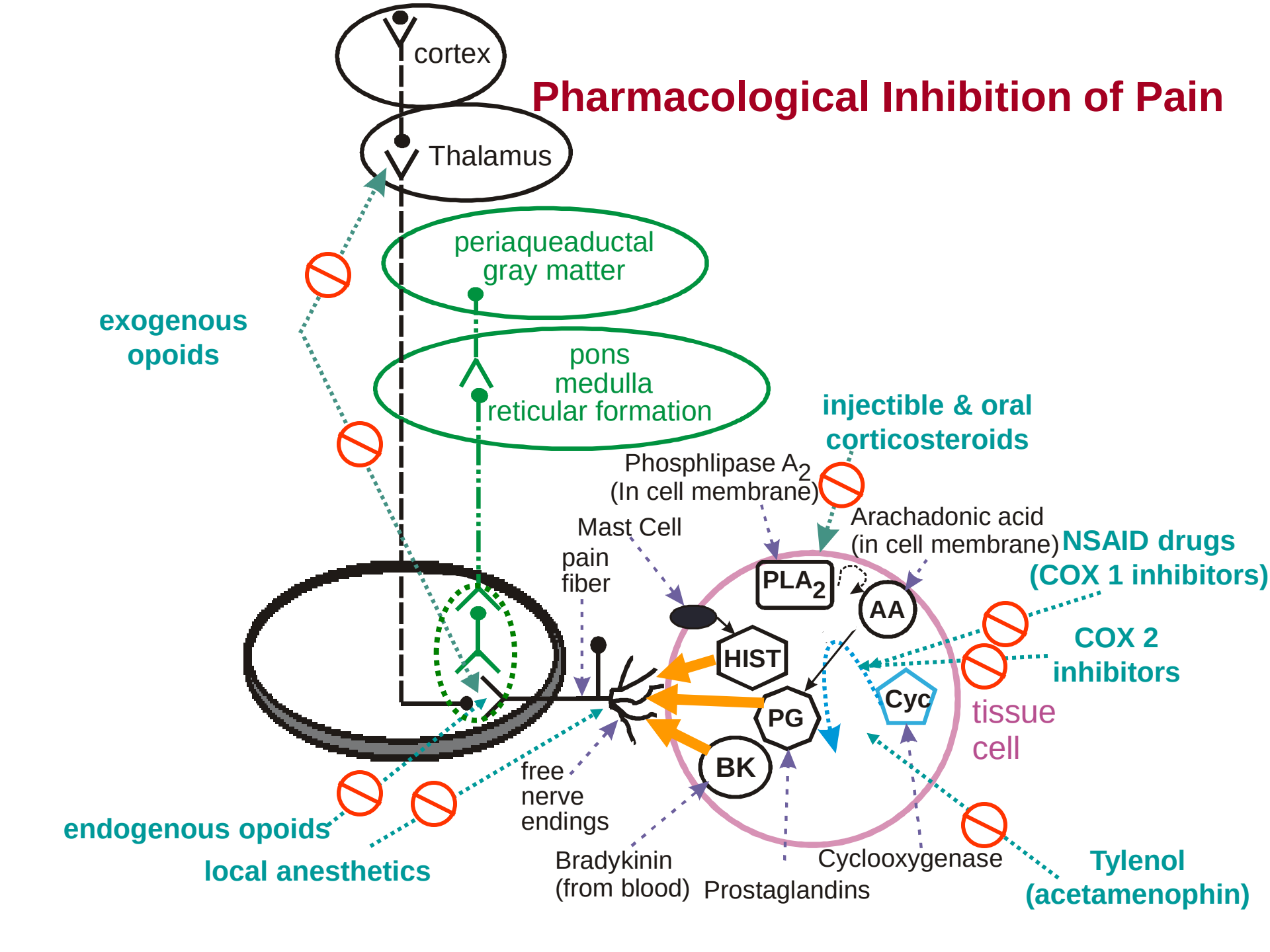
- **Acetaminophin (TYLENOL) not an NSAID – no anti inflammatory properties**
  - Exact mechanisms for pain control unknown
    - May interfere with prostaglandin synthesis via COX-3 enzyme inhibition
    - Antipyretic (fever reduction) effects is exerted by blocking the effects of endogenous **pyrogens** on the hypothalamic heat-regulating center, possibly by inhibiting prostaglandin synthesis
    - Excessive use may be toxic to both the liver and the kidneys

Arachidonic Acid Cascade

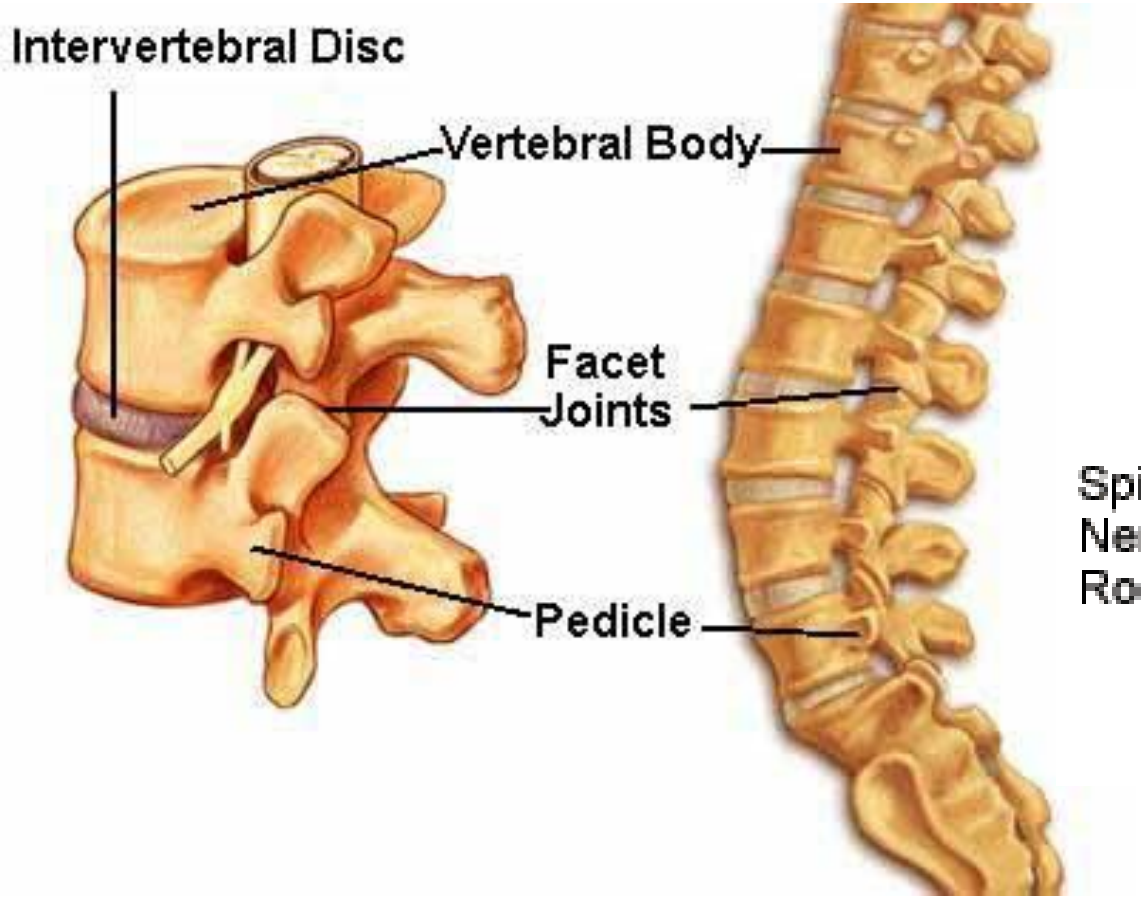


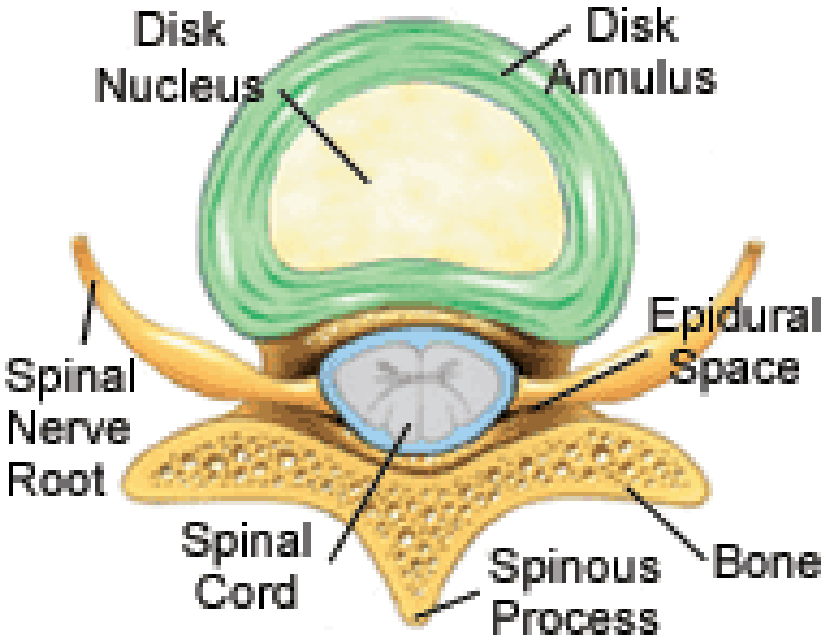
Pain Production and Transmission




Pharmacological Inhibition of Pain
cortex
Thalamus
periaqueaductal gray matter
pons
medulla
reticular formation
exogenous opoids
injectible & oral corticosteroids
Phosphlipase A2 (In cell membrane)
Arachadonic acid (in cell membrane)
NSAID drugs (COX 1 inhibitors)
Mast Cell
pain fiber
PLA2
AA
HIST
COX 2 inhibitors
Cyc
PG
tissue cell
BK
free nerve endings
endogenous opoids
local anesthetics
Bradykinin (from blood)
Prostaglandins
Cyclooxygenase
Tylenol (acetamenophin)

Low Back Pain – Spinal anatomy





http://www.medicinenet.com/low_back_pain/article.htm

http://www.webmd.com/back-pain/tc/low-back-pain-topic-overview

Low Back Pain

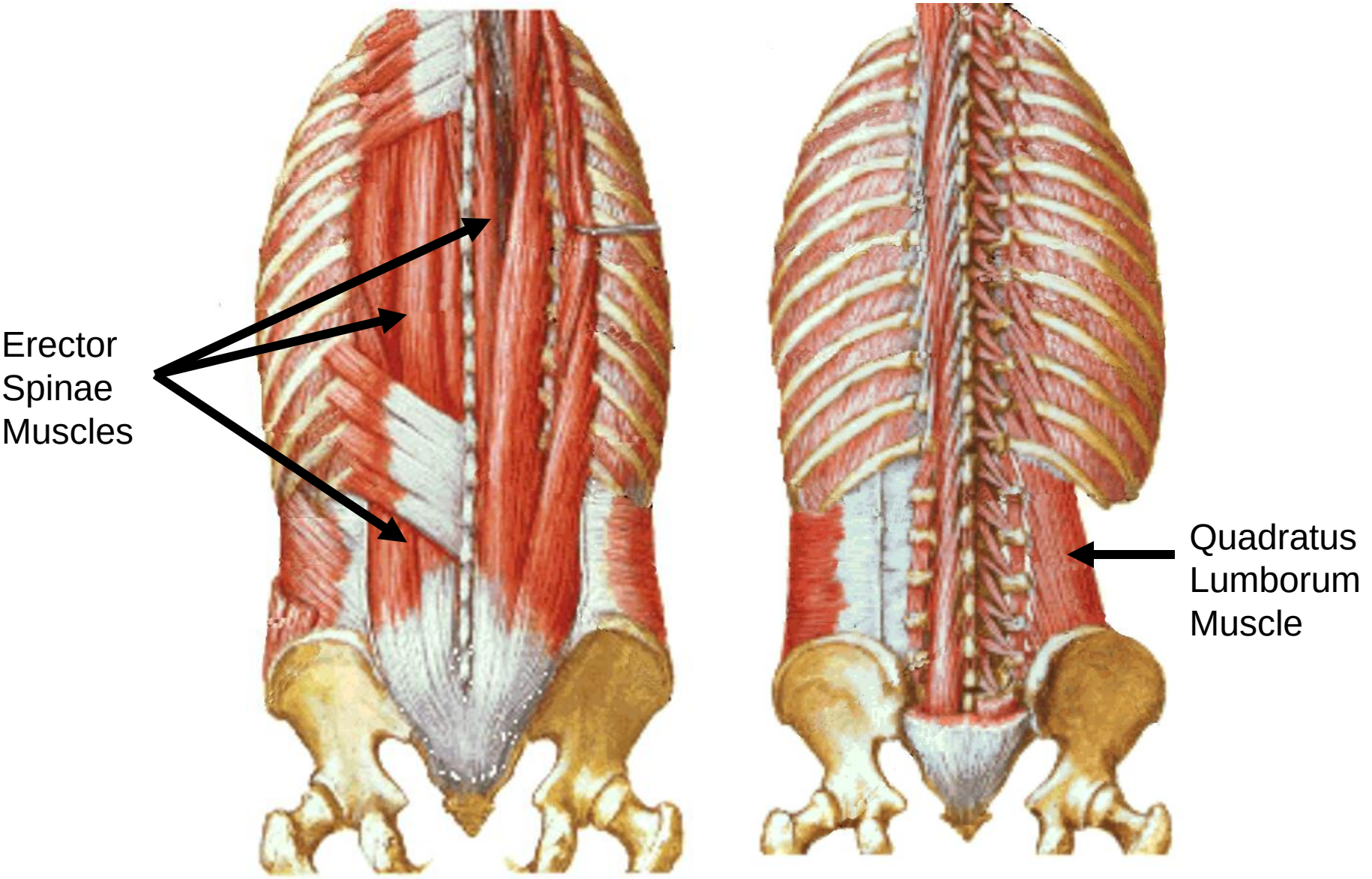
- Ranks 2nd to headache as the most common location / site for pain
- Affects over 65 Million Americans each year – cost 10's of billions of $

- **Causes of Low Back Pain**
  - Muscle Spasms: most common cause – may be due to:
    - Muscle strength / flexibility imbalance between lower body flexors & extensors
      - Abdominals
      - Hamstrings
      - Erector spinae muscles
      - Quadratus lumborum
      - Piriformis – tight piriformus ➞ sciatic nerve compression ➞ back / leg pain
      - Iliopsoas
      - Gluteal muscle
  - Muscle or connective tissue strains & associated inflammation
  - Herniated disk: disk rupture ➞ fragments of disk impinge upon nerve roots
  - Degenerative disk: protein degeneration in disk core ➞ pinched nerve root

Low Back Pain

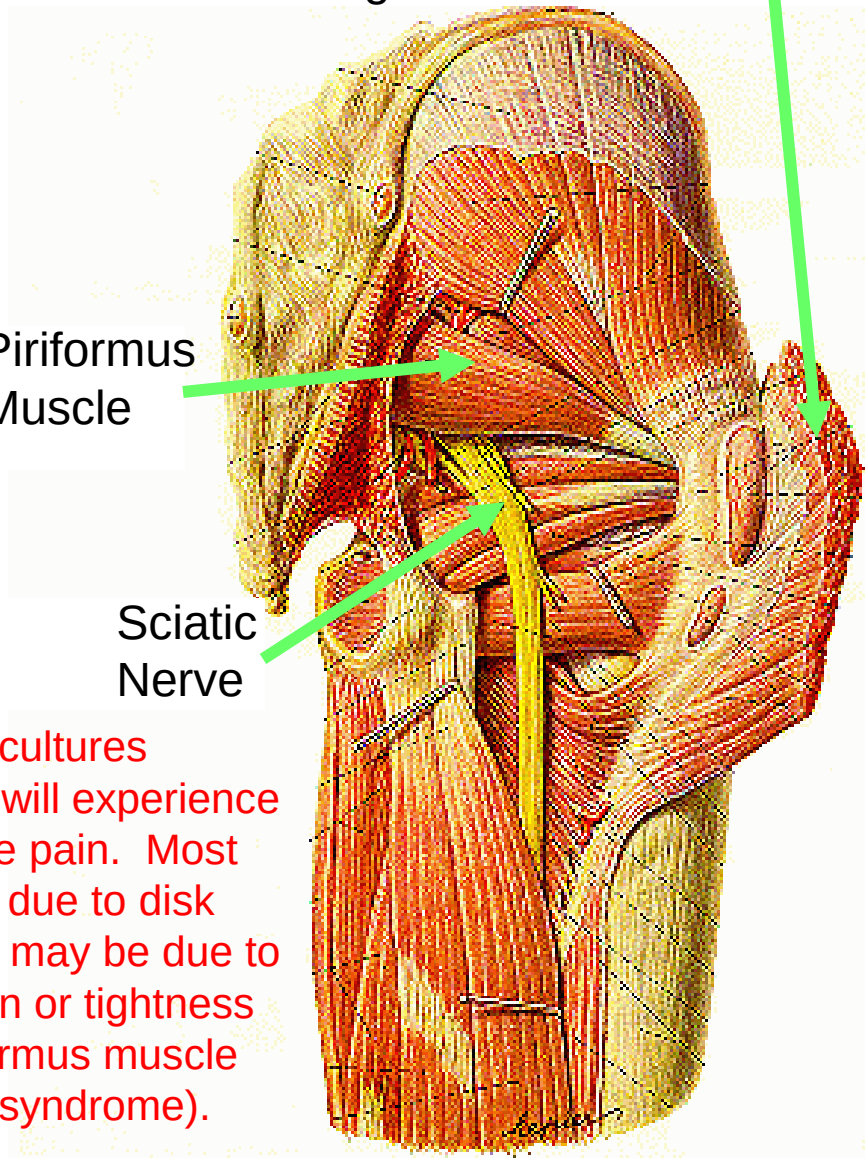
- **Causes of Low Back Pain - continued**
  - Ostoeoarthritis: cartilage breakdown between facet joints ➞ pain
  - Sciatica: compression / inflammation of nerves in lower back ➞ leg / hip pain
    - Most often caused by a herniated disk, spinal stenosis, or piriformus syndrome
  - Osteoporosis: osteoperotic microfracture
  - Spinal Stenosis: openings in the vertebrae are too small for spinal cord
  - Cancer: metastatic disease (tumors rarely originate in the spine)
  - Trauma: such as a car accident or fall
  - Cumulative Trauma Disorder: repetitive awkward movement or lifting ➞ spasm
    - a single awkward or twisting-pulling movement may also initiate a spasm
  - Referred Pain: bladder infections, kidney stones, endometriosis, ovarian cysts and ovarian cancer may all refer pain to the low back.

Muscle Spasms & Back Pain



Muscle Spasms & Back Pain

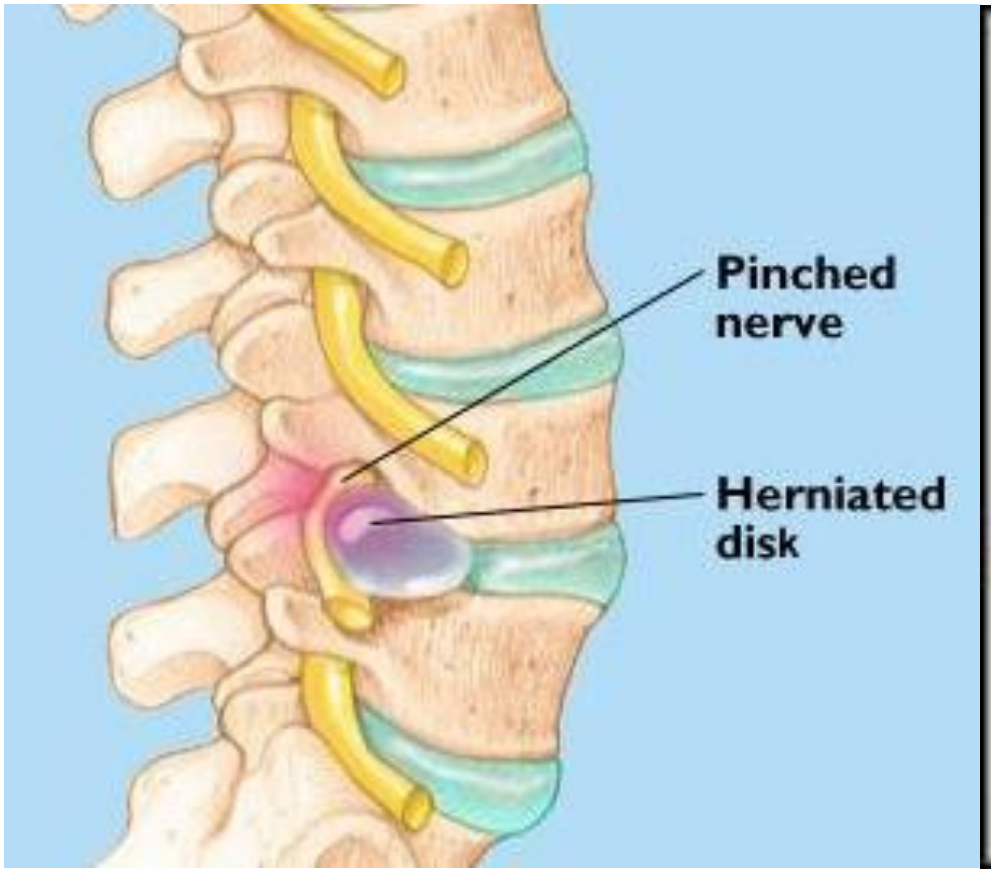
Anterior view of right hip – pelvic area

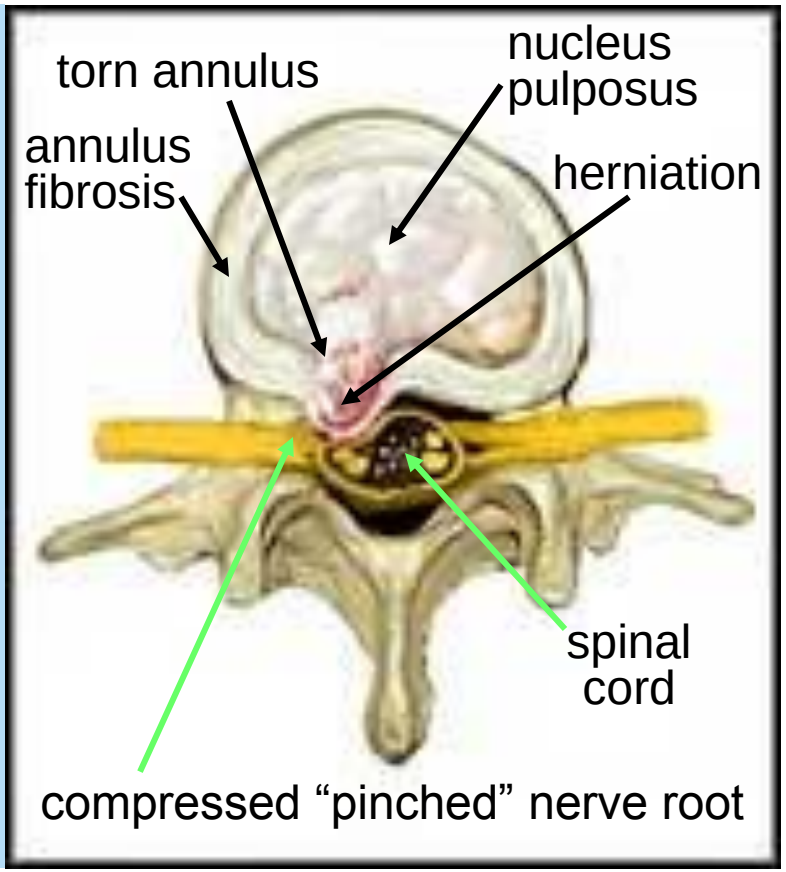


In Western cultures 40% - 50% will experience sciatic nerve pain. Most often this is due to disk disease but may be due to inflammation or tightness of the Piriformus muscle (Piriformus syndrome).

Posterior view of right hip with gluteal muscles retracted

Causes of Low Back Pain

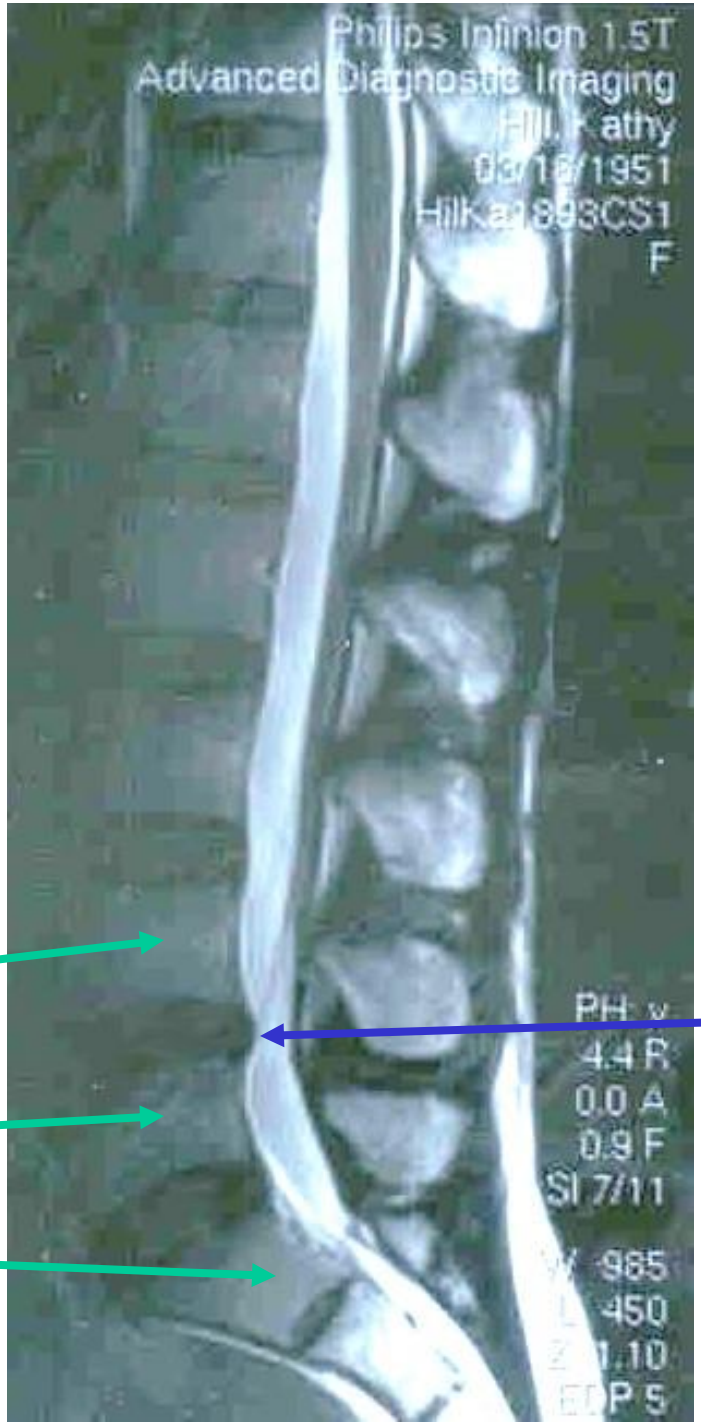




Herniated or “Prolapsed Disk” impinging on a nerve root

Over 90% of herniated discs occur in the lowest two levels of the lumbar spine, between L4 / L5 and L5 / S1

Causes of Low Back Pain



MRI
Left Side View

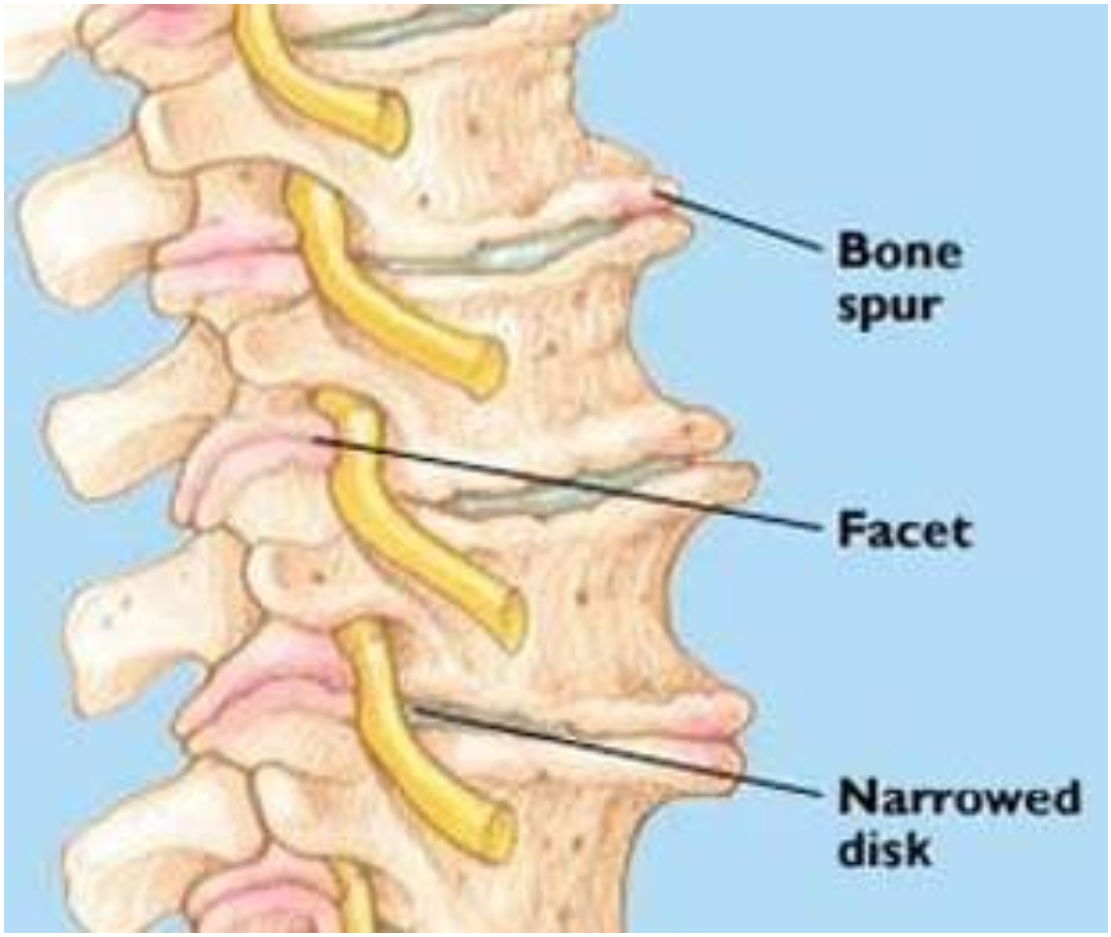
L4

L5

S1

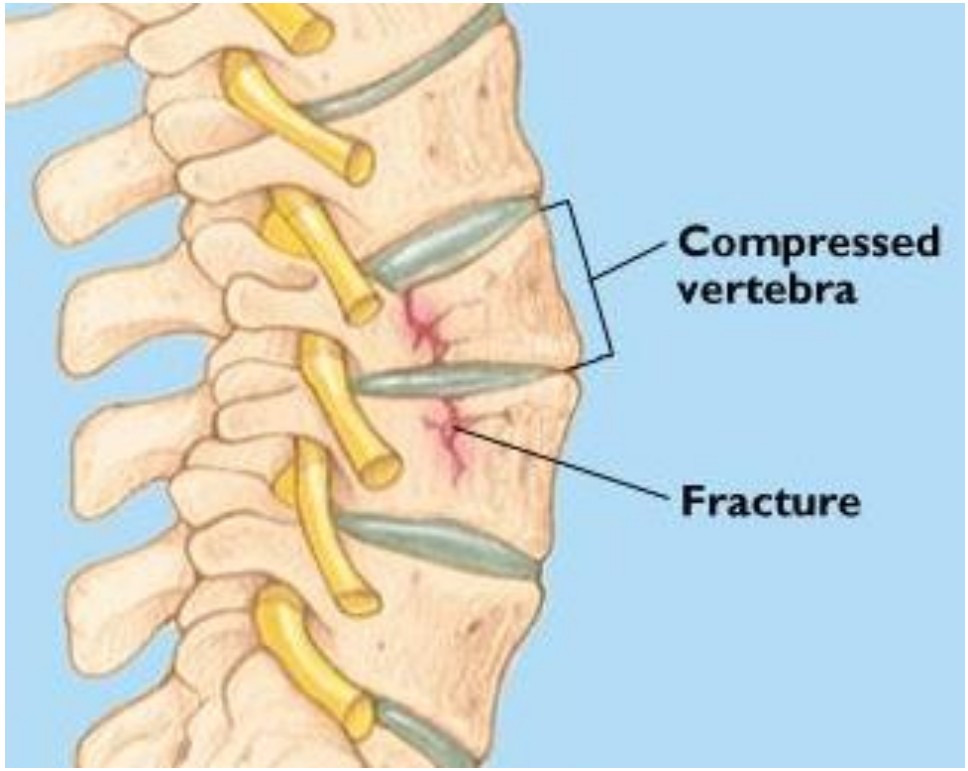
Disk Herniation (Spinal Cord Impingement)

Causes of Low Back Pain

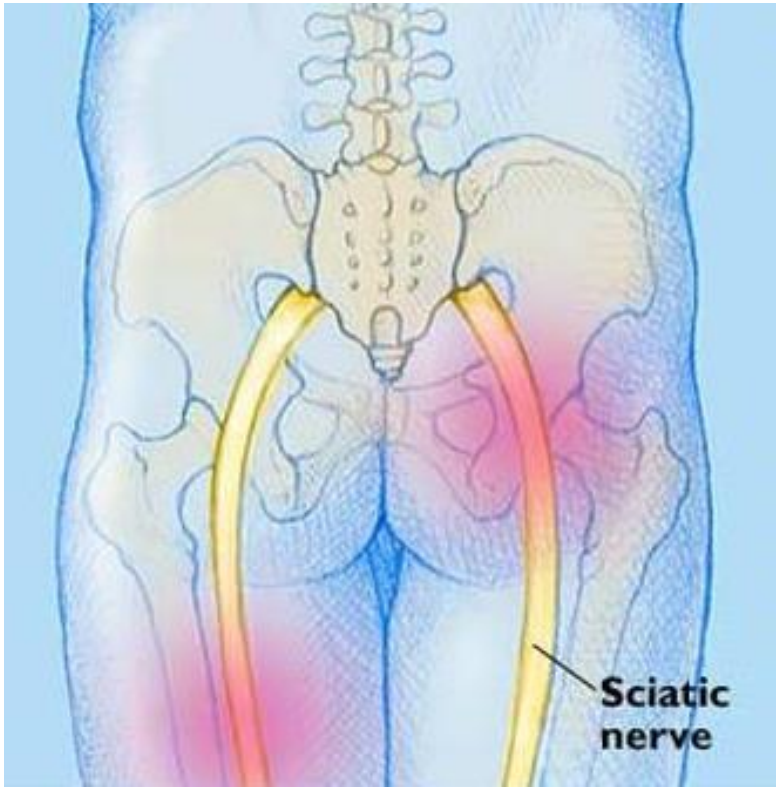


Osteoarthritis - (degenerative arthritis) can cause breakdown of cartilage between the facet joints. When the joints move, the lack of the cartilage causes pain as well as loss of motion and stiffness.

Causes of Low Back Pain



Osteoperotic Micro-fracture



Sciatica

Treatment of Low Back Pain

- 70% of patients will get better in 2 or 3 weeks, treated or untreated
- 90% of patients' pain subsides within 6 weeks, treated or untreated
- 98% of patients' pain subsides within 3 months, treated or untreated

- **Conservative Therapy**
  - Physical therapy: stretching, strengthening, TENS, ultrasound, heat / cold
  - Spinal Manipulation (chiropractic)
  - Iontophoresis: use of electrical current to move steroids through the skin
  - Pharmacolgical agents:
    - NSAID's
    - Muscle relaxers
      - **Soma** - blocks inter-neuron activity in descending reticular formation and spinal cord → sedation → muscles relax
      - **Skelaxin** – depression of CNS due to unknown mechanism → sedation
      - **Flexeril** – ↓ γ & α motor activity → ↓ muscle spasm
    - Narcotics: opioids
    - Antidepressants
    - Anticonvulsants

Treatment of Low Back Pain

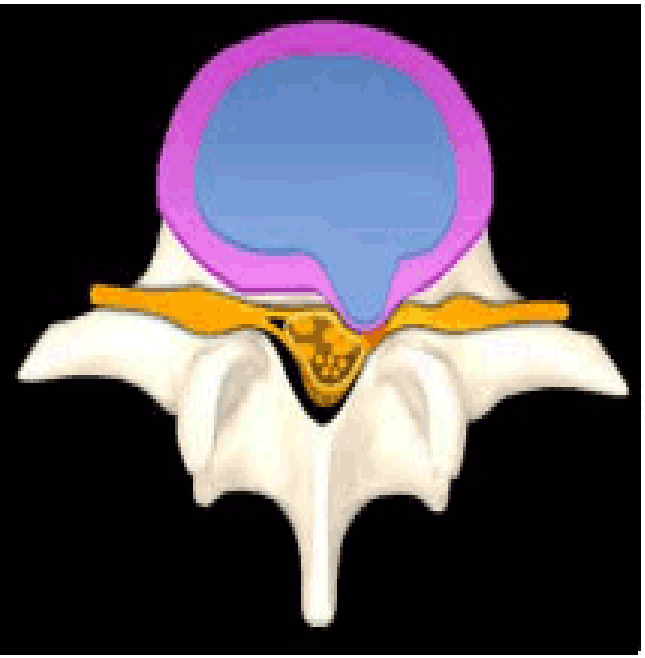
Minimally Invasive Therapy (injections or surgery)

- Steroid Injections into the sheath around nerve root → ↓ inflammation
  - Nerve root blocks done with lidocaine – steroid combination
  - Facet joint blocks done in the same manner
  - These type of procedures usually relive pain temporarily
  - Allows physician to see if that area is indeed the problem area
    - If pain goes away with injection the problem area is located
- Surgery:
  - **Percutaneous Disk Decompression (Nucleoplasty)**
    - Insertion of disk removal instrument into disk
      - laser, radiofrequecy ablation device, or excision instrument
    - Disk material is removed or destroyed creating negative pressure inside disk
    - Herniated portion of disk is “sucked” back into normal disk space
  - **Other minimally invasive procedures are under development**

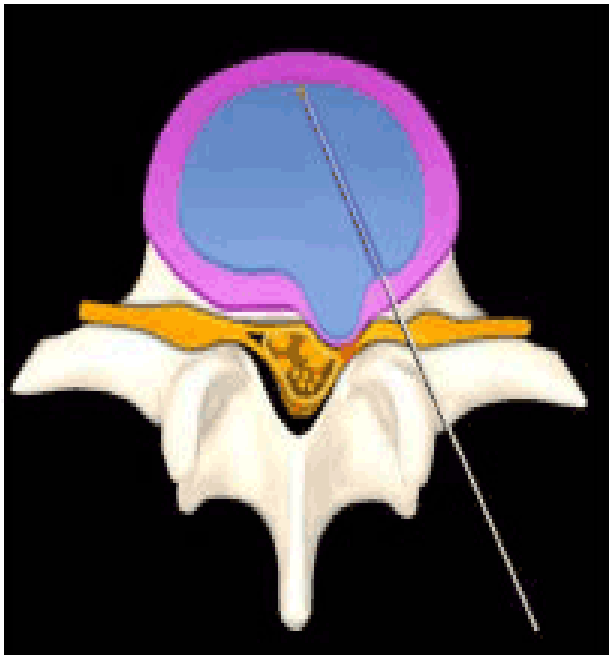
Treatment of Low Back Pain

Decompression Procedure

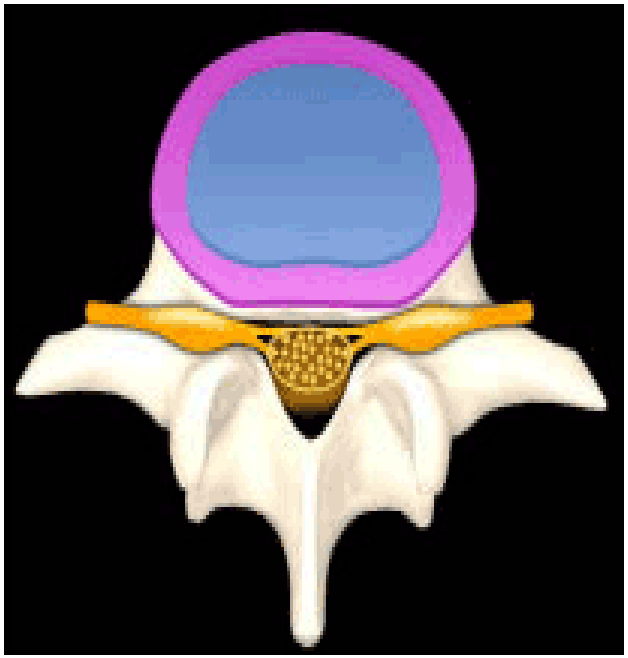
Herniated disk impinging on nerve root



Under sedation and local anesthesia, the introducer needle then the coblation device is introduced into the back. Disk pulp is removed



Nerve root impingement is negated



Treatment of Low Back Pain

Invasive Therapy

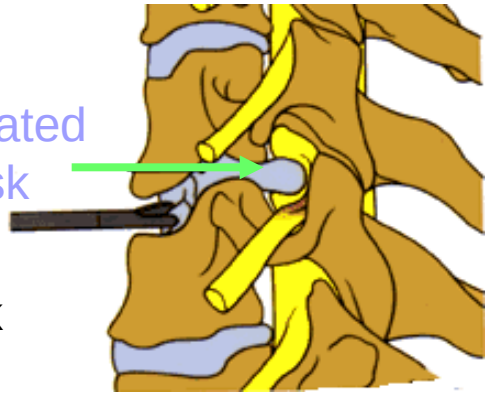
- **Discectomy:** removal of disk – usually accompanied by spinal fusion
  - ↓ compression on nerve root
  - May be done arthroscopically
- **Laminectomy:** ↑ diameter of the spinal canal by lamina removal
  - May be done for cervical stenosis
  - May be done to facilitate discectomy → ↓ compression on nerve root.
- **Perminant Nerve block**
  Destruction of a nerve root(s) by a chemical agent
  (e.g., phenol or alcohol)
- **Neurectomy**
  Surgical excision of a peripheral nerve
- **Rhizotomy**
  Surgical destruction of a certain dorsal nerve roots as they enter the spinal cord
- **Sympathectomy**
  Surgical resection of sympathetic afferent nerve fibers
- **Cordotomy**
  Surgical resection of pain pathway nerves in the spinal-cord
- **Surgical Decompression of cord with Laminectomy + Fusion**

Discectomy (cervical)

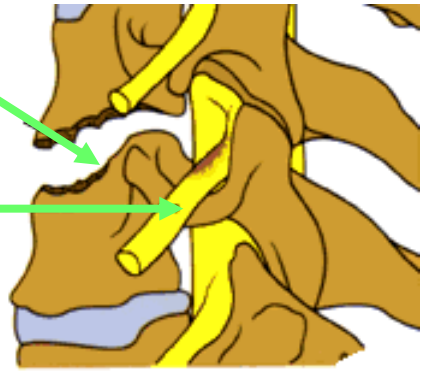
incision is made,

resections are done,

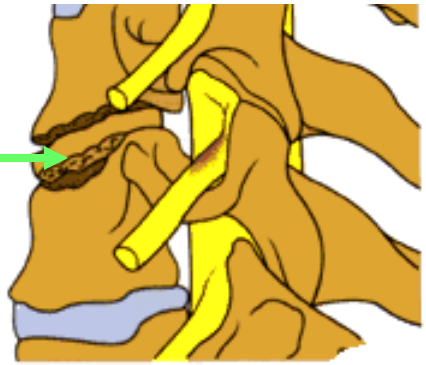
doctor begins to excise disk



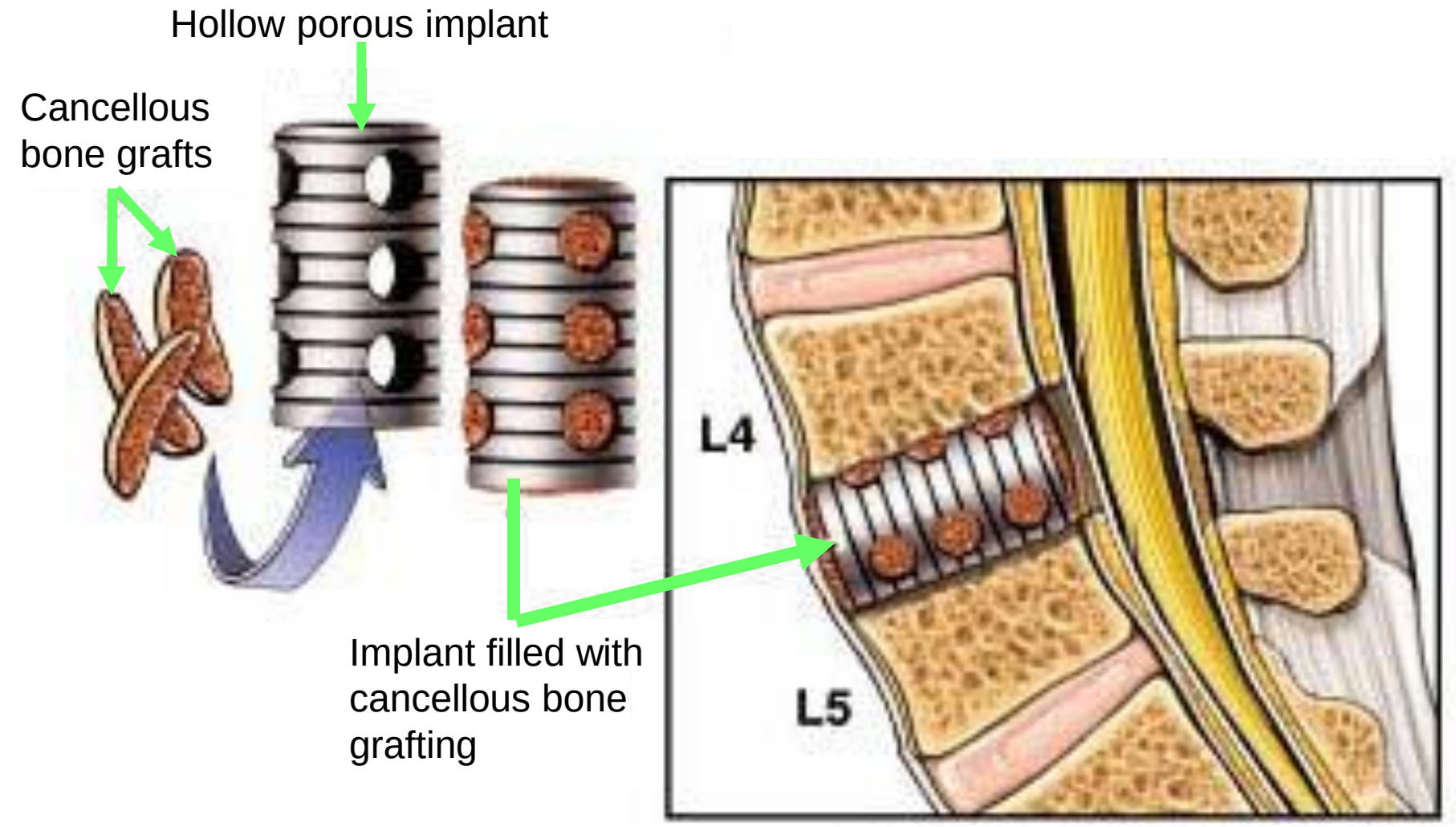
disk is excised



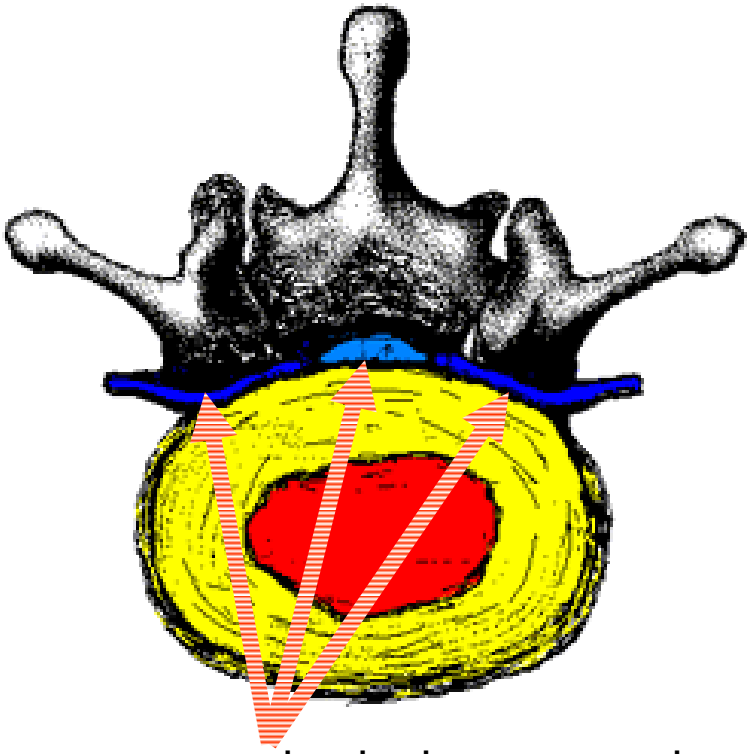
bone graft is inserted
to “fuse” disk



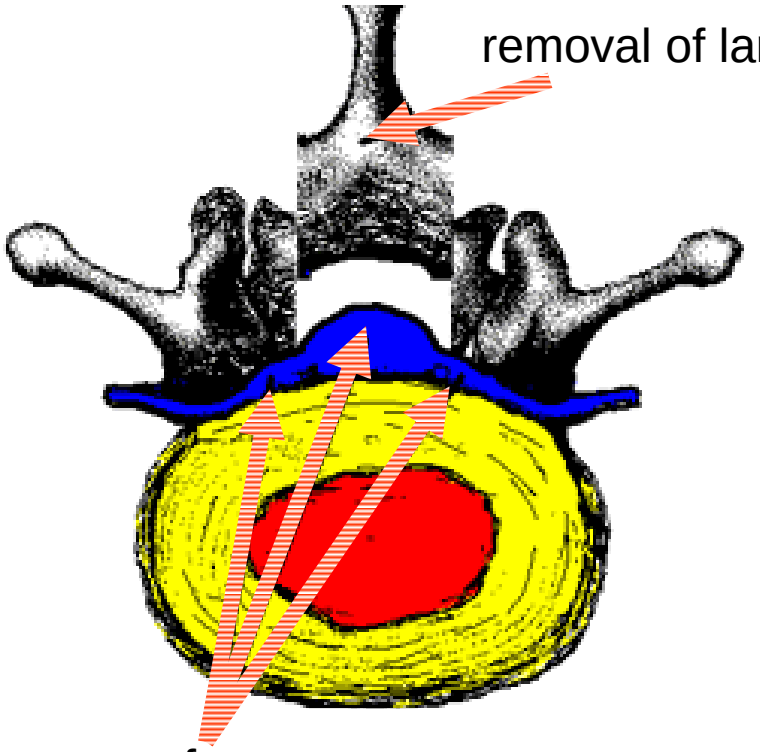
Fusing a Disk Space



Lamenectomy



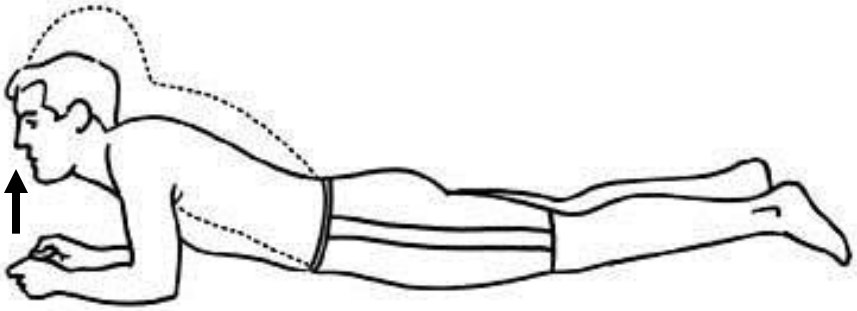
compressed spinal nerves and nerve roots

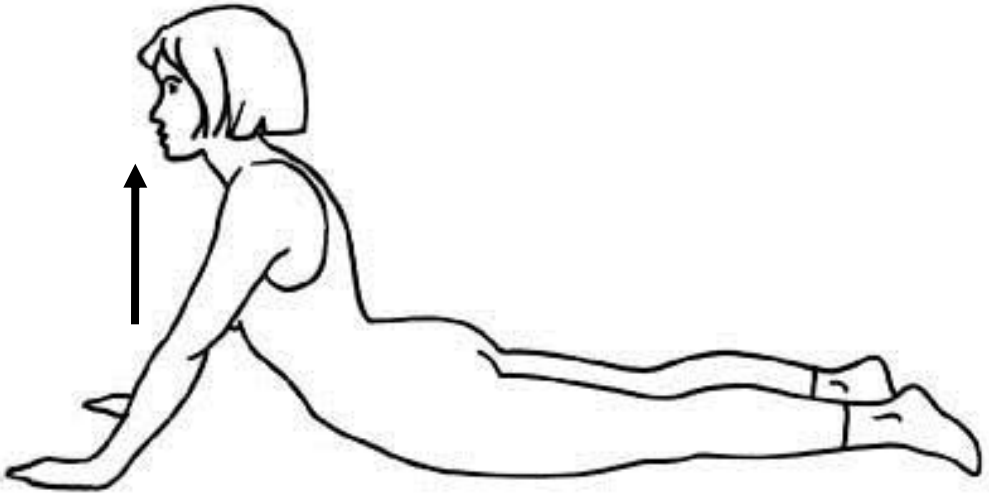


extra space for nerves, nerve roots, and spinal cord

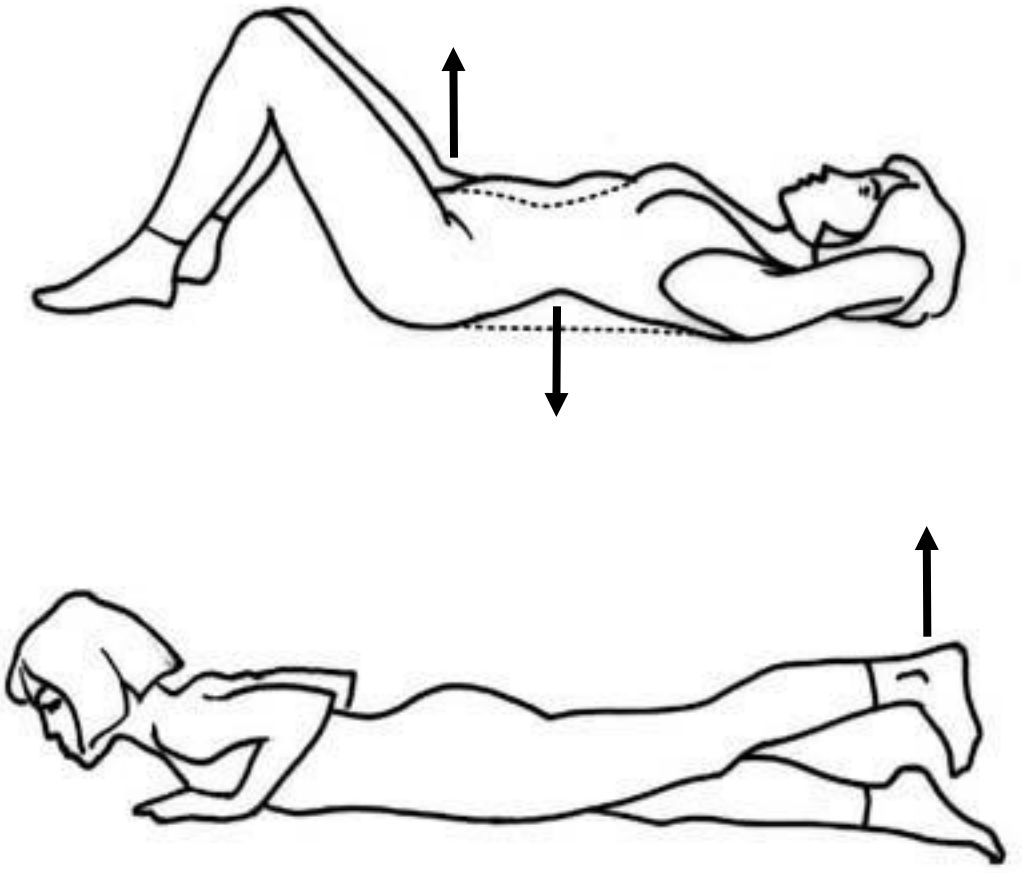
What to do when it hurts

Exercises to Stretch & Strengthen the Back
Mackinzie Approach

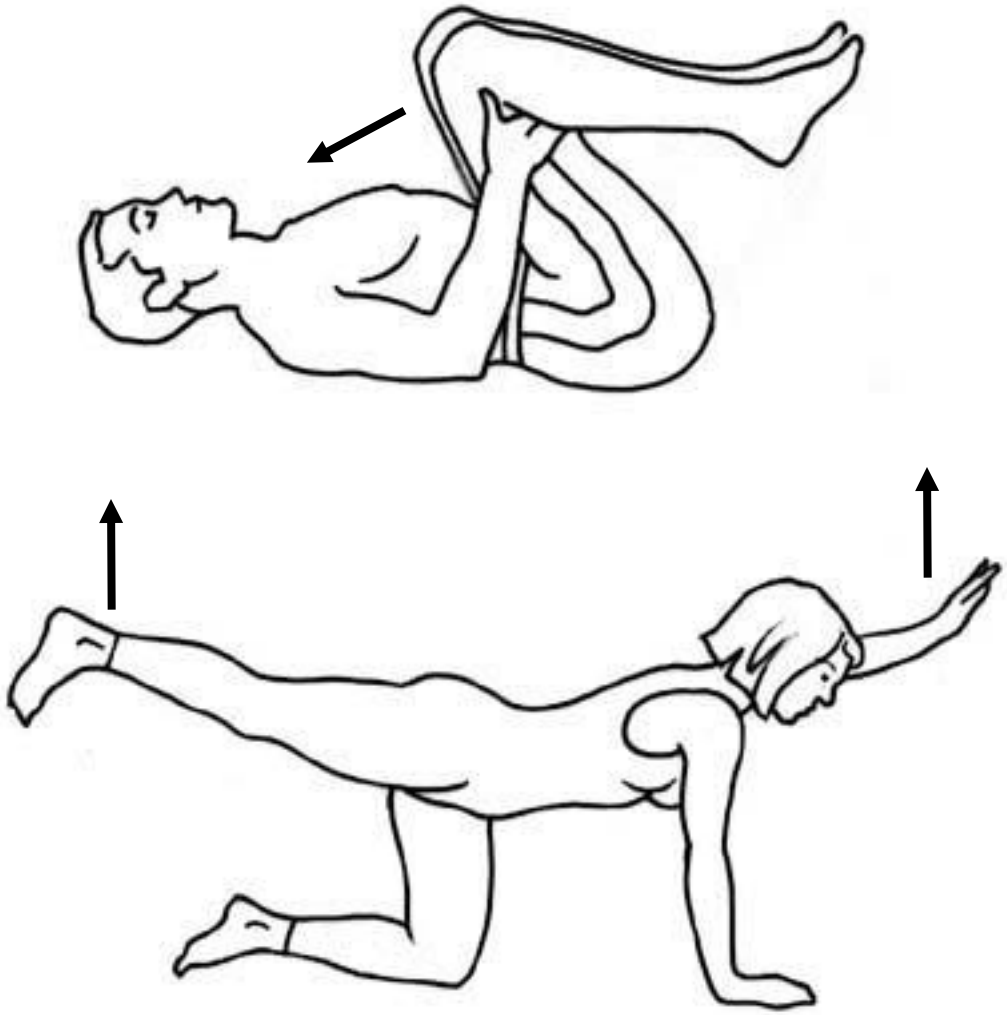




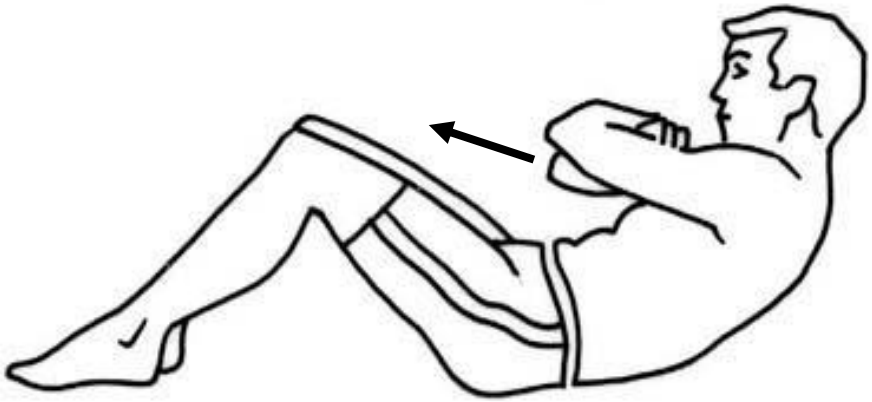
Exercises to Stretch & Strengthen the Back



Exercises to Stretch & Strengthen the Back



Exercises to Stretch & Strengthen the Back



Time Magazine Cover
February 23, 2004

<u>Inflammation</u>: from Latin roots meaning "to set on fire"

Inflammation

- **Inflammation** - a specific response to a non-specific injury or pathology
  - **Purpose:** bring fluid, proteins, cells and other substances to damaged tissues
  - Systemic inflammatory responses are similar, regardless of causality
  - The intensity of the response is proportional to injury or pathology severity
  - Something must cause inflammation
    - Tissue damage, chemical substances, micro-organisms, necrotic tissue……..
    - **Antigen** - substance that induces a state of sensitivity & immune responsiveness
    - **Pathogen** - a disease causing agent

- **Signs of inflammation**
  - Heat, swelling, redness, pain, fever, loss of: mobility, range of motion, function
  - ⬆ erythrocyte sedimentation rate (ESR), ⬆ C-reactive protein (CRP)

- **Function of inflammation - essential for the healing process**
  - Alerts the organism to injury
  - Minimize the spread of pathogens and antigens
  - Restrict tissue damage to smallest possible area
  - Neutralizes or destroys causative agent and removes damage tissue & debris
  - Prepares injured area for the healing process & initiates repair

Relative sequence of inflammation events: (superficial injury example)

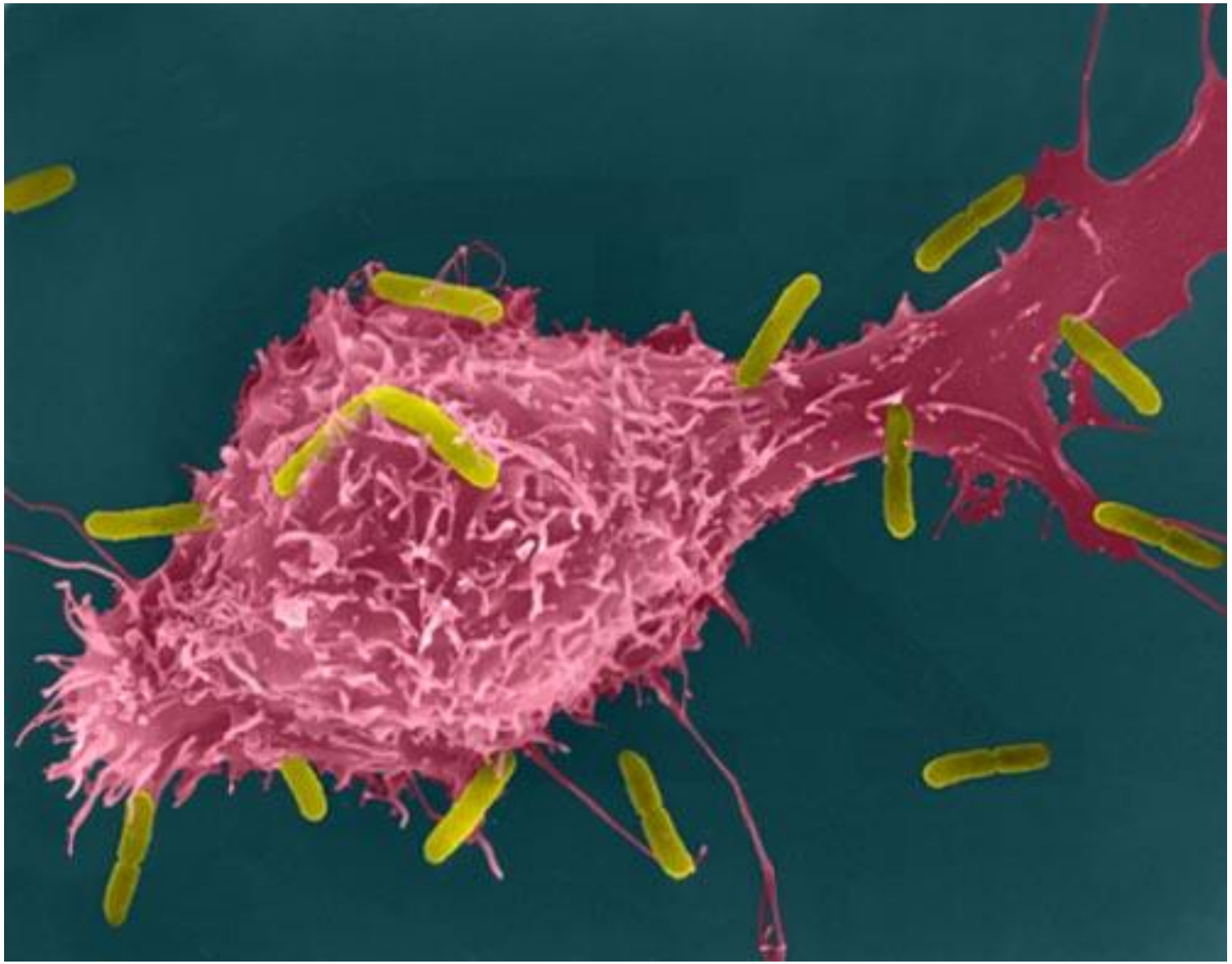
1. Momentary vasoconstriction (*reflex*) then vasodilation of arterioles ➞ ↑ blood and pressure in the area **(Hyperemia)**
1. **Antibodies** and **Compliment System Proteins** are present in tissues and bind to the **antigen** (bacteria for example)
1. Antigen **+** injured tissue activate **Comp.Sys.** ➞ antigen destruction + ↑ inflammatory mediators **(Chemotaxis)**
1. Platelets release histamine, serotonin, coagulation factors, and lysosomal enzymes
1. **Macrophages** already in injured tissue respond to signals given off by antigen and engulf it
1. Macrophages release Cytokines ➞ ↑ vascular permeability, fever + **activated endothelium** ➞ **Tissue Factor**
1. Tissue Factor (**Hageman Factor**) + **activated endothelium** ➞ **Thrombin** & **Fibrin (Pro-Coagulatory State)**
1. Capillary **Fibrinogen** + endothelial derived Thrombin and Fibrin ➞ Fibrin mesh in **tissues** & **lymph spaces**

   This results in a **" walling off "** of the injured area preventing the spread of the antigen
1. Mast cells release Histamine **+** capillary endothelial cells release NO ➞ swelling begins with **Transudate fluid**

   Transudate fluid serves to dilute toxins released by bacteria and other noxious agents
2. **Inflammatory Mediators (mainly TNF-α),** toxins, or burned tissue ➞ ↑ capillary endothelial permeability

   ↑ capillary permeability ➞ **Exudate fluid** proteins leak into injury ➞ ↑ osmolarity at injury ➞ ↑ fluid at injury
2. Exudate contains **Immunoglobulins** which mark antigens for phagocytosis – this is called **Opsonization**
2. In response to chemotaxis **Neutrophils** arrive: phagocytosis + release of chlorine, peroxide, & leukotrienes
2. **T-Lymphocytes** arrive and are activated by Macrophages ➞ cytokine & antigen damaging enzyme release
2. Cytokines stimulate & recruit Macrophages & activate **B-Lymphocytes**
2. **B-cells** engulf & digest antigen + participate in antibody production
3. Monocytes / macrophages (ones not already in the tissues) arrive after about 5 hours
4. Phagocytosis of pathogens & dead cells continue ➞ area eventually cleared of debris & healing begins

Macrophage (red structure) attacking E-coli bacteria



Leukocyte migration into injured cell

Selectin, ICAM PECAM: cell adhesion molecules produced by damaged endothelium

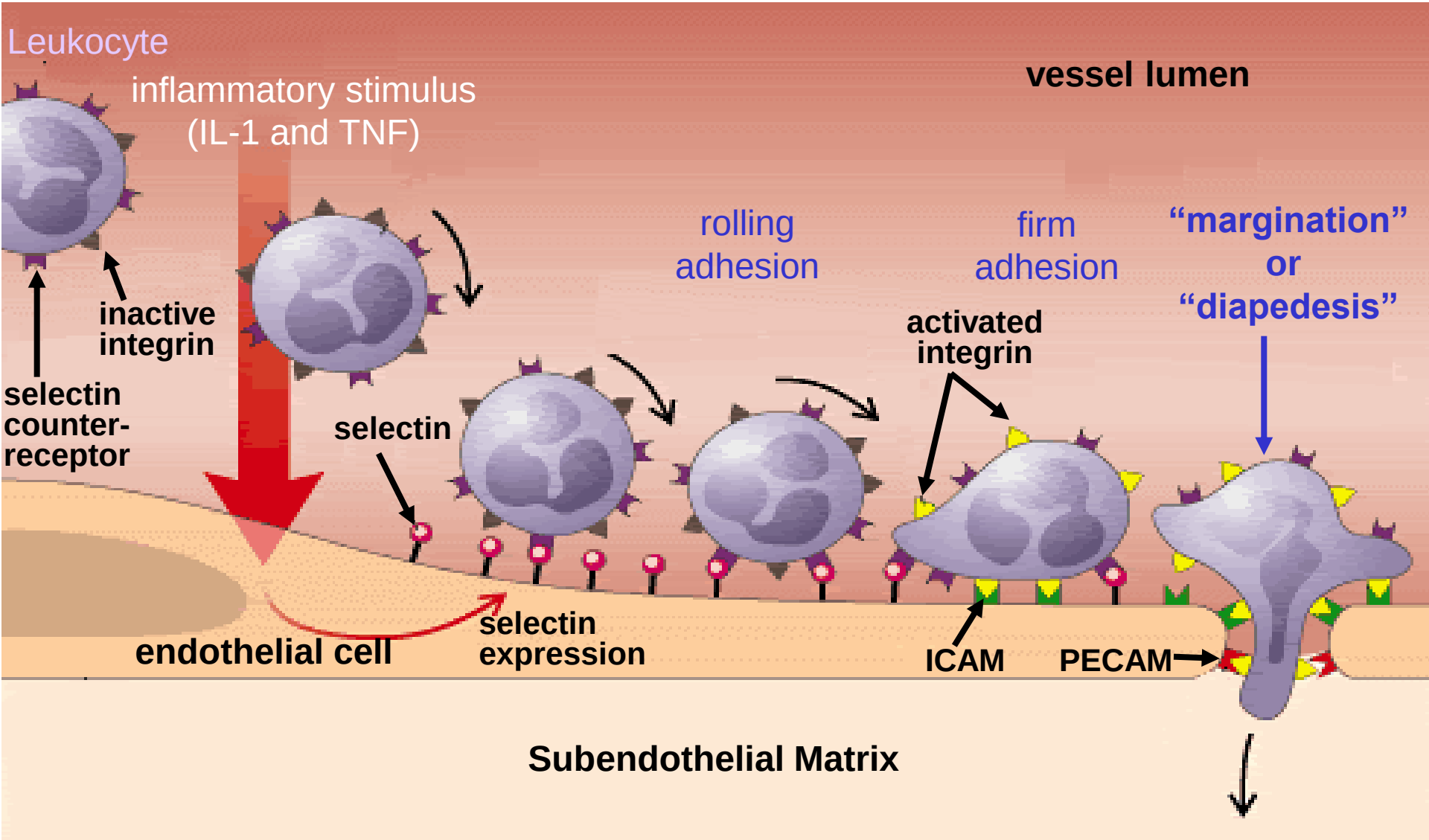
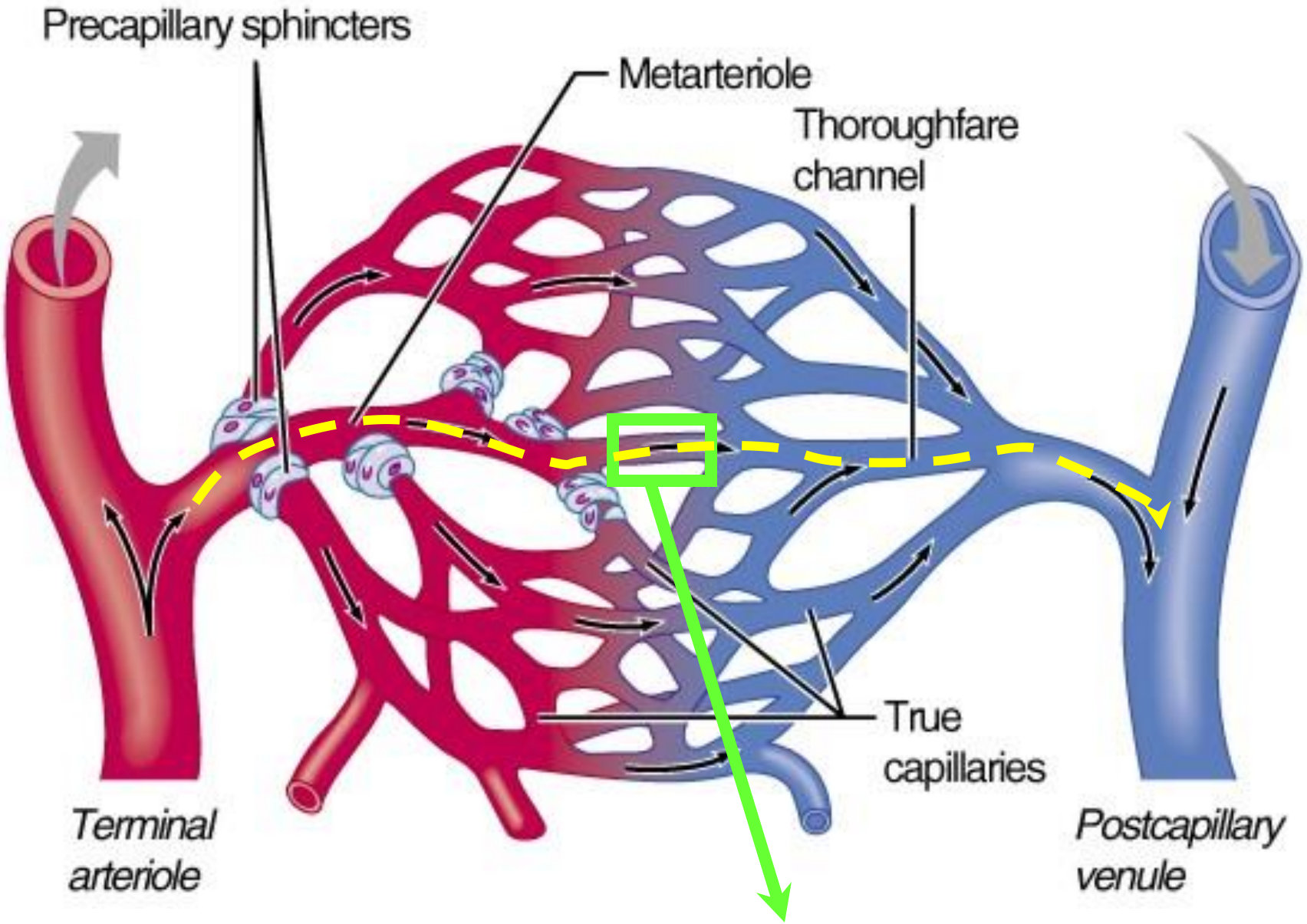
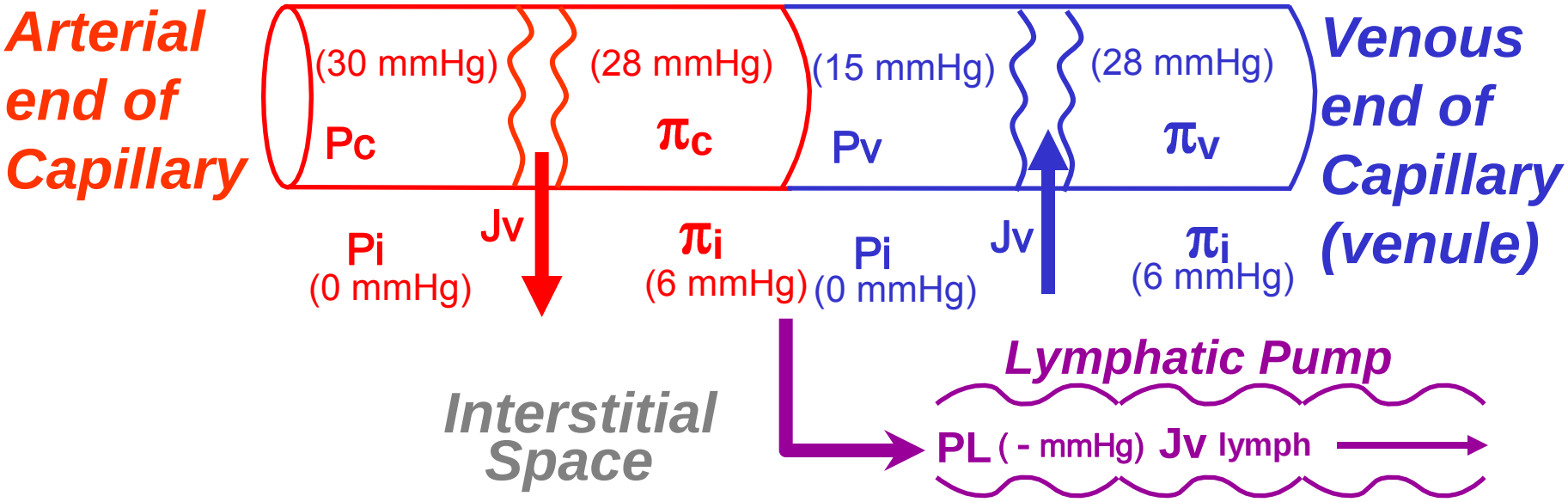


Illustration of a Vascular Bed



Capillary & Venule Filtration / Absorption and Lymph Flow



negative pressure created by the lymphatic pumps – eventually dumps 1/10th of the filtrate material into subclavian veins. (only route for proteins)

$$Jv \cong Fc/v \times S \times [(Pc/v - Pi) - (\pi c/v - \pi i)]$$

$$Jv_{lymph} \cong Fc \times S \times (Pi - PL)$$

Note: the values for these equations alter with body position

- **Jv** = filtration / absorption flow (represented by the red & blue arrows)
- **Fc / v** = filtration constant (higher in fenestrated cap. or ↑ by histamine)
- **S** = surface area (in skeletal muscle, S ↑ 7 X during exercise)
- **Pc / v** = capillary / venule hydrostatic (pushing) pressure (mmHg)
- **Pi** = interstitial hydrostatic (pushing) pressure (mmHg)
- **PL** = lymphatic hydrostatic pressure (mmHg)
- **πc / v** = capillary / venule oncotic (sucking) pressure (mmHg)
- **πi** = interstitial oncotic (sucking) pressure (mmHg)
- **Jv_{lymph}** = lymphatic flow rate (ml / min / 100 grams of tissue)

Capillary & Venule Filtration / Absorption and Lymph Flow

Normal

$$Jv \cong Fc \times S \times [(Pc - Pi) - (\pi c - \pi i)]$$

$$[(30 - 0) - (28 - 6)]$$

$$8$$

8 mmHg net hydrostatic pressure pushing fluid out of arterial end

$$Jv \cong Fv \times S \times [(Pv - Pi) - (\pi v - \pi i)]$$

$$[(15 - 0) - (28 - 6)]$$

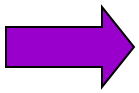
$$-7$$

-7 mmHg net oncotic pressure sucking fluid back in to venous end

---

Injury

Cuts
Burns
Bruises



Pc ↓, Pi ↑, πc ↓, πi ↑, **Fc** ↑, net result: ↑ **Jv** → edema

$$Jv \cong \uparrow Fc \times S \times [(Pc - Pi) - (\pi c - \pi i)]$$

$$[(25 - 5) - (15 - 11)]$$

$$16$$

Similar results occur when venule end is injured but usually both are injured concurrently resulting in a net ↑ in **Jv** outward → edema.

$$Jv \cong \uparrow Fv \times S \times [(Pv - Pi) - (\pi v - \pi i)]$$

$$[(10 - 5) - (12 - 11)]$$

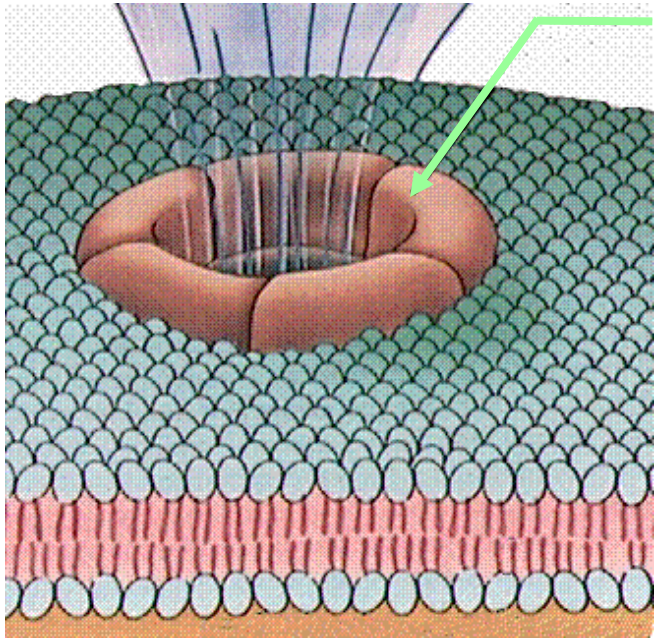
$$4$$

Physiological Sequelae of Injury & Inflammation

- **Edema:** the buildup of excess fluid in the extracellular spaces - occurs in 2 stages
  - **Transudate** - fluid transfer as result of primarily hydrostatic forces
    - Injury + early acting inflammatory mediators → arteriolar dilation → ↑ fluid
    - Less viscous and fewer cellular components than exudate fluid
  - **Exudate** - fluid accumulation that penetrates through tissues
    - More cells, proteins, & solid materials than transudate fluid
    - Drained away by lymphatics which help limit the extent of edema in inflammation
  - Collagen deposition is ↑ in edematous area if edema remains uncontrolled:
    - ↑ fibrosis and joint contractures
    - ↑ stiffness & ↓ range of motion
    - Tissue atrophy
- **Selected Non-injury (disease) causes of edema**
  - Renal disease: proteins lost in urine + ↑Na^+ retention → ↓ **πc** + ↑ Pc → ↑ edema
  - Liver disease: ↓ production of plasma proteins → ↓ **πc** → ↑ edema
  - Heart failure: ↓ $\dot{Q}$ → ↑ Pc and ↑ Pv in periphery → edema
  - Heart failure → ↓ flow of blood to kidney → ↑ Na^+ retention → ↑ Pc in periphery → edema
    - **(the renal system tries to maintain blood pressure by ↑ blood volume)**
  - Starvation: ↓↓ protein intake → ↓ **πc** (starved kids: “kwashiorkor” “ascites” swollen bellies)
  - Allergic reactions: ↑↑ histamine → ↑↑ vasodilation + ↑ Fv and ↑ Fc → edema
  - Cyclic edema: pre-menstrual retention of H_2O → ↑ Pc in perphery → edema

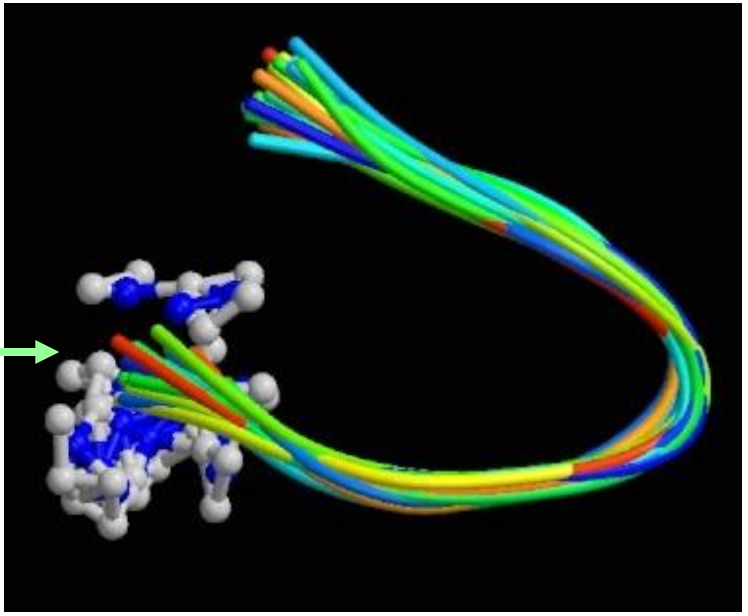
Mediators of Inflammation

- **Compliment system** – immune system activated proteins
- (C1-C9, B, D, + subtypes)
- "Cascade" System (activation of one C-protein ➞ activation of the next)
  - C3a, C4a, C5a subtypes:
    - ↑ vascular permeability, activate mast cells ➞ histamine & heparin release
  - C3b C4b causes opsonization (marking a foreign particle for phagocytosis)
  - C5a is substance that functions in chemotaxis
  - C5b leads to production of membrane attack complexes using C6-C9
    - membranes of antigen cells are compromised ➞ lysis



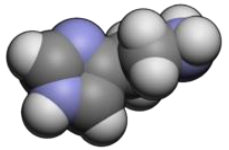
membrane attack complex allowing salt and other interstitial substances into cell causing it to lyse

structure of a complement protein

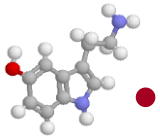


Mediators of Inflammation

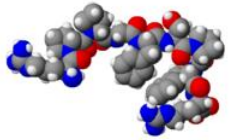
- **Histamine** - primary mediator of the early inflammatory response
  - Synthesized in liver – circulates in plasma in inactive forms
  - Located in mast cells, platelets, & basophils
    - Mast cells located just below epithelia and around blood vessels
  - Causes pain, vasodilation, bronchiole constriction, & secretion of gastric HCL
  - Also causes ↑ capillary permeability → edema & swelling



- **Serotonin** - neurotransmitter that is also a primary inflammatory mediator
  - Also known as **5-hydroxytriptamine or 5-HT**
    - Involved in appetite, anger, aggression, mood, sleep, sexuality, **anxiety**, **depression**
  - Secreted by mast cells, GI mucosa, and PAF stimulated platelets
  - Excites pain receptors, ↑ vasoconstriction, ↑ vascular platelet aggregation
  - Induces arachadonic acid production



- **Bradykinin** - polypeptide present in the blood – ↑ vascular permeability
  - Most powerful stimulator of pain receptors (most potent nociceptive agent)
    - Bee venom is mostly bradykinin
  - Hageman factor (clotting factor XII) → ↑ kallikrein → ↑ kininogen → ↑ bradykinin



(Note here one of many links among clotting, pain, and inflammation)

Complement system activation

Pain

Mediators of Inflammation

- **Eicosanoids – products of the Arachadonic Acid Cascade**
  - **Prostaglandins** - arachidonic acid metabolite
    - Released by damaged cells and nearby macrophages
    - Cause dilation of blood vessels and leakage of fluid into surrounding tissues
    - Both excites and enhances the sensitivity of pain receptors
    - Play a role in slow suffering type of pain that accompanies tissue injury
  - **Prostacyclin** - arachidonic acid metabolite
    - Relaxes blood vessels and bronchial tubes
    - Prevents platelet aggregation
  - **Leukotrienes** – arachadonic acid metabolite that is also released by neutrophils
    - Causes chemotaxis (summoning) of neutrophils
    - ↑ vascular permeability
    - Extremely potent bronchoconstrictors and vasodilators
      - Play a role in anaphylaxis (hypersensitivity reactions)
    - Implicated in the inflammation associated with:
      - Asthma: ↑ bronchoconstriction, ↑ mucous formation, ↑ airway inflammation
      - Rheumatoid arthritis, psoriasis, and chronic inflammatory bowel disease (IBS)
  - **Thromboxanes**
    - Cause vasoconstriction
    - ↑ platelet aggregation

Mediators of Inflammation

- **Free Radicals:** oxidizing agents – atoms or molecules with unpaired electrons
  - "Reactive oxygen species" or "oxidants" : removes e^-'s from other substances
    - Examples: Hydrogen peroxide (H_2O_2), hydroxyl radical (OH), superoxide anion ($O2^-$)
  - Produced in normal metabolism
    - Oxygen gains electrons (is reduced) in ET chain in mitochondria ➞ oxidant production
  - Produced by phagocytotic cells (especially neutrophils) to kill antigens
  - Released in excess by macrophages in chronic inflammation ➞ cell damage
  - Normally kept in check (oxidants + antioxidants = innocuous products like water)
    - Natural endogenous antioxidants:
      - Glutathione peroxidase, superoxide dismutase, alphalipoic acid, CoQ10
    - Nutrient antioxidants
      - Vitamins C & E, selenium, bioflavinoids **(supplementation effectiveness ???)**
  - Production **>** neutralization ➞ excess oxidation in cells ➞ cell death (apoptosis)
    - Called "oxidative stress"
      - **Lipid peroxidation** in cell membranes ➞ atherosclerosis

        The process whereby free radicals "steal" electrons from the lipids in cell membranes, resulting in endothelial cell damage ➞ atherosclerosis.
      - Excess oxidation of nucleic acids (DNA) ➞ mutations ➞ cancer
      - Also implicated in aging, alcoholic liver damage, smoking related emphysema, Parkinson's disease, Alzheimers, schizophrenia, MS, ALS……

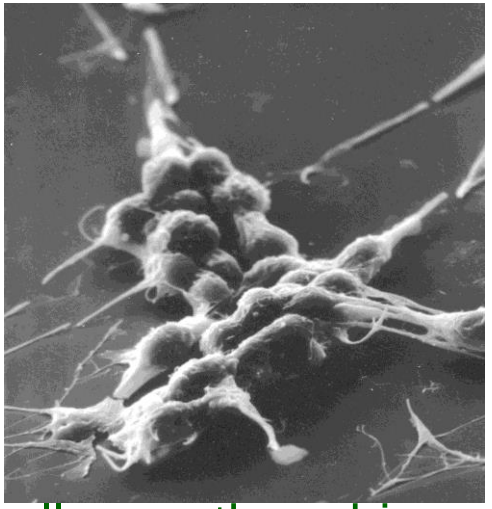
Mediators of Inflammation

- **Cytokines** – polypeptides produced by macrophages
  - **Tumor Necrosis Factor** – released by macrophages
    - Pyrogen
    - Activates other macrophages
    - Causes vascular endothelial cell retraction (↑ vascular permeability → exudate)
    - **Contributes to rheumatoid and other autoimmune diseases**
  - **Interlukins** – stimulates and enhances immune functions
    - IL1 →↑ monocyte activation/production and chemotxais of neutrophils and lymphocytes
    - IL1 → causes vascular endothelial cell retraction (↑ permeability) and is a pyrogen
    - **Increasingly implicated in the development of autoimmune diseases**
  - **Platelet Derived Growth Factor** – ↑ fibroblasts in the area, ↑ angiogenesis
  - **Interferons** – virus fighters that may play a role in fighting certain cancers

- **Nitric Oxide** (NO) – locally synthesized in endothelium & macrophages
  - ↑ vascular dilation & permeability (Nitric Oxide is also known as EDRF)
  - Plays a role in the killing of harmful cell bacteria
  - NO is the product produced in coronary arteries as a result of taking nitroglycerin
  - E_2 loss in menopause linked to ↓ amounts of endogenous NO → ↑ risk for CAD

Mediators of Inflammation

- **Platelets** – anuclear disk shaped cells that, when **"activated"**, release:
  - Lysozomes – organelles that contain digestive enzymes
  - ADP, ATP, Serotonin, Histamine
  - Fibrinogen, Thrombin, & Clotting Factor V
  - Von Willebrand Factor – helps platelets bind to collagen
  - PAF and phopholipase A2 ➞ Thromboxane A2
    - PAF and thromboxane A2 "activate" other platelets
  - Cytokines and chemokines ➞ chemotaxis of neutrophils



- Platelets are **"activated"** when thy come in contact with collagen, thrombin thromboxane A2, ADP, and each other
  - Activated platelets adhere to one another via integrins (adhesion receptors)
    - Platelet aggregation
  - Activated platelets adhere to endothelial cells in vessel walls
  - Activated platelets form irradiating arms called pseudopods
  - Activated platelets & fibrin form a **"platelet plug"** repair in damaged vessel walls
- Platelets contain actin and myosin filaments which contract during aggregation helping to re-enforce the platelet plug and close a small wound
  - **Note relationship of coagulation, inflammation, & healing with platelets)**

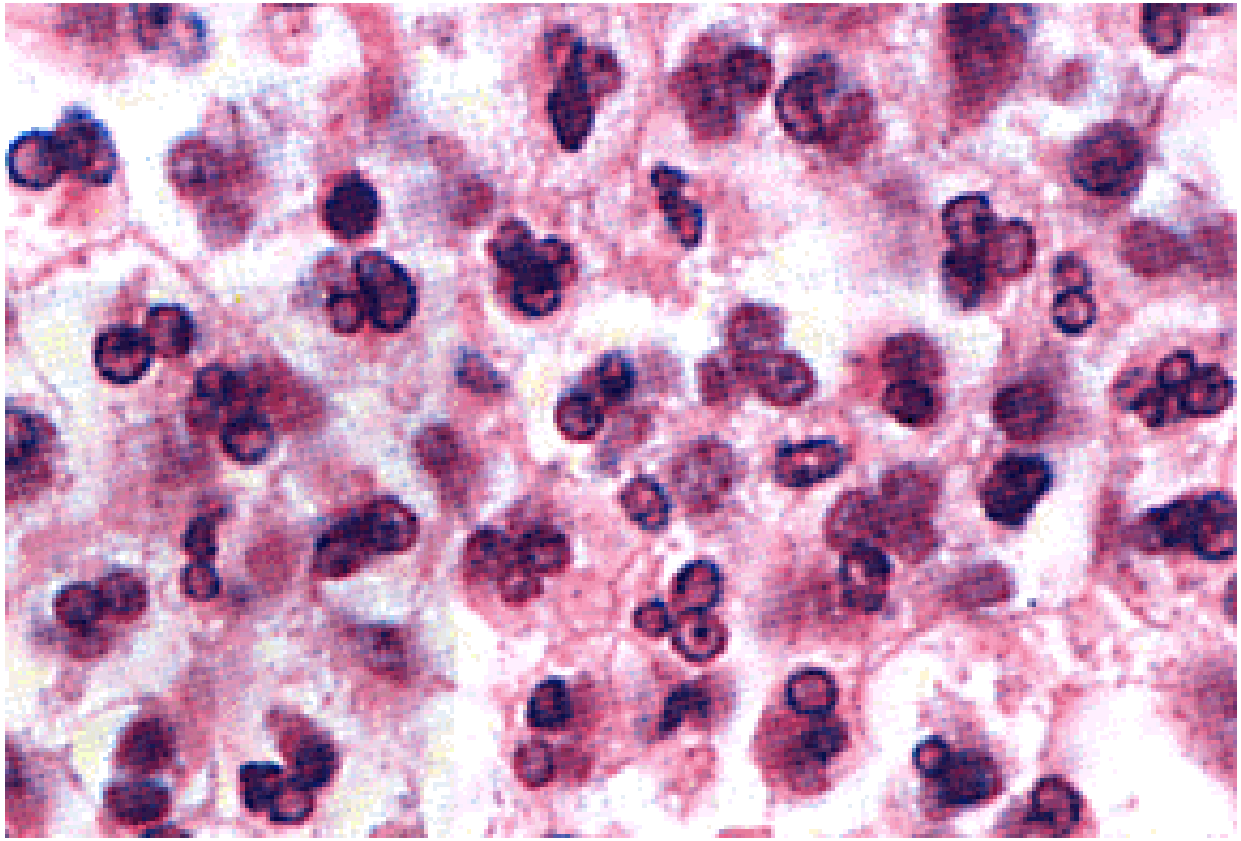
A platelet:

note “granules” containing inflammatory mediators

Chronic Inflammation

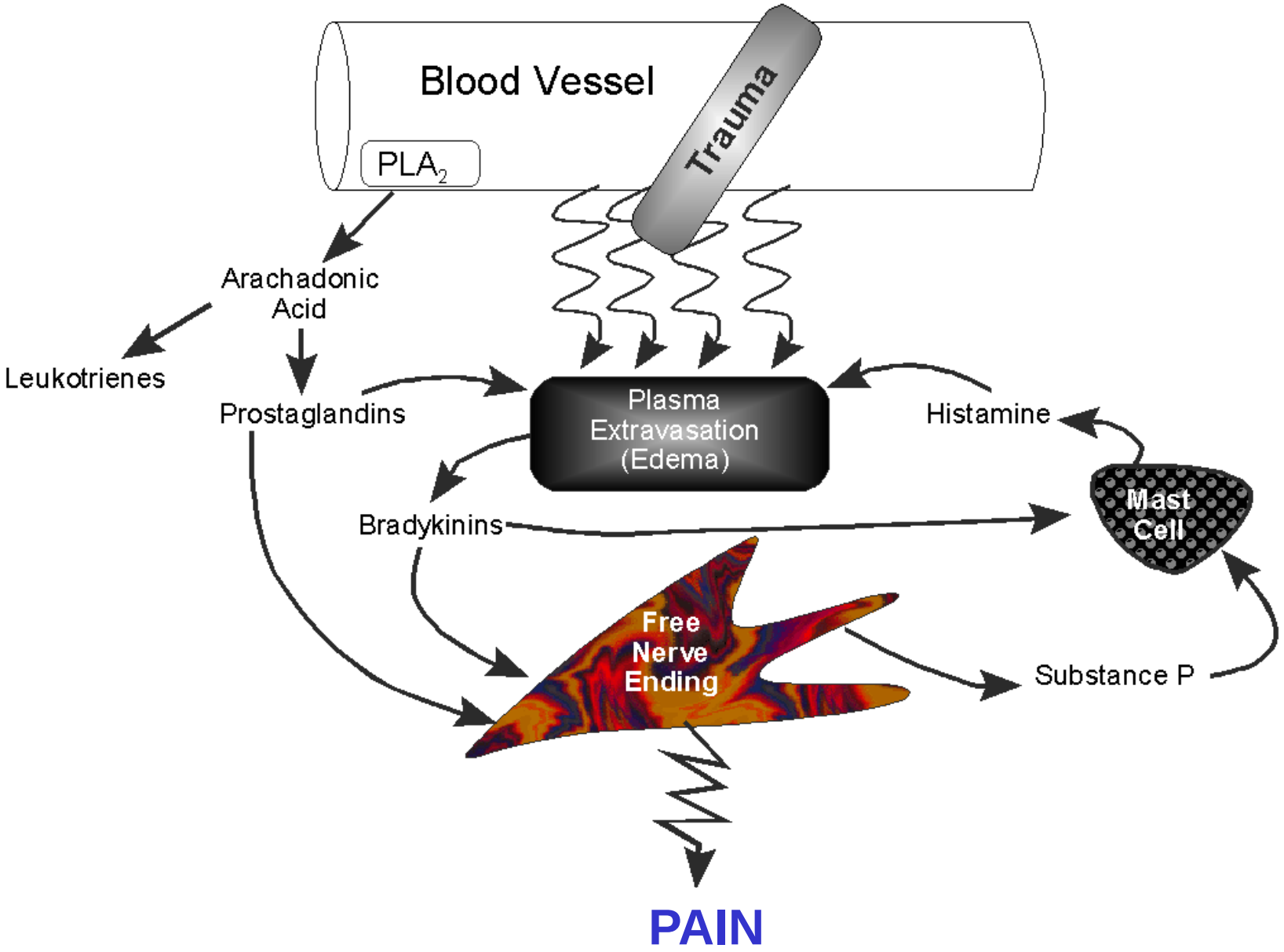
- **Acute Inflammation is resolved (or perpetuated) in 1 of 3 ways:**
  - Healing process takes place tissue regenerates (rare) or a scar forms (likely)
  - Inflammation progresses and suppurative (pus forming) processes begin
  - The inflammation becomes **chronic** (subsides or eases then returns)
- **Suppurative Processes**
  - Toxins are secreted from bacteria, neutrophils and macrophages + tissue ischemia
    - This results in excess tissue destruction & necrosis
  - As bacteria & immune cells die near dead tissue, pus begins to form **(abscess)**
    - Abscess prevents antigens from spreading via fibrin, fibrinogen, & thrombin pocket
  - Abscesses may drain through skin, be absorbed by tissues, or drained surgically
- **Chronic Inflammation**
  - Initiated by:
    - Excessive **MICROTRAUMA** to muscles and connective tissues
    - Asbestos and other non-living foreign material that cannot be dissolved by the body
    - Bacteria & viruses that avoid and resist host defenses (TB, mycobacteria, fungi)
    - Altered tissues or tissue displacement in or around tumors
  - **Possible Fibroblast proliferation → fibrosis→↑ risk of scarring & loss of tissue function**
  - Exact cause of many chronic inflammation disorders is not known
    - may have to do with immunological responses

Magnification of Supporative cells (pus) in acute appendicitis

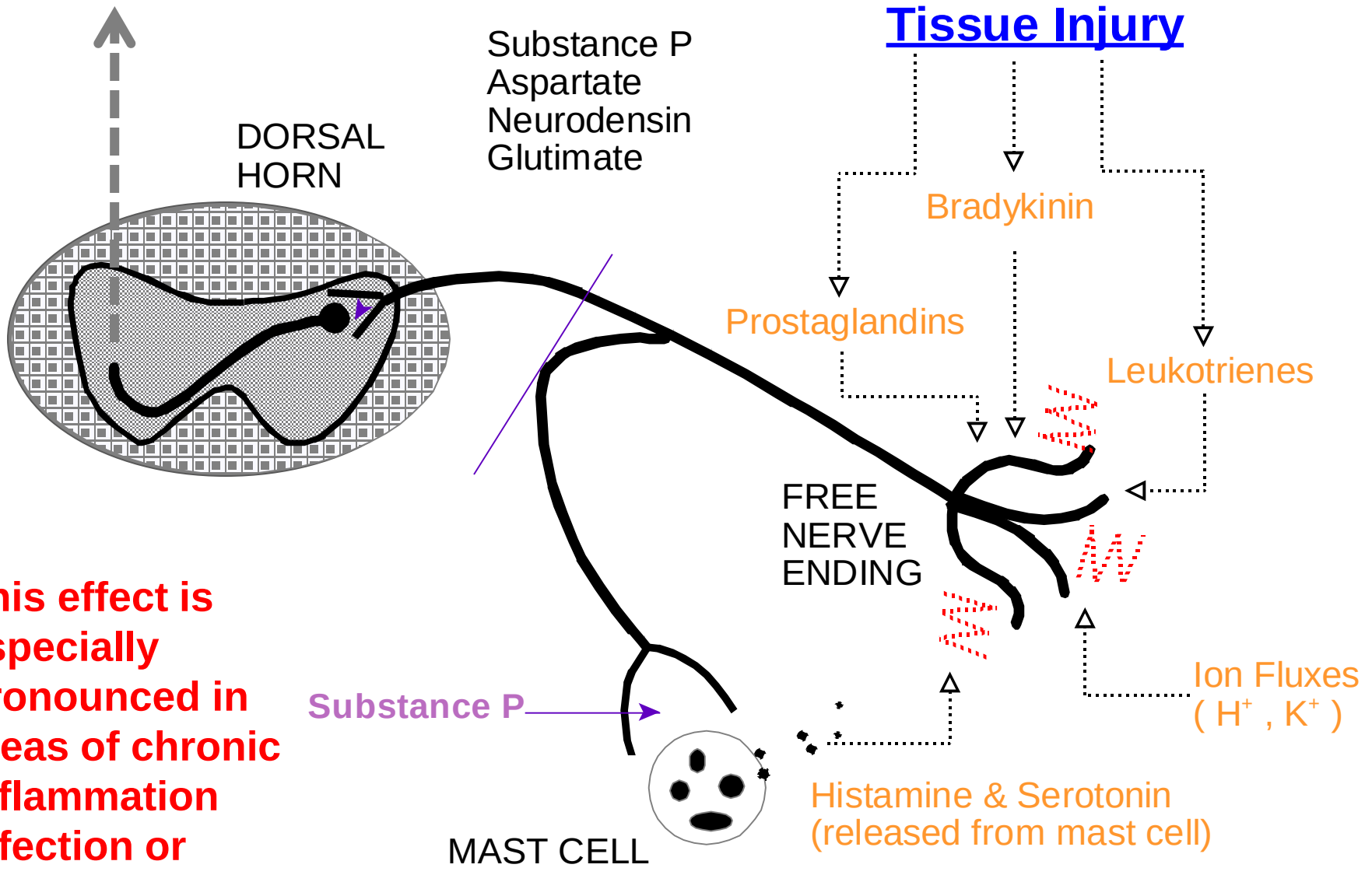


pus: living and dead neutrophils (which have been phagocytized by macrophages) along with liquefied tissue

Positive Feedback Mechanisms in Inflammation



Positve Feeback Mechanism for Pain



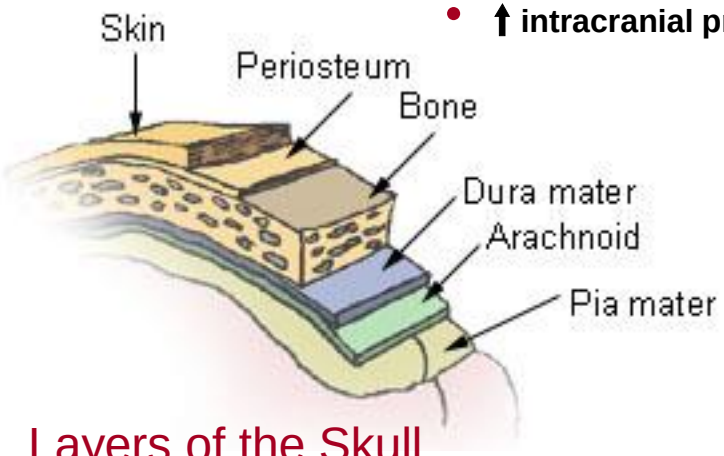
This effect is especially pronounced in areas of chronic inflammation infection or unhealed injury

Physiological Sequelae of Bleeding

- **Hemorrhage** – bleeding….**exsanguination: bleeding to death**
- **Bleeding outside the body:**
  - **Loss of 10% - 15% of blood volume can be tolerated in most people**
    - Blood donation usually depletes 8% - 10%
  - **Involves Positive feedback: desanguination – may result in hyovolemic shock**
    - Bleeding → ↓ BP → activation of baroreceptors → ↑ HR → ↑ bleeding
  - **May result in a hematoma (blood confined to a limited tissue space)**
    - Hematoma is usually defined as blood under the skin: subcutaneous hemorrhage
    - Hematomas serve to limit the amount of blood loss from an injury
    - If not resolved, hematomas can re-stimulate the inflammatory process
  - **↑ risk of bleeding with hemophilia, thrombocytopenia, anti-coagulation**
  - **Subcutaneous hemorrhage is eventually marked by Ecchymosis**
    - **Bruises – Contusions –** capillaries rupture → bleeding into interstitial tissue
    - May be associated with serious injuries: fractures, internal bleeding, & compartment syndrome
    - Aging → thinner skin + ↓ fat under the skin → more prone to bruises
    - Treatment: RICE and tylenol **(NSAID's within 24 hours → ↑ bleeding)**

Physiological Sequelae of Bleeding

- **Bleeding inside the body (internal hemorrhage)**
- **Common Causes:**
  - **Gastrointestinal (GI) lesions:** Colon, rectal, or stomach cancer
  - **Tissue malformation or dissection:** aortic aneurysms, arteriovenous malformations
  - **Ulcers** - Excess acid → 1/8th"- 2" holes in stomach or duodenum (1st 12" of small intestine)
    - Caused by: Helicobacter pylori bacteria, genetic predisposition, overuse of NSAIDS, & stress
      - Notes: smoking delays healing of ulcers
    - Symptoms: upper abdominal pain (relieved by eating, milk, antacids), nausea, vomiting of blood
      - Pain is worse 2 hours after a meal or when stomach is empty (middle of the night)
    - Complications: desanguination, anemia, duodenum perforation (surgery required), peritonitis
    - Treatment: antibiotics, antacids, H2 antagonists (ZANTAC), PPI's (NEXIUM, PRILOSEC)
  - **Trauma**
    - Head Trauma (closed head injuries)
    - Extra-axial (outside brain) vs. intra-axial bleeding (inside brain which is a c. hemorrhage or stroke)
      - Extra-axial broken down into: 1. Epidural 2. Subdural 3. Subarachnoid.
      - ↑ intracranial pressure → serious injury that can lead to permanent neurologic dysfunction



Layers of the Skull

Hemostasis - Cessation of Blood Flow

- **Step 1: Vascular Spasm** http://faculty.ucc.edu/biology-potter/hemostasis.htm
  - Vessel rupture ➞ vessel constriction (minutes - hours) due to
    - Reflexes
    - Myogenic response: stretch ➞ ↑ [Ca^{++}] in smooth muscle ➞ vasoconstriction
    - Platelets release thromboxane A_2 ($THRA_2$), a vasoconstrictor and platelet activator
    - Approximation of two endothelial surfaces causes them to stick together
  - The more cross-sectional area of a vessel is traumatized, the greater the vascular spasm http://www.mhhe.com/biosci/esp/2002_general/Esp/folder_structure/tr/m1/s7/trm1s7_3.htm
    - Sharp cut results in more bleeding than a crushing type of injury
- **Step 2: Formation of Platelet Plug**
  - Used to seal small breaks in small vessels that occur hundreds of time / day
  - Exposed collagen has (-) charge ➞ (+) charged platelets are attracted
  - Von Willebrand factor helps bind platelets to collagen ➞ platelet adhesion
  - Adhered platelets become activated ➞ swell & form irradiating processes
  - Platelets release $THRA_2$ & ADP ➞ ↑ activation of nearby platelets
  - Activated platelets are "sticky" & adhere to one another ➞ platelet aggregation
  - High actin & mysoin content in platelets contract ➞ platelet plug is formed
    - Note: activated platelets exude substances critical to both coagulation & healing
      - Phospholipids, PDGF, IGF-I, platelet factor IV

Hemostasis - cessation of blood flow

- **Step 3: Coagulation - coagulation can be initiated by:**
  - Trauma to the vascular wall and adjacent tissues - **Extrinsic pathway**
    - Traumatized tissues release thromboplastin ➞ coagulation initiated
  - Exposed collagen (endothelium damage) - **Intrinsic pathway**
    - Activation of Hageman Factor ➞ coagulation initiated
- **2 pathways: Extrinsic & Intrinsic**
  - **Extrinsic**- begins with substances extrinsic to the blood (completed in 15 sec.)
    - Damaged tissue releases tissue thromboplastin (tissue factor)
    - Thromboplastin activates Factor X

    - Activated Factor X + platelet phospholipids form prothrombinase
    - Prothrombinase activates prothrombin to form thrombin
    - Thrombin causes fibrinogen to form long “hair-like” structures called fibrin
    - Fibrin strands form a “web” - plasma turns gel-like & traps other elements ➞ clot
  - **Intrinsic**- injury (collagen exposure) within vessel (completed in 3 - 6 minutes)
    - Hageman factor comes in contact with collagen and activates Factor X

    - Activated Factor X + platelet phospholipids form prothrombinase
    - Prothrombinase activates prothrombin to form thrombin
    - Thrombin causes fibrinogen to form long “hair-like” structures called fibrin
    - Fibrin strands form a “web” - plasma turns gel-like & traps other elements ➞ clot

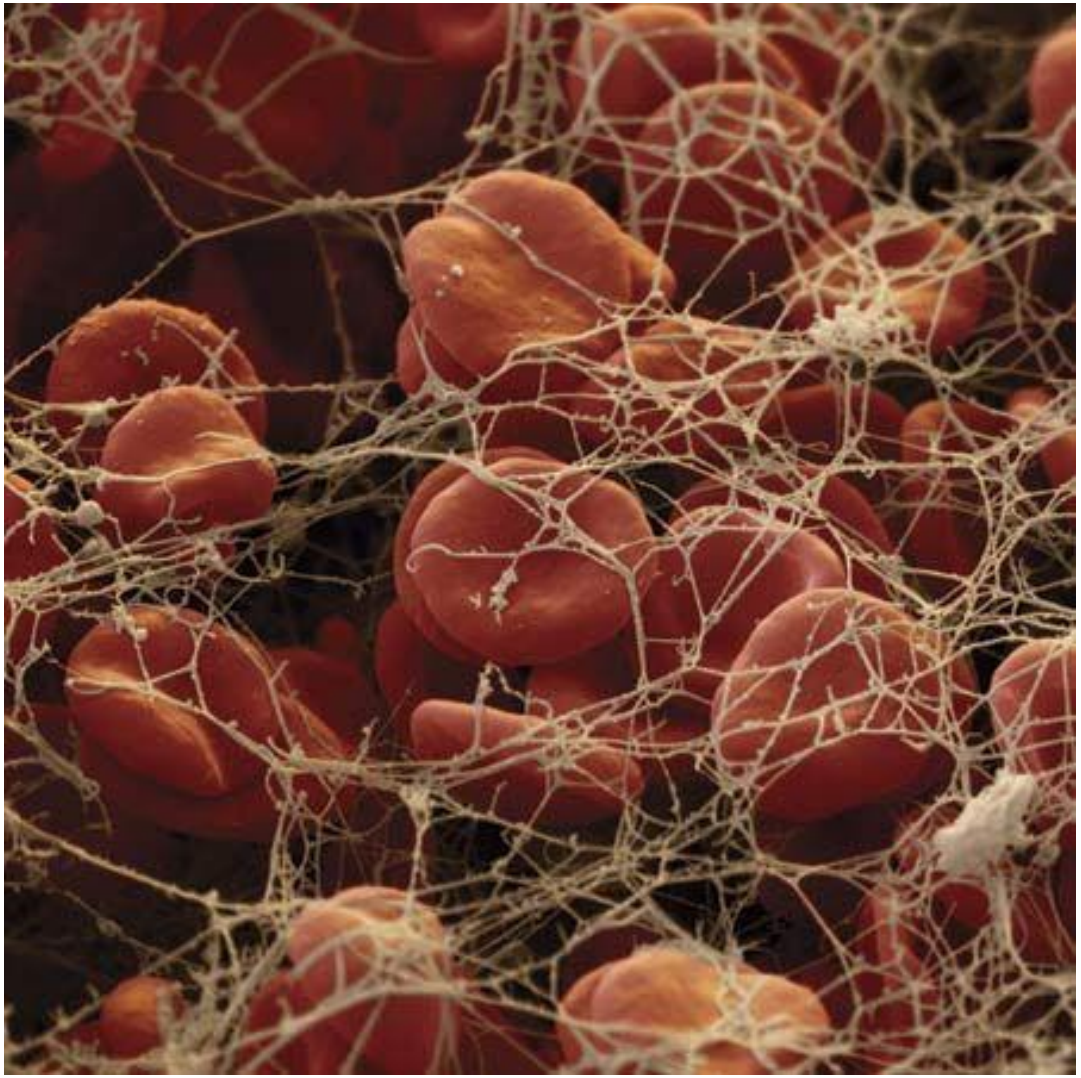
Hemostasis - Notes on Mechanisms

- **Almost all clotting factors + fibrinogen are formed by the Liver**
  - Hepatitis, cirrhosis, etc. → ↑ bleeding and bruising tendency
- **Vitamin K:** necessary for the formation of 5 of the clotting factors
  - Vitmain K deficiency → ↑ bleeding and bruising tendency
- **Clot contraction** - within 20-60 minutes, clots undergo syneresis
  - Actomyosin protein complex contracts in much the same way as skeletal muscle
  - A pull is created on fibrin strands → edges of injured tissue drawn together
- **Clot lysis** - after healing takes place, the clot must be lysed
  - Injured tissues release **plasminogen** and **tissue plasminogen activator (TPA)**
  - These substances are in the clot itself and are activated after a period of days
    - TPA converts plasminogen to plasmin, a proteolytic enzyme that dissolves the clot
    - TPA (& Streptokinase…) can be used to dissolve clots in MI's, strokes, & embolisms
      - Can be used up to 4.5 hours after ischemic stroke symptom onset
- **Coagulation time** - time required for a capillary tube of blood to clot
  - Capillary tube filled with blood is broken off at 30 second intervals
  - Blood is considered coagulated when fibrin threads appear at broken tube ends
  - Normal time: 6 - 10 minutes

Hemostasis - Notes on Mechanisms

- **Thrombus:** a blood clot in the cardiovascular system
- **Embolus:** a circulating plug (solid, liquid, or gaseous) composed of a thrombus or other material that may occlude a blood vessel
  - Thromboembolic conditions caused by:
    - Roughened endothelial surface → collagen exposed to blood → coagulation
    - ↓ blood flow → excess thrombin not eliminated by liver → coagulation
    - Stagnation of blood → small quantities of thrombin are formed → coagulation
      - **Atrial fibrillation** → ↓ flow of blood in left atria → thrombus formation
- **Prothrombin time ("PT time" or "pro time)**
  - Coagulation time for mixture of thromboplastin (tissue factor), calcium, & decalcified plasma
    - **PT time mean: 12 – 15 seconds**
- **International Normalized Ratio (INR)**
  - PT time ratio which normalizes for different thromboplastin reagents and equipment
    - **INR mean 2 - 3**
  - Used to monitor the effect of anticoagulant drugs (Heparin, Coumadin) to ensure nominal anticoagulation
    - Drugs used to prevent thromboembolic conditions (stroke, MI, TIA) or keep IV patent:
      - **HEPARIN** inactivates Factor X and inhibits conversion of prothrombin to thrombin
        - **LOVONOX** – low molecular weight Heparin
      - .75 mg / kg / hour → clotting time ↑ from 6 min. to 30 min. or more
      - **COUMADIN**: depresses clotting factor formation in liver (especially vitamin K related factors)
        - Results in 50% reduction in coagulation activity after 12 hrs, 80% after 24 hrs
      - **New Drugs: RIVAROXABAN** → inhibition of Factor Xa, no monitoring required
        DABIGATRAN → inhibition of Thrombin, no monitoring required

A blood clot: Erythrocytes trapped in fibrin mesh



Material for

TEST 2

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