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I. **Anti-inflammatory drugs**
II. **Anti-allergic drugs**
III. **Immunomodulators**

Plan of lecture:

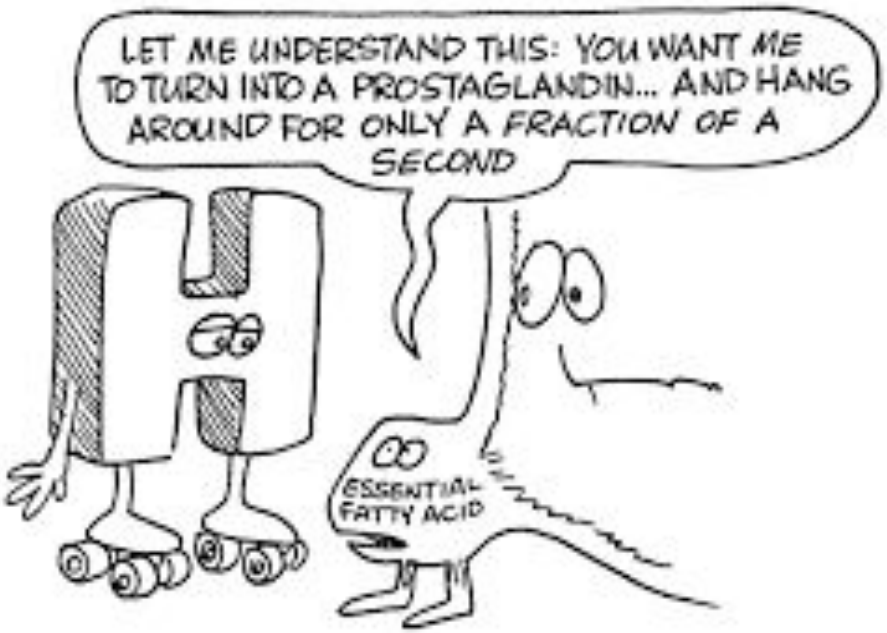
- **Anti-inflammatory agents**
- **Anti-allergic drugs**
- **Immunomodulators**

Inflammation

- **Inflammation is a complex protective response of the organism to injury caused by damaging agents.**
- **It is aimed at inactivation or removal of these agents and promoting healing.**
- The traditional names for signs of inflammation come from Latin:
  - *Dolor (pain)*
  - *Calor (heat)*
  - *Rubor (redness)*
  - *Tumor (swelling)*
  - *Functio laesa (loss of function)*

Mediators of inflammation

- Prostaglandins
- Bradykinin
- Serotonin
- Histamine
- Interleukins-2 – 6, 10, 12,13
- Platelet activating factor
- Gamma-Interferon
- Tumor Necrosis Factor
- Transforming Growth Factor
- Lymphotoxin



The role of some prostaglandins in the body

- **PGE 2** – vasodilation, bronchodilation, inhibition of gastric acid secretion, stimulation of gastric mucus secretion, sensitization of pain receptors to chemical and mechanical stimuli, promotion of anterior pituitary hormones release;
- **PGF2α** - uterus contraction, bronchoconstriction, decrease in intraocular tension;
- **TXA2** (thromboxane), produced by platelets, - induction of platelet aggregation, vasoconstriction;
- **PGI 2** - inhibition of platelet aggregation, potent vasodilation;

Cyclo-oxygenase (COX)

- Exists in the tissue as constitutive isoform (COX-1).
- At site of inflammation, cytokines stim the induction of the 2nd isoform (COX-2).
- Inhibition of COX-2 is thought to be due to the anti-inflammatory actions of NSAIDs.
- Inhibition of COX-1 is responsible for their GIT toxicity.
- Most currently used NSAIDs are somewhat selective for COX-1, but selective COX-2 inhibitors are available.

NSAIDs – nonsteroidal anti-inflammatory drugs

1. Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonselective COX inhibitors

- **1. Salicylates**
- *Acetylsalicylic acid (Aspirin)
- * Salicylamide
- **2. Pyrazolone derivatives**
- *Phenylbutazone
- *Metamizol (Analginum)
- **3. Indole derivatives**
- *Indomethacin
- **4. Propionic acid derivatives**
- *Naproxen
- **5. Antranilic acid derivatives**
- *Mephenamic acid
- **6. Aryl – acetic acid derivatives**
- *Diclophenac sodium
- **7. Oxicam derivatives**
- *Piroxicam
- **8. Dihydropyrrolizine carboxylic acid derivative**
- *Ketorolac

Selective COX inhibitors

- ***Preferential COX-2 inhibitors***
- Nimesulide
- Meloxicam
- Nabumeton
- ***Selective COX-2 inhibitors***
- Celecoxib
- Parecoxib
- Rofecoxib

NB!!!These drugs cause little gastric mucosa damage, they do not inhibit platelet aggrigation!!!

Mechanism of action of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

- **Act by inhibiting CycloOXygenases (COX) => no PG production**

– COX-1: Constitutively expressed => house-keeping function

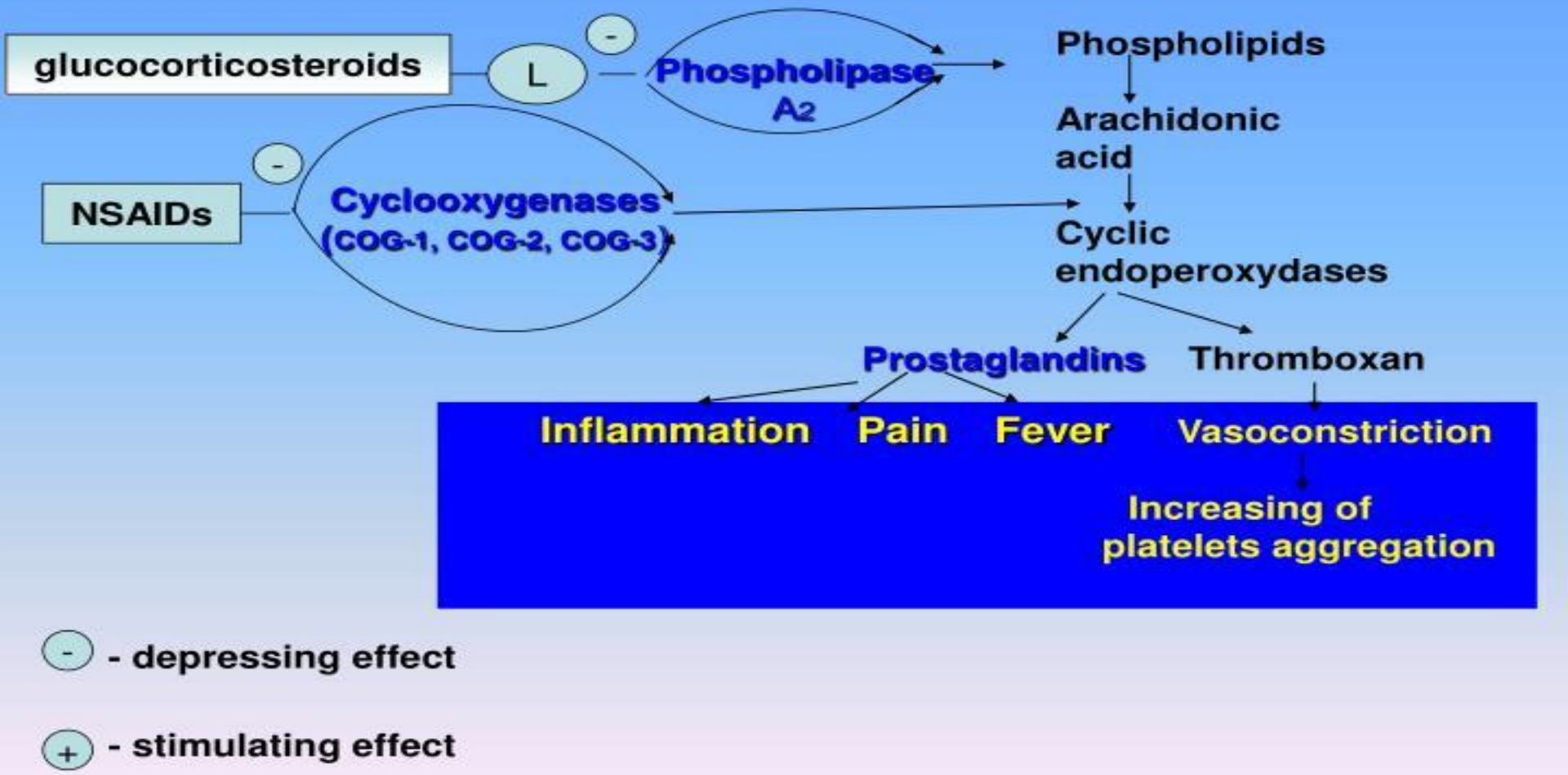
– COX-2: Induced by pro-inflammatory factors (TNFα, IL-1)

– COX-3: Just recently discovered

- **PGs do not cause pain, but sensitize nocireceptors to stimulation (e.g. by 5-HT, Bradykinine, capsaicin, …)**
- IL-1 release from activated macrophages (bacteria, etc.) induces COX-2 in the brain =>PG E produced => affects thermoregulation => fever=> **NSAIDs have anti-pyretic effects**
- Classical NSAIDs: inhibit both COX-1 and COX-2 (inhibition is reversible, with the exception of Aspirin) => housekeeping PGs reduced => side effects (gastrointestinal, bronchospasms,…)
- 2nd generation NSAIDs: COX-2 specific => only the inflammatory response is inhibited => fewer side effects.

Mechanism of anti-inflammatory drugs' action

Groups of anti-inflammatory agents and mechanism of action:1) nonsteroidal anti-inflammatory drugs – NSAIDs, 2) glucocorticosteroids (GCS)



(-) - depressing effect

(+) - stimulating effect

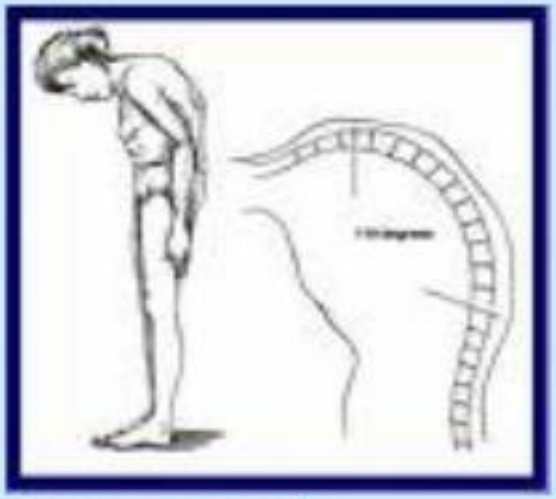
Pharmacological effects of NSAIDs

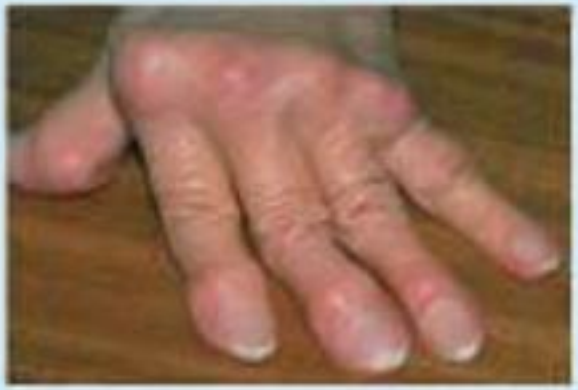
- Anti-inflammatory
- Analgesic
- Antipyretic
- Antiplatelet (Aspirin)
- Closure of ductus arteriosus in newborn

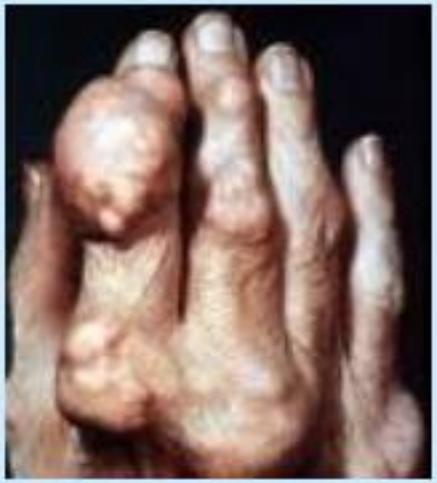
Clinical uses of NSAIDs

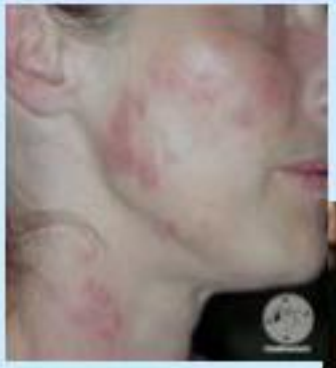
- 1. Pain: headache, toothache, myalgia, backpain;
- 2. Fever;
- 3. Arthritises: rheumatiod arthritis, osteoarthritis, gout, ankylosing spondylitis;
- 4. Dismenorrhoea (especially ibuprofen);
- 5. Unclosure of ductus arteriosus (especially aspirin);
- 6. Prevention of MI, stroke, and reinfarction (aspirin);

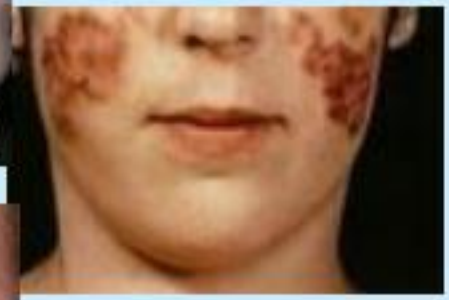
Rheumatoid diseases

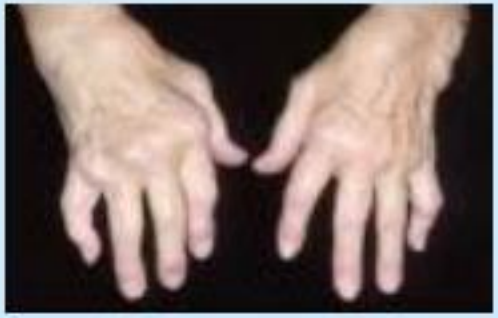


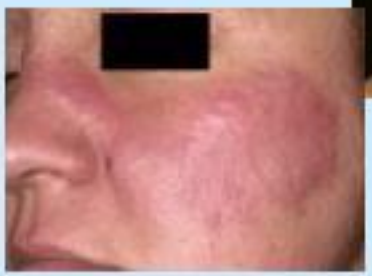


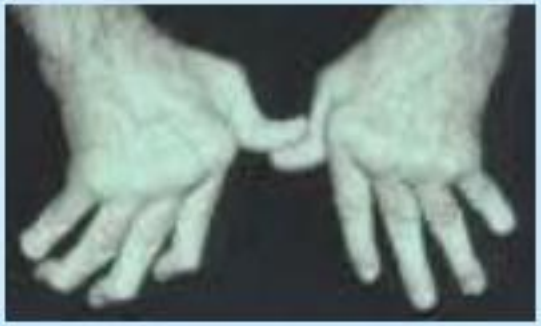












Side effects of nonsteroid anti-inflammatory drugs

Gastro-intestinal tract	Peptic ulcers and multiple micro-erosions Esophagitis and strictures Erosive damaging of large and small intestines
Kidney	Reversible acute kidney insufficiency Water-electrolyte disorders Chronic kidney insufficiency and interstitial fibrosis Interstitial nephritis Nephritic syndrome
Cardio-vascular system	Increasing of arterial hypertension Increasing of static cardiac insufficiency Increasing of stenocardia
Liver	Increasing of transaminases level Life-threatening liver insufficiency
CNS	Headache, somnolence confusion, disorders of behavior aseptic meningitis
Blood system	Thrombocytopenia Hemolytic anemia Granulocytopenia and aplastic anemia
Bones, joints	Disorders of cartilages and subchondral tissue
Other	Increasing of asthma and polypus of nose, skin rash

Contraindications

- A) Pregnancy
- B) Haemophilic patients
- C) Hypersensitivity reactions
- D) Viral infections mainly in children
- E) Peptic ulcers

Drugs interaction

- Potentiates the gastric irritant effect of alcohol
- Potentiates the hypoglycaemic effects of oral hypoglycaemic drugs

The Salicylates - ASPIRIN

- Duration of action ~ 4 hr.
- Orally taken.
- Weak acid (pK_a ~ 3.5); so, non-ionized in stomach easily absorbed.
- Hydrolyzed by esterases in tissues and blood to salicylate (active) and acetic acid.
- Most salicylate is converted in liver to H_2O-sol conjugates that are rapidly excreted by kids.

ASPIRIN - Therapeutic Uses

- Antipyretic, analgesic.
- Anti-inflammatory: rheumatic fever, rheumatoid arthritis (joint dis), other rheumatological diseases. High dose needed (5-8 g/day).
- But many pts cannot tolerate these doses (GIT); so, proprionic acid derivatives, ibuprofen, naproxen tried first.
- Prophylaxis of diseases due to platelet aggregation.
- Pre-eclampsia and hypertension of pregnancy (excess TXA_2).

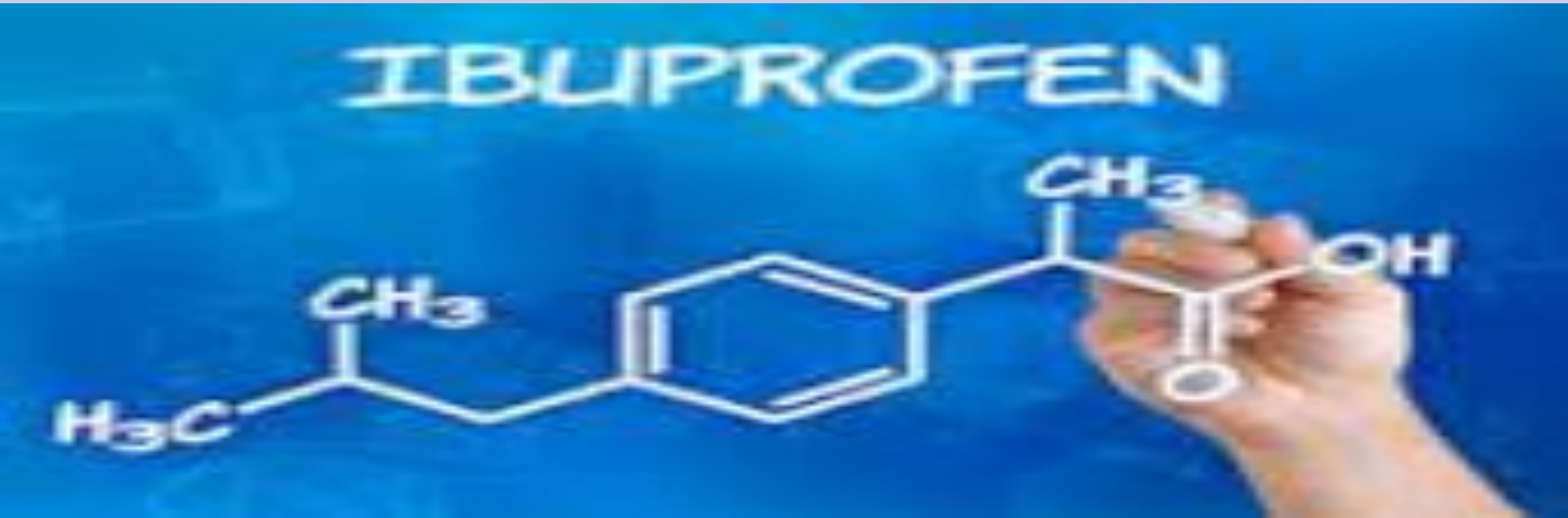
Propionic acid derivatives

IBUPROFEN:

- Pharmacokinetics
- Rapidly absorbed after oral ingestion.
- Half-life 1-2 hours
- Highly bound to plasma proteins
- Excreted through kidney as metabolites.

IBUPROFEN

- The same mechanism & pharmacological actions of aspirin Except that it is reversible inhibitor for COX enzymes
- More potent as antiinflammatory than aspirin!!!



Clinical uses

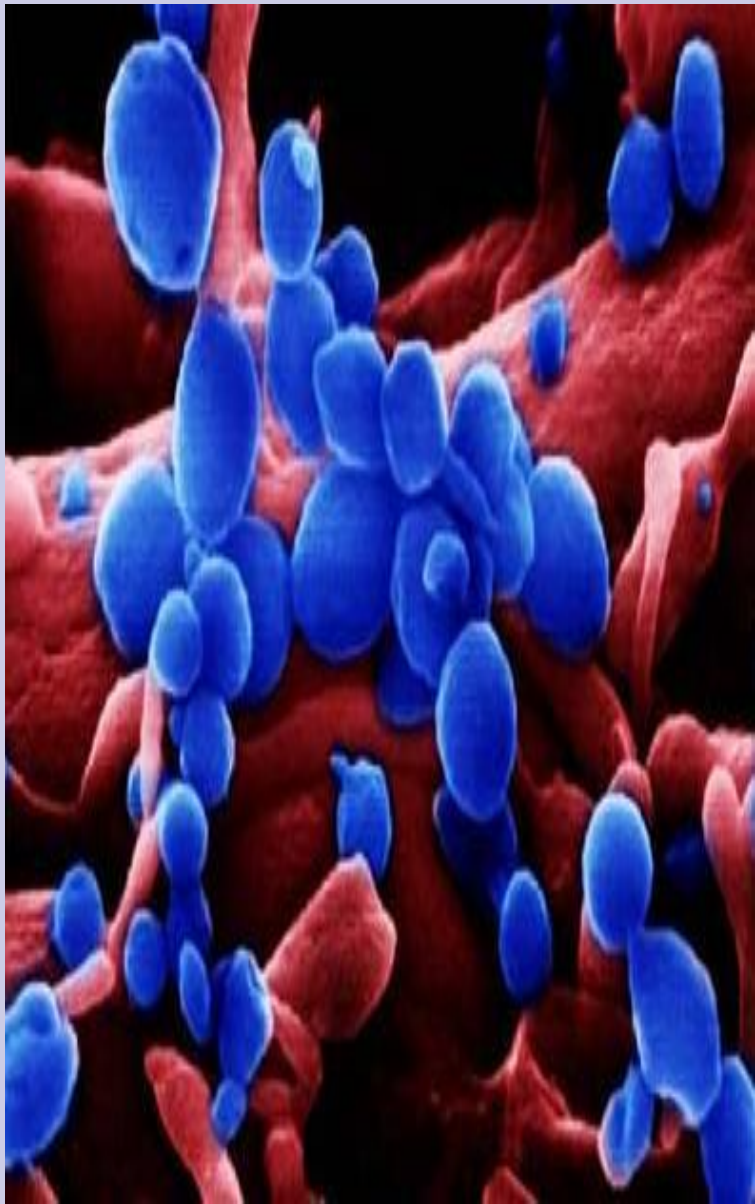
- A) Analgesic
- B) Antipyretic
- C) Anti-inflammatory
- D)Acute gouty arthritis
- E) Patent ductus arteriosus

Preparations of Ibuprofen

- Oral preparations.
- Topical cream for osteoarthritis.
- A liquid gel for rapid relief of postsurgical dental pain.
- Intravenous route as In patent ductus arteriosus

Adverse effects

- 1.Gastric upset (less frequent than aspirin).
- 2.Fluid retention
- 3.Hypersensetivity reactions
- 4.Ocular disturbances
- 5.Rare hematologic effects (agranulocytosis & aplastic anaemia).



Contraindications

- 1. Peptic ulcer
- 2. Allergic patients to aspirin
- 3. Kidney impairment
- 4.Liver diseases
- 5.Pregnancy
- 6.Haemophilic patients

The concomitant administration of ibuprofen antagonizes the irrevesible platelet inhibition of ASPIRIN (limit cardioprotective effect of aspirin).

Piroxicam

- Mechanism of actions:
- A) Non-selective inhibitors to COX1 & COX2
- B) Traps free radicals
- C) Inhibits polymorphonuclear leukocytes migration
- D) Inhibits lymphocyte function.

Pharmacokinetics

- Well absorbed orally
- Half- Life 45 hours
- Given once daily

Adverse effects

- Less frequent gastric upset (20%).
- Dizziness.
- Tinnitus.
- Headache.
- Allergy.

Acetic acid derivatives

DICLOFENAC

- Mechanism of action
- Non-selective inhibitor to COX1 & COX2.
- More potent as anti-inflammatory than analgesic and antipyretics.

Clinical uses DICLOFENAC

- A) Any inflammatory conditions
- B) Musculoskeletal pain
- C) Dysmenorrhoea
- D)Acute gouty arthritis
- E) Fever
- F) Locally to prevent or treat post opthalmic inflammation
- G) A topical gel for solar keratoses

Adverse effects DICLOFENAC

- Gastric upset
- Renal impairment
- Elevation of serum aminotransferase
- Salt & water retention

Preparations of DICLOFENAC

- Diclofenac with misoprostol decreases upper gastrointestinal ulceration, but result in diarrhea.
- Diclofenac with omeprazole to prevent recurrent bleeding.
- 1% opthalmic preparation for postoperative opthalmic inflammation.
- A topical gel 3% for solar keratoses.
- Rectal suppository as analgesic or for postoperative nausea.

Selective COX 2 inhibitors

- ***Advantages:***
- 1. Highly selective inhibitors to COX2 enzyme.
- 2. Potent anti-inflammatory.
- 3. Have analgesic & antipyretic properties.
- 4. Highly bound to plasma proteins.

Selective Cox 2 inhibitors

- 5. Lower incidence of gastric upset.
- 6. No effect on platelet aggregation (COX1).
- 7. Renal toxicities (they are not recommended for patients with severe renal insufficiency).
- 8. High incidence of cardiovascular thrombotic events with some of them as ROFECOXIB.

Selective Cox 2 inhibitors

- 9- They are recommended in postoperative patients undergoing bone repair.
- 10- Also, indicated in primary familial adenomatous polyposis, dysmenorrhea, acute gouty arthritis, acute musculoskeletal pain, ankylosing spondylitis.

SAIDs – steroidal anti-inflammatory drugs

Steroidal anti-inflammatory drugs

- **1. Short-acting glucocorticoids (natural)**
  - Hydrocortisone
  - Cortisone
- **2. Intermediate-acting glucocorticoids**
  - Prednisone
  - Prednisolone
  - Methylprednisolone
  - Triamcinolone
- **3. Long-acting**
  - Betamethasone
  - Dexamethasone
  - Paramethasone
- **4.Topically acting glucocorticoids**
  - Beclomethasone dipropionate
  - Budesonide
  - Fluocinolone acetonide
  - Fluocortolone

Preparations of SAIDs

Drugs	Anti-inflam.	Salt retaining	Topical
Cortisol	1	1.0	1
Cortisone	0.8	0.8	0
Prednisone	4	0.8	0
Prednisolone	5	0.3	4
Methylpredni-solone	5	0	5
Intermediate acting			
Triamcinolone	5	0	5
Paramethasone	10	0	-
Fluoprednisolone	15	0	7

Preparations of SAIDs

Drugs	Anti-inflam.	Salt retaining	Topical
Long acting			
Betamethasone	25-40	0	10
Dexamethasone	30	0	10
Mineralocorticoids			
Fludrocortisone	10	250	10
DOCA	0	20	0

MECHANISM OF ACTION OF SAIDs

Corticosteroids

Phospholipids

Phospholipase A2

Arachidonic acids

Lipoxygenase

Leukotriene

Cycylooxygenase

Prostaglandins, Thromboxane, Prostacyclins.

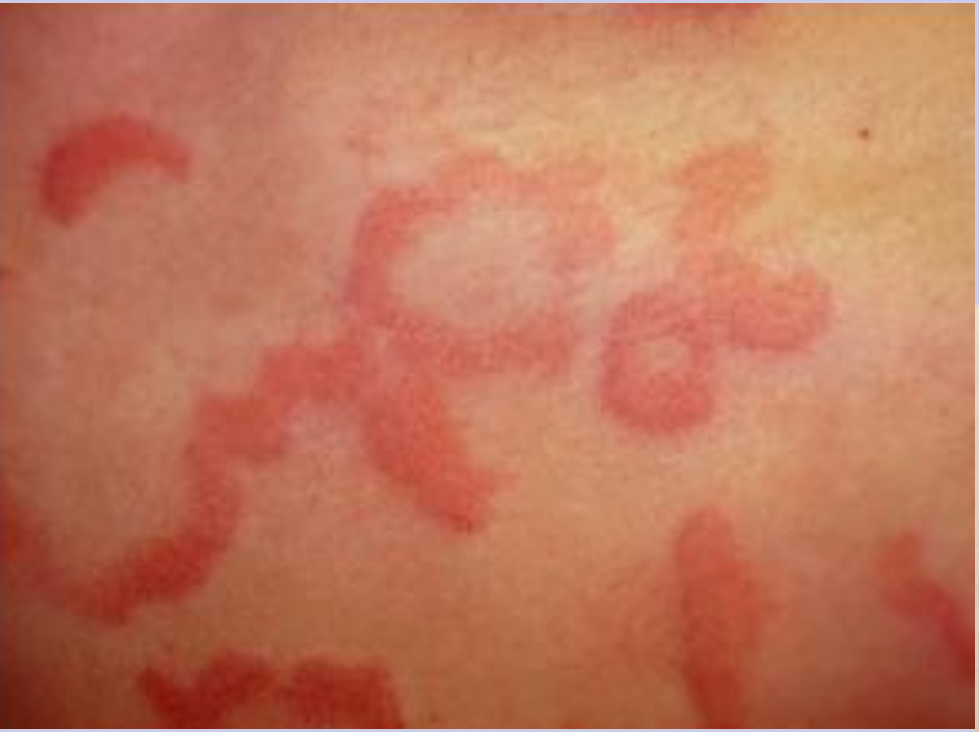
Clinical uses of SAIDs

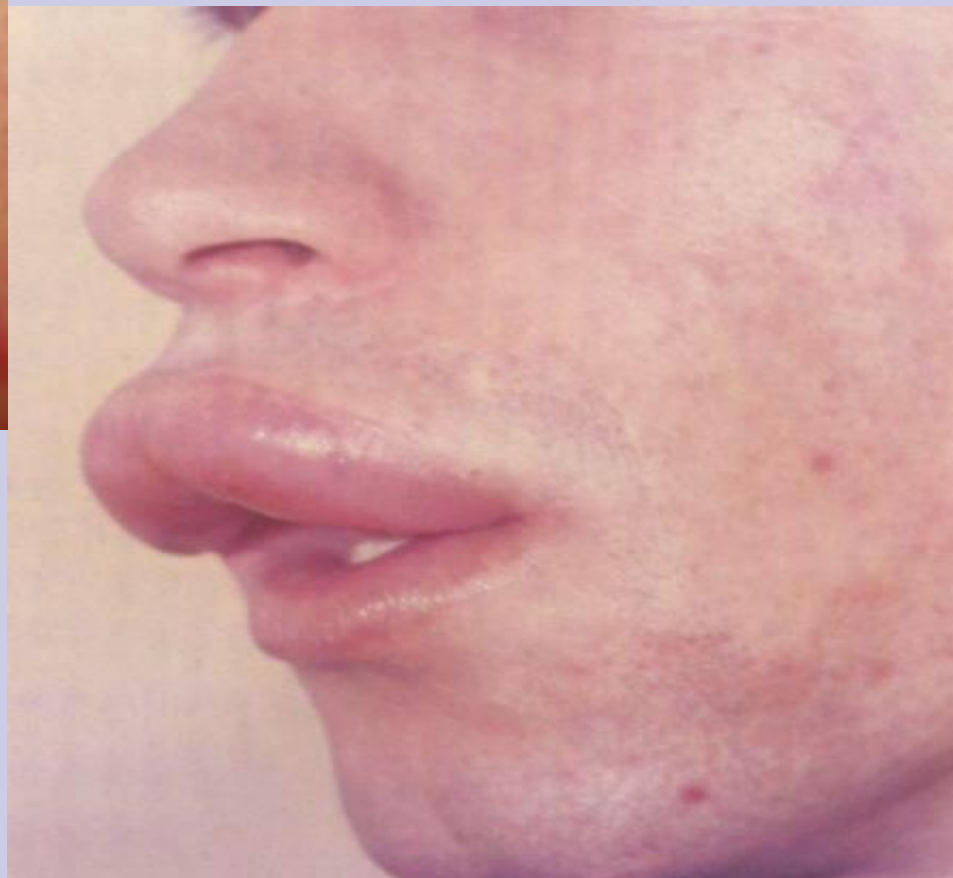
- Adrenal insufficiency
- Arthrities
- Collagen diseases (systemic lupus erhymatosis, scleroderma)
- Bronchial asthma
- Severe allergic reactions
- Autoimmune diseases
- Skin diseases
- Ulcerative colitis, Crohn’s disease
- Cerebral edema
- Organ transplantation and skin allograft
- Septic shock

Main side effects of SAIDs

- Susceptibility to infections
- Delayed healing of wounds
- Osteoporosis
- Growth retardation in children
- Peptic ulceration
- Cushing habitus
- Hyperglycaemia
- Muscular weakness
- Psychiatric disorders
- Withdrawal syndrom

ANTI-ALLERGIC DRUGS





Allergy

- An allergy is a hypersensitivity disorder of the immune system.
- Allergic reactions occur when a person's immune system reacts to normally harmless substances in the environment.
- A substance that causes a reaction is called an allergen. These reactions are acquired, predictable, and rapid.
- Allergy is one of four forms of hypersensitivity and is formally called type I (or immediate) hypersensitivity.
- Allergic reactions are distinctive because of excessive activation of certain white blood cells - lymphocytes called B cells, whose role is production of antibodies, called Immunoglobulin E (IgE).
- Mast cells are activated and release mediator of allergy (HISTAMINE) that results in an inflammatory response.

Clinical Symptoms Associated With Histamine Release

- **mild/cutaneous**
  - erythema, urticaria, and/or itching
- **mild to moderate**
  - skin reactions, tachycardia, dysrhythmias, moderate hypotension, mild respiratory distress
- **severe/ anaphylactic**
  - severe hypotension, ventricular fibrillations, cardiac arrest, bronchospasm, respiratory arrest

Histamine exerts its effects on many tissues and organs:

It is not a drug but is important due to its physiological and pathophysiological actions. Therefore, drugs that inhibit its release or block its receptors have therapeutic value.

Physiological Actions of Histamine

- Primary stimulant for gastric acid and pepsin secretion (H2) (acid secretion is enhanced by gastrin and vagal stimulation)
- Has a role as a neurotransmitter (H3) (both in the CNS and peripheral sites)

Pathophysiological Actions of Histamine

- Cellular mediator of immediate hypersensitivity reaction and acute inflammatory response
- Anaphylaxis
- Seasonal allergies
- Duodenal ulcers
- Systemic mastocytosis
- Gastrinoma (Zollinger-Ellison Syndrome)

Pharmacological Effects of Histamine

- Ranges from mild allergic symptoms to anaphylactic shock

- Involves both the H1 and H2 receptors
  - dilatation of small blood vessels flushing (H1)
  - decreased TPR and BP (H1 initial response, H2 sustained reaction)
  - increased capillary permeability, edema (H1)

Types of hypersensitivity reaction

Immediate-type hypersensitivity

1. **Anaphylaxis** – results from cross-linking of membrane-bound IgE on blood basophils or tissue mast cells by antigen. This interaction causes cells to degranulate, releasing substances (histamine, leukotrienes)

   Examples: hay fever, anaphylactic shock

   (Oedema of Quincke, Stevence-Johnson syndrome)

2. **Cytotoxic reaction** – results from the formation of antigen-antibody complexes between foreign antigen and immunoglobulins. It results in lysis of cells that keep antigen.

   Examples: blood transfusion reactions and in hemolytic disease of the newborn; aplastic anemia from chloramphenicol

Immediate-type hypersensitivity

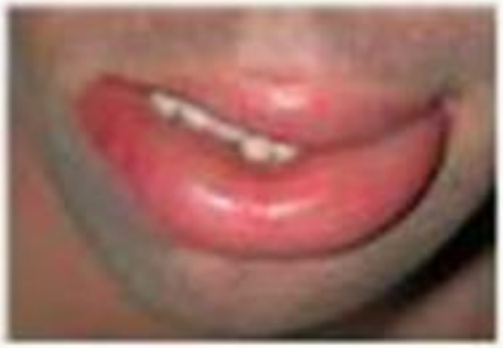
3. **Immune complex reaction** – is due to the presence of elevated levels of antigen-antibody complexes. The formation of these complexes activates complement to produce components that increase vascular permeability and recruit neutrophils to the site of complex deposition.
   Examples: skin rashes, serum sickness, glomerulonephritis.

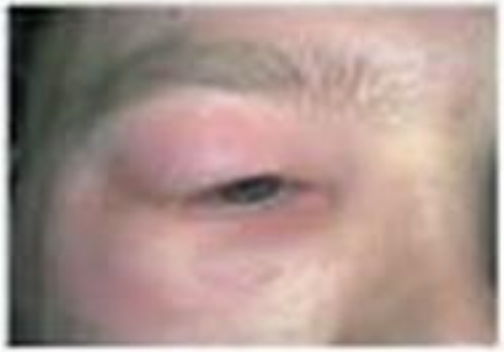
Delayed-type hypersensitivity – is characterized by the influx of the activated macrophages and neutrophils; and release copious amounts of enzymes that contribute to the extensive tissue damage and local inflammation.

Examples: parasitic granuloma**; tuberculin skin test.**

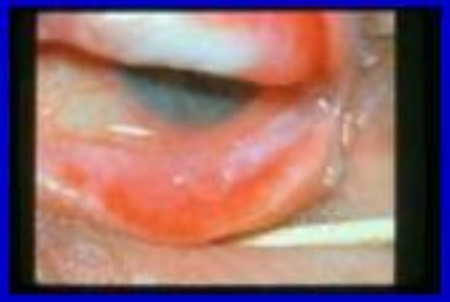
Quincke's Oedema, Angioneurotic Oedema

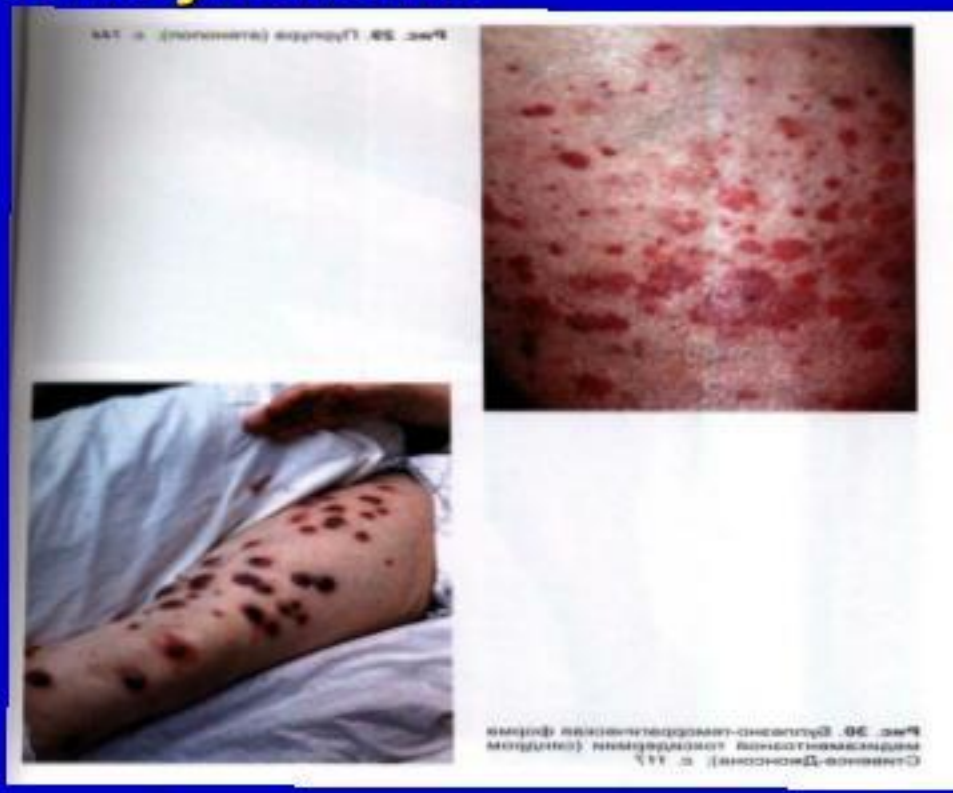
- oedema of the subcutaneous tissue, particularly of the lips, eyelids and genitalia, though any part of the body may be involved
- The tongue and larynx may also be affected, it may be life threatening
- Quincke's oedema may occur in urticaria, anaphylaxis, and serum sickness
- Etiologic factors include medications (e.g. penicillin, aspirin, phenytoin)
- infections and food related products for Quincke's oedema associated with urticaria

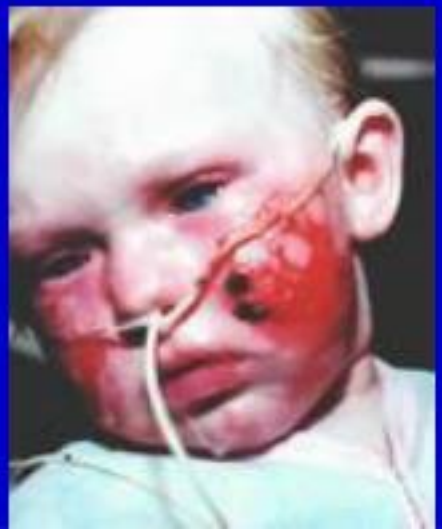




Stevens-Johnson syndrome







Antiallergic drugs

- 1. Antihistaminics
- 2. Corticosteroids
- 3. Mast cell stabilisers
- 4.Antileukotriene drugs

ANTIALLERGIC AGENTS

I. For the treatment of IMMEDIATE-TYPE reaction:

- ↓ synthesis and release of histamine and other active substances – cromolyn, ketotifen, glucocorticoids
- H_1-histaminoblockers – dimedrole, diprazin, diazolin, loratidine etc.
- agents that bind with histamine – histaglobulin
- ↓ manifestations of hypersensitivity – adrenomimetics, M-cholinoblockers, zafirlucast, euphylline
- ↓ tissue alteration –steroid and non-steroid anti-inflammatory agents

II. For the treatment of DELAYED-TYPE reaction

- *immunosuppressant* – cyclosporine, azathioprine
- ↓ *tissue alteration* – anti-inflammatory steroid and non-steroid, slowly-acting agents (chloroquine, gold-containing agents, dalson etc.)

HISTAMINE RECEPTORS

receptors	localization	Effects of activation	blockers:
H_1	bronchial sm. muscles	↑ tonus	Dimedrol Diprazin Diazolin etc.
	intestinal sm. muscles	↑ tonus	
	heart	↓ AV	
	vessels	↓ arteries, ↑ veins	
	capillary	↑ permeability	
	nerve endings	↑ pain perception and itching	
	CNS	different	
H_2	gastric glands	↑ secretion	Cimetidine, Famotidin etc.
	heart	+ ino- and chrono-	
	arteries	↓ tonus	

H_1(HISTAMINE)-BLOCKERS

AGENTS	antihistamine activity			sedative	M-cholinolytic	irritative
	onset	strength	duration, hrs			
dimedrol	fast	++	3-5	++	++	+
diprazin	-»-	++++	6-8	+++	+++	+
suprastin	-»-	++	4-6	++	+	+
tavegil	-»-	+++	8-12	+	+	+
diazolin	slow	++	>24	-	-	+
fencarol	-»-	++	6-8	+	+	+
terfenadin	-»-	++	12-24	+	-	-
loratidin	-»-	++	24	+	-	-

Histamine-related Drugs

- Mast Cell Stabilizers (
)
- H1 Receptor Antagonists (
)
- H2 Receptor Antagonists (
)
- H3 Receptor Agonist and Antagonists (
)

First Generation **ANTIHISTAMINE** Agents

Ethanolamines: DIPHENHYDRAMINE (Benadryl)
CLEMASTINE (Tavist)

Ethylenediamine:TRIPELENNAMINE

Alkylamine:CHLORPHENIRAMINE (Chlortrimeton)

Phenothiazine:PROMETHAZINE (Phenergan)

Piperazines: HYDROXYZINE (Vistaril)
CYCLIZINE (Antivert)

First Generation Agents

Uses:

- Adjunctive in anaphylaxis and other cases where histamine release can occur (H_2 antagonist, and epinephrine must also be used in anaphylaxis)
- Antiallergy (allergic rhinitis, allergic dermatoses, contact dermatitis)
- Sedative/sleep aid
- To prevent motion sickness (MECLIZINE, CYCLIZINE)

Side effects of H_1-histamine receptors blockers of 1st generation

1) Depression of CNS (disorders of coordination, increased tiredness, dizziness, tremor, euphoria, nervousness, insomnia)

2) Disturbance of GI functioning : decreasing of appetite, nausea, vomiting, pain in epigastria, constipation of diarrhea

3) As a result of M-cholinoblocking activity – dryness of mucous membranes, eye disorders - blurred vision, impotence, ischuria, tachycardia, headache, psychosis

4) in case of repeated administration - tachyphylaxis

First Generation Agents

Drug interactions:

- Additive with classical antimuscarinics
- Potentiate CNS depressants
  - opioids
  - sedatives
  - general and narcotic analgesics
  - alcohol

Second Generation Agents

Examples

- CETIRIZINE (ZYRTEC)
- FEXOFENADINE (ALLEGRA)
- LORATADINE (CLARITIN)
- DESLORATADINE (CLARINEX- FDA APPROVED IN 2002)
- LORATADINE (CLARITIN HIVES RELIEF - FDA APPROVED IN 2004)
- AZELASTIN (INTRANASAL SPRAY)
- ASTEMIZOLE
- ACRIVASTINE

Uses

- Antiallergy

Comparative antiallergic activity

H_1 histamine blockers of 1st generation

diprasine>tavegil>dimedrol>suprastin>
fenkarol>diasoline

H_1 histamine blockers of 2nd and 3rd generations

cetirizine>
terfenadine=fexofenadine>
astemizole>loratadine

Histamine H1- Antagonists

- First Generation:

!!!Sedating!!!

- Second Generation:

!!!Non sedating!!!

Advantages of 2nd generation antihistaminics

- Higher H1 selectivity, absence of anticholinergic side effects
  - Absence of inhibitory action on CNS
  - Additional antiallergic mechanisms: some of them are acting on leukotrienes or by antiplatelet activating factor

Mast cell stabilisers

- Cromolyn sodium (Sodium cromoglycate)
- Nedocromil sodium
- Ketotifen
- Corticosteroids (vide supra)

Cromolyn sodium –inhibits mast cell release of histamine, leukotrienes.

Uses: bronchospasm prevention.

Ketotifen – acts like cromolyn and blocks H_1-receptors.

Readily absorbed in GIT. $T_{1/2}$=20 hours.

Uses: allergic bronchitis, hey fever, allergic dermatitis.

Adverse effects: drowsiness, thrombocytopenia.

Histaglobulin – is a preparation of the human γ-globulin. Increases the production of antihistamine antibodies.

Uses: bronchial asthma, allergic dermatitis and different allergic disease.

Antileukotriene drugs

- Montelukast
- Zafirlukast

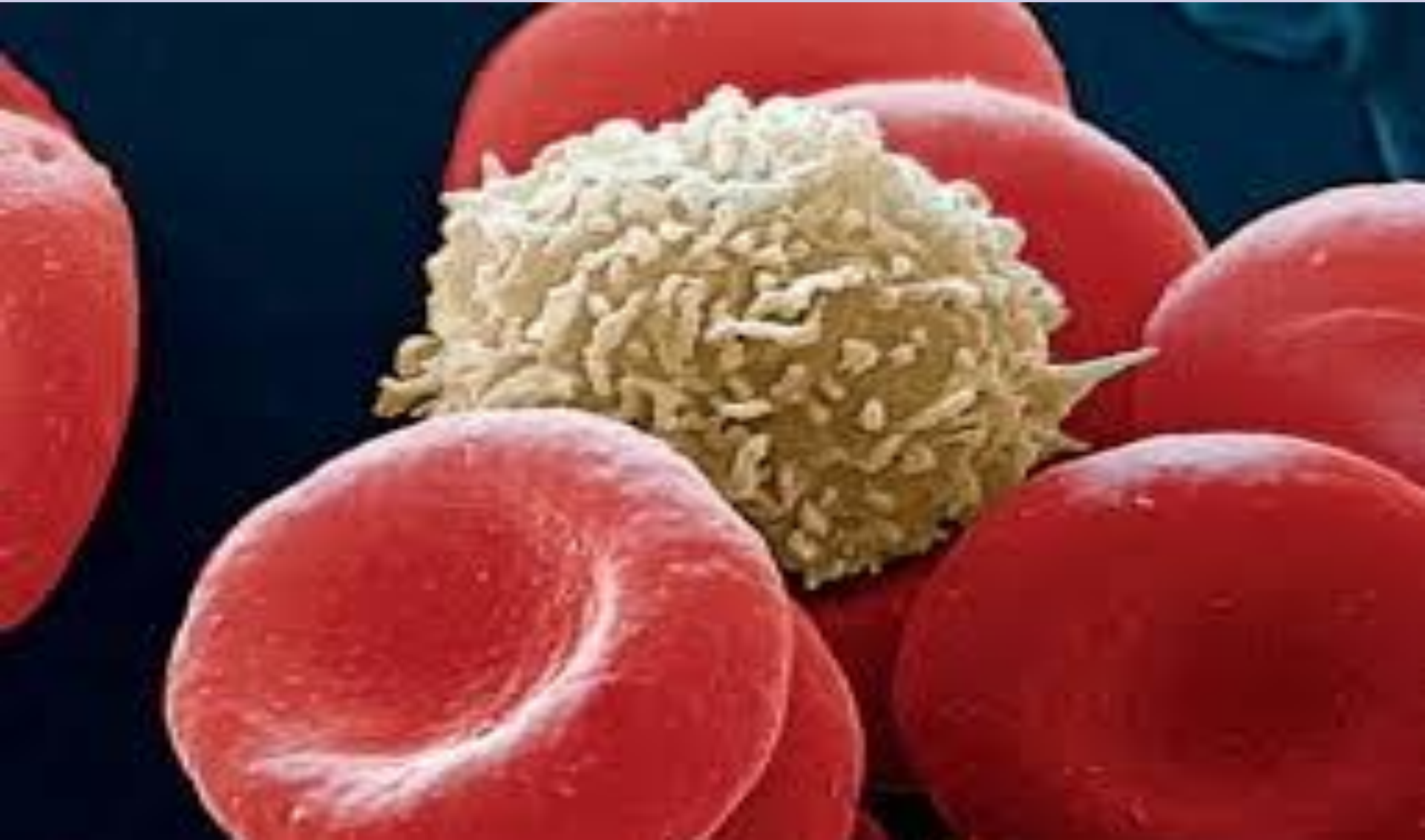
Mechanism: competitive block of LT1 receptors

Clinical use: bronchial asthma

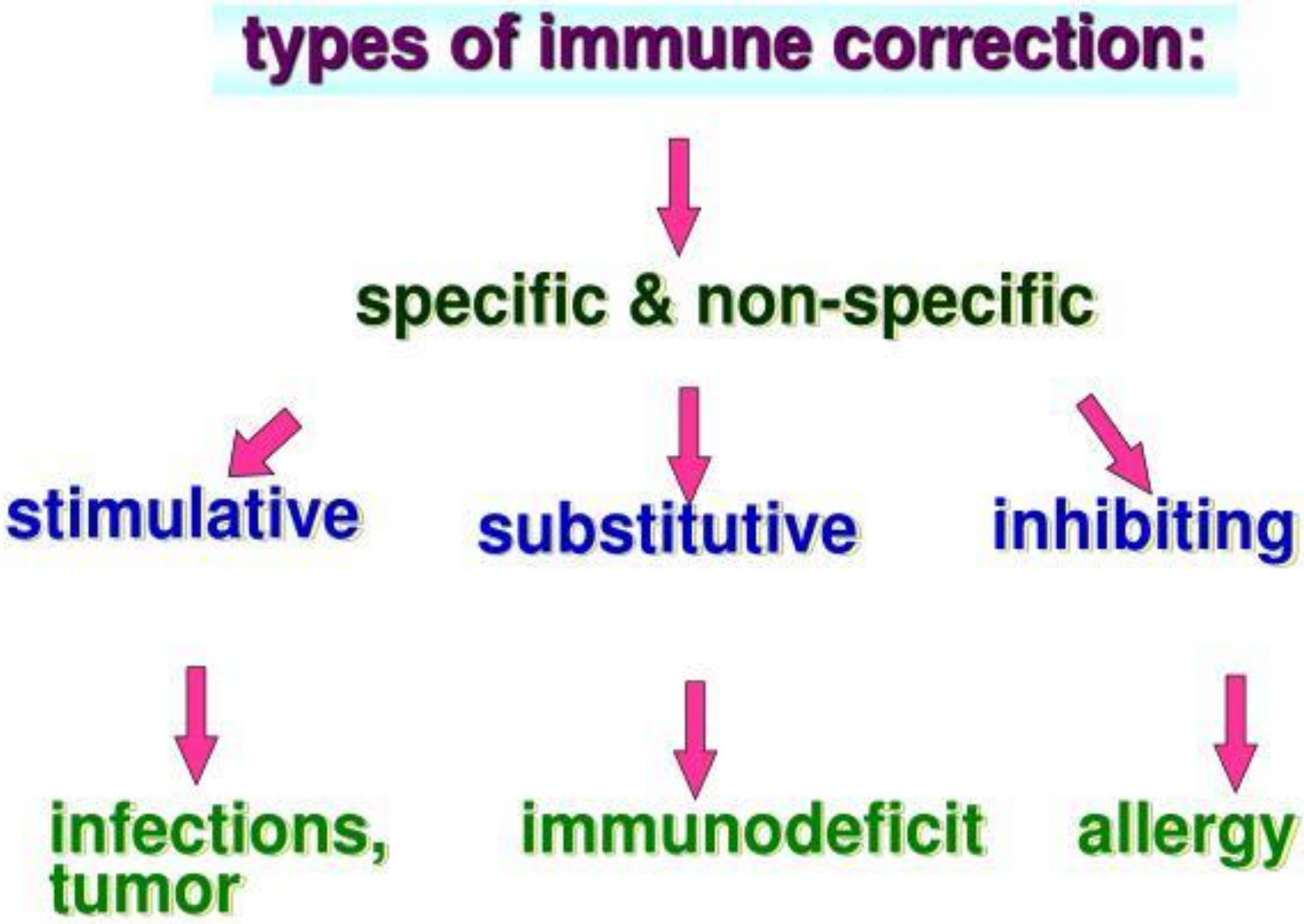
PHARMACOTHERAPY OF ANAPHYLACTIC SHOCK:

- ✓ Adrenomimetics (adrenaline, ephedrine, noradrenaline, mesaton)
- ✓ Glucocorticoids (prednisolone, hydrocortisone, dexamethasone)
- ✓ H_1- blockers (diprazin, dimedrol, suprastin)
- ✓ Miotropic agents (euphylline)
- ✓ Analeptics (cordiamine, sulfocamphocaine)

Immunomodulators



IMMUNOPHARMACOLOGY –



CLASSIFICATION OF IMMUNOSTIMULATORS

group	*agents*
mainly stimulate nonspecific immunity	derivatives of purine and pyrimidine (methyluracil, pentoxyl)
mainly stimulate monocytes (macrophages)	sodium nucleinate, zymozan, vaccines (BCG), pyrogenal, prodigiosane
mainly stimulate T- lymphocytes	dibazol, thymalin, tactivin, vilozen, zinc agents, interleukines (IL-2)
mainly stimulate B-lymphocytes	myelopid, taficin, rigin, dalargin, amastin etc.
mainly stimulate NK and K-cells	interferons, filgrastim, molgramostim, placenta extract
others (plant origin, hormones, vitamins etc.)	adaptogens; vitamins C,E,A; anabolic steroids and non-steroids

1. **Stimulators of nonspecific immunity – methyluracil, pentoxyl.**

- ✓ **Effects:** hasten cellular regeneration, wound closing; stimulate cellular and humoral immunity.
- ✓ **Indications:** mild leucopenia, badly closed wounds, burns, bone crash.
- ✓ **Adverse effecs:** usually well-tolerated.

2. **Stimulators of macrophages and T-lymphocytes – sodium nucleate, BCG, pyrogenal.**

Obtaining: sodium nucleate is obtained by hydrolysis of yeast; pyrogenal – microbial polysaccharide from Pseudomonas aeruginosa.

Therapeutic uses:

sodium nucleate – different diseases with leucopenia;

BCG – leukemia; carcinoma of breast, urinary bladder, intestine;

pyrogenal – chronic prostatitis, chronic inflammation of female reproductive system; inflammation and damage of peripheral and central nervous system.

3. Mostly stimulate NK & K-cells

Interferons possess antimicrobial, antiproliferative and anticancer activity.

There are **three types of interferons:**

- α-(leukocyte)
- β-(fibroblast)
- γ-(T-lymphocyte)

Uses:

- ✓ **Natural α-interferon** are used locally for common cold, herpes keratitis.
- ✓ **Recombinant α-interferon (reaferon, laferon)** are used for hepatitis B & C; leukemia; carcinoma of urinary bladder and intestine.
- ✓ **Recombinant β-interferon (betaferon)** – for multiple sclerosis.

Cytokines with colony-stimulating properties:

- granulocyte colony-stimulating factor (filgrastim);
- granulocyte-macrophage colony-stimulating factor (molgrastim).

Filgrastim stimulates formation of granulocytes; **molgramostim** – mixed granulocyte-macrophage colony. They hasten recovery from neutropenia in patients after chemotherapy and after bone marrow transplantation.

Poludan, amixin – stimulates the synthesis of endogenous interferon. Poludan is used locally for viral ophthalmic disease; amixin - at hepatitis B & C.

CLASSIFICATION OF ИMMUNO-SUPPRESSANT & CYTOTOXIC AGENTS

- antimetabolites: mercaptopurine, azathioprine, methotrexate, and ftoruracil
- alkylating agents: cyclophosphane, chlorbutine, sarcolysin, myelosan, etc
- antibiotics: cyclosporin A, actinomycin, dactinomycin, rubomycin, doxorubicin
- hormones and their antagonists : prednisolone, dexamethasone, phosphoestrol etc.
- antibodies: antilymphocytic globulin (ALG)
- NSAIDs: butadion, indomethacin etc.
- miscellaneous: vincristin, vinblastin, asparaginase; chloroquine.

1. Alkylating agents

Mechanism of action: alkylations of DNA within the nucleus

Indications: leukemia, Hodgkin's disease, ovarian and breast cancer

2. Antimetabolites

Mechanism of action : analogs of physiologic metabolites. **Mercaptopurine** and **azathioprine** – analogs of purines; **methotrexate** – folic acid; ftoruracil – pyrimidines. Inhibit DNA and protein synthesis.

Indications: leukemia; intestinal cancer, breast and gastric cancer; organs transplantation; autoimmune diseases

3. **Antibiotics**

Mechanism of action : inhibit DNA synthesis. Also cyclosporin inhibits T-lymphocytes differentiation, caused antigen action.

Indications: breast, endometrial, and thyroid carcinoma; cancer of lungs and kidney; organs transplantation; autoimmune diseases

4. Periwinkle alkaloids **(vincristin, vinblastin)**

Mechanism of action : mitosis inhibition.

Indications: leukemia, Hodgkin's disease.

5. Enzymes **(L-asparaginase)**

Mechanism of action : spliting of L-asparagine.

Indications: lymphosarcoma, leukemia.

ADVERSE EFFECTS OF IMMUNOSUPPRESSANTS

initial:

- disturbance of bone marrow function
- disturbance of GIT function
- predisposition to infections
- allergic reactions

postponed:

- cancerogenic (cytotoxic agents)
- disturbance of reproductive system (10-70%) and teratogenic effect
- growth retardation in children
- others: hyperpigmentation, lungs fibrosis, hemorrhagic cystitis, alopecia; hepatotoxicity (antimetabolites)


Thank You!!!