B.PHARM 5TH SEMESTER

PHARMACOLOGY-II BP503T UNIT-III

AUTACOID

The word autacoid comes from the Greek: ¨***autos*** *(self)* & ¨**akos** (medicinal agent, or remedy)

INTRODUCTION:

- Histamine, serotonin, prostaglandins, & some vasoactive peptides belong to a group of compounds called autacoids .
- They all have the common feature of being formed by the tissues on which they act so they function as local hormones
- The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands.

TYPES: The important autacoids include:

- Histamine,
- Hydroxytryptamine (5-HT, serotonin),
- Prostaglandins,
- Leukotrienes, and
- Kinins.

HISTAMINE

Histamine (Beta-aminoethyl-imidazole) is formed from **decarboxylation of Imidazole ring** containing amino acid histidine. Histamine is a basic amine, stored in mast cell and basophil granules, and secreted when C3a and C5a interact with specific membrane receptors or when antigen interacts with cell-fixed immunoglobulin E. Histamine plays a central role in immediate **hypersensitivity (Type 1) and allergic responses.**

The actions of histamine on bronchial smooth muscle and blood vessels account for many of the symptoms of the allergic response. In addition, certain clinically useful drugs can act directly on mast cells to release histamine, thereby explaining some of their untoward effects.

Histamine has a major role in the regulation of gastric acid secretion and also modulates neurotransmitter release. **Stimulation of IgE receptors also activates phospholipase A_2 (PLA_2)**, leading to the production of a host of mediators, including platelet-activating factor (PAF) and metabolites of arachidonic acid. Leukotriene D_4, which

is generated in this way, is a potent contractor of the smooth muscle of the bronchial tree.

Kinins also are generated during some allergic responses. Thus the mast cell secretes a variety of inflammatory mediators in addition to histamine, each contributing to the major symptoms of the allergic response. **Epinephrine and related drugs that act through b_2 adrenergic receptors increase cellular cyclic AMP and thereby inhibit the secretory activities of mast cells**. **So are given in anaphylactic shock treatment.** However, the beneficial effects of b adrenergic agonists in allergic states such as asthma are due mainly to their relaxant effect on bronchial smooth muscle.

Cromolyn or Cromoglicate sodium is used clinically because it inhibits the release of mediators from mast and other cells in the lung.

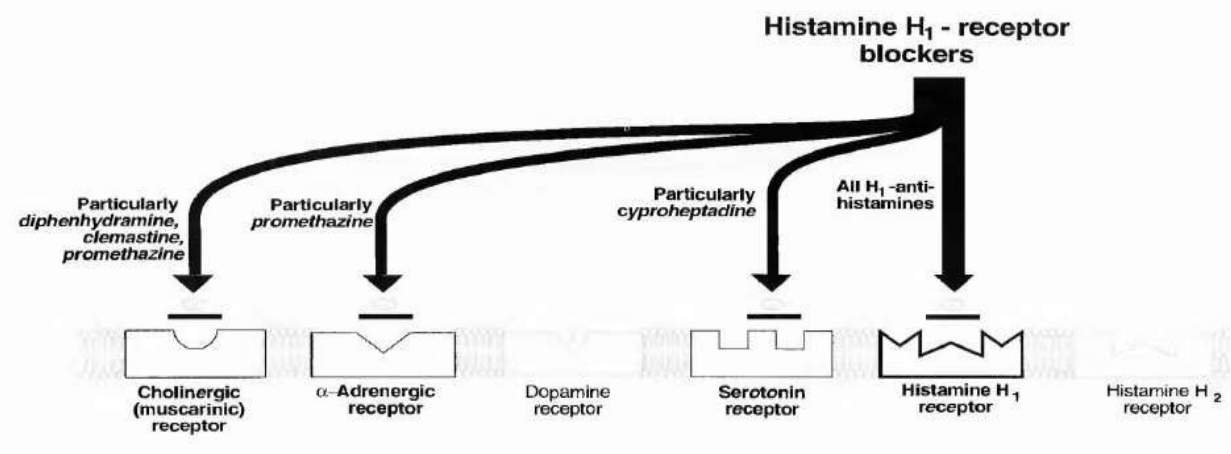
Drug which release histamine: **Tubocurarine, succinylcholine, morphine, Polymyxin B, bacitracin, Vancomycin**-induced "red-man syndrome" involving upper body and facial flushing and hypotension may be mediated through histamine release. Bradykinin is a poor histamine releaser, whereas kallidin (Lys-bradykinin) and substance P, with more positively charged amino acids, are more active.

- Histamine produces effects by acting on H_1, H_2 or H_3 (and possibly H_4) receptors on target cells.
- The main actions in humans are:
    - **Stimulation of gastric secretion (H_2)**
    - **Contraction of most smooth muscle**, except blood vessels (H_1)
    - **Cardiac stimulation (H_2)**
    - **Vasodilatation (H_1)**
    - Increased vascular permeability (H_1).
- Injected intradermally, histamine causes the **'triple response'**: ***reddening*** (local vasodilatation), ***weal*** (direct action on blood vessels) and flare (from an 'axon' reflex in sensory nerves releasing a peptide mediator).
- The main pathophysiological roles of histamine are:
    - as a stimulant of gastric acid secretion (treated with H_2-receptor antagonists)
    - as a mediator of type I hypersensitivity reactions such as urticaria and hay fever (treated with H_1- receptor antagonists).
- H_3 receptors occur at presynaptic sites and inhibit the release of a variety of neurotransmitters.

H_1 antagonists

A. Sedating H_1 antagonists (1st generation antihistaminics**)**

1. **Chlorpheniramine , Clemastine**
2. **Diphenhydramine- Mainly used as a mild hypnotic, also** show significant **antimuscarinic** effects
3. **Cyproheptadine - Used also for migraine due to additional** 5-hydroxytryptamine antagonist activity
4. **Promethazine- Also used for motion sickness, Used for anaesthetic premedication to prevent post- operative vomiting, , weak blockade at α_1 adrenoceptors**
5. **Hydroxyzine – used also to treat anxiety**
6. **Alimemazine- Used for premedication**
7. **Doxylamine, Triprolidine** - Mainly used as an ingredient of proprietary **decongestant** and other medicines



B. Non-sedating H_1 antagonists (2nd generation antihistaminics, Do not penetrate the blood-brain barrier**)**

1. Desloratidine: Metabolite of loratidine
2. Fexofenadine: Metabolite of Terfenadine
3. Levocetrizine: Isomer of cetrizine
4. **Terfenadine: Grapefruit juice inhibits metabolism; rare fatal arrhythmias or QT interval prolongation** as it blocks the K+ conduction in heart leading to ventricular tachycardia. The arrhythmiac

potential increases when given with erythromycin, ketoconazole etc.

5. **Mizolastine: May cause QT interval prolongation**
6. **Azelastine:** in addition to inhibit histamine release, it also inhibits inflammation triggered by leukotrienes and given as nasal spray for rhinitis.
7. **Acrivastine**
8. **Loratidine**

Some important drugs:

I. Antihistaminic which increases the appetite and weight gain: Buclizine

II. (used for underweight children), **Cyproheptadine, Astimazol**

III. **Appetite suppressant**

While the adnergic drugs called anorectics like **Fenfluramine and Desfluramine is appetite suppressant.**

IV. local anaesthetic property :

Mepyramine also have **local anaesthetic property** also or membrane stabilizing activity (antiarrythimic)

V. Cinnarizine: is drug choice for vertigo, it is antihistaminic, anticholinergic, anti-5-HT and vasodilator

It inhibits vestibular sensory nuclei, post-rotatary labyrinthine refluxes by **reducing the calcium influx from endolympth** into vestibular sensory cells.

VI. Diphenhydramine is generally combined with Thecolic acid to reduce the sedative effect of diphenhydramine.

H_2 blockers: are used to treat ulcers and includes the drug like **cimetidine, ranitidine** etc.

EICOSANOIDS

The cell damage associated with inflammation acts on cell membranes to cause leukocytes to release lysosomal enzymes; arachidonic acid is then liberated from precursor compounds, and various eicosanoids are synthesized.

The cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins, which have a variety of effects on blood vessels, on nerve endings, and on cells involved in inflammation.

The discovery of cyclooxygenase isoforms (COX-1 and COX-2) led to the concepts that the constitutive COX-1 isoform tends to be homeostatic in function, **while COX-2 is induced during inflammation and tends to facilitate the inflammatory response**.

On this basis, highly selective COX-2 inhibitors have been developed and marketed on the assumption that such selective inhibitors would be safer than nonselective COX-1 inhibitors but without loss of efficacy.

The lipoxygenase pathway of arachidonate metabolism yields leukotrienes, which have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability.

Kinins, neuropeptides, and histamine are also released at the site of tissue injury, as are complement components, cytokines, and other products of leukocytes and platelets. Stimulation of the neutrophil membranes produces oxygen-derived free radicals.

Superoxide anion is formed by the reduction of molecular oxygen, which may stimulate the production of other reactive molecules such as hydrogen peroxide and hydroxyl radicals. The interaction of these substances with arachidonic acid results in the generation of chemotactic substances, thus perpetuating the inflammatory process.

In mammals, the main eicosanoid precursor is **arachidonic acid (5, 8, 11, 14-eicosatetraenoic acid)**, a 20-carbon unsaturated fatty acid containing four double bonds (hence eicosa, referring to the 20 carbon atoms, and tetraenoic, referring to the four double bonds).

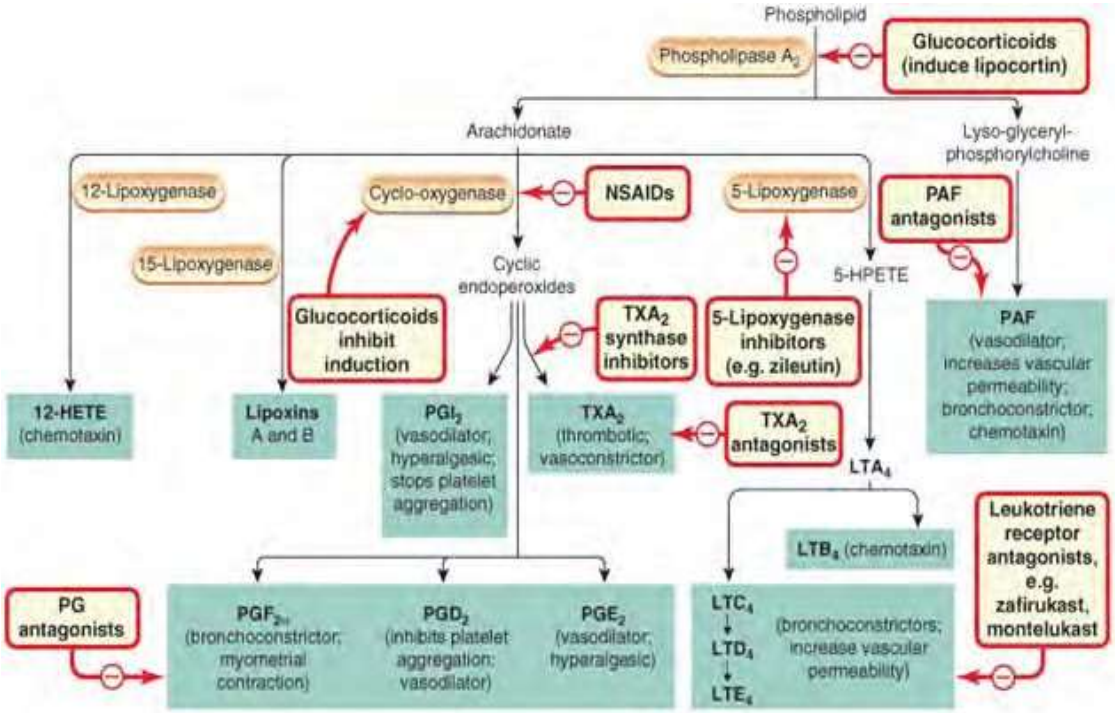
In most cell types, arachidonic acid is esterified in the phospholipid pool, and the concentration of the free acid is low. The **principal eicosanoids are the prostaglandins, the thromboxanes and the leukotrienes, although other derivatives of arachidonate, for example the lipoxins,** are also produced.

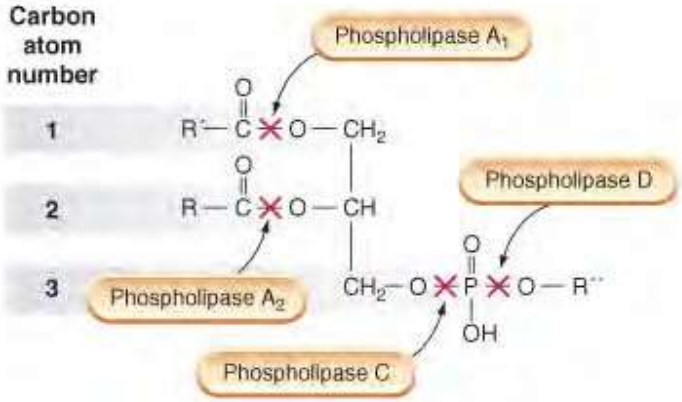
In most instances, the initial and rate-limiting step in eicosanoid synthesis is the liberation of arachidonate, either in a one-step process or a two-step process, from phospholipids by the enzyme phospholipase A_2 (PLA_2).

Several species exist, but the most important is probably the highly regulated cytosolic PLA_2. This enzyme generates not only arachidonic acid (and thus eicosanoids) but also **lysoglyceryl-phosphorylcholine (lyso-PAF), the precursor of platelet activating factor, another inflammatory mediator.**

The free arachidonic acid is metabolised by several pathways, including the following.

- Fatty acid cyclo-oxygenase (COX). Two main isoform forms, COX-1 and COX-2, transform arachidonic acid to prostaglandins and thromboxanes.
- Lipoxygenases. Several subtypes synthesize leukotrienes, lipoxins or other compounds


Phospholipid
Phospholipase A2
Glucocorticoids (induce lipocortin)
Arachidonate
Lyso-glyceryl-phosphorylcholine
12-Lipoxygenase
Cyclo-oxygenase
NSAIDs
5-Lipoxygenase
PAF antagonists
15-Lipoxygenase
Cyclic endoperoxides
5-HPETE
Glucocorticoids inhibit induction
TXA2 synthase inhibitors
5-Lipoxygenase inhibitors (e.g. zileutin)
PAF (vasodilator; increases vascular permeability; bronchoconstrictor; chemotaxin)
12-HETE (chemotaxin)
Lipoxins A and B
PGI2 (vasodilator; hyperalgesic; stops platelet aggregation)
TXA2 (thrombotic; vasoconstrictor)
TXA2 antagonists
LTA4
LTB4 (chemotaxin)
Leukotriene receptor antagonists, e.g. zafirukast, montelukast
PG antagonists
PGF2α (bronchoconstrictor; myometrial contraction)
PGD2 (inhibits platelet aggregation; vasodilator)
PGE2 (vasodilator; hyperalgesic)
LTC4
LTD4
LTE4
(bronchoconstrictors; increase vascular permeability)


Carbon atom number
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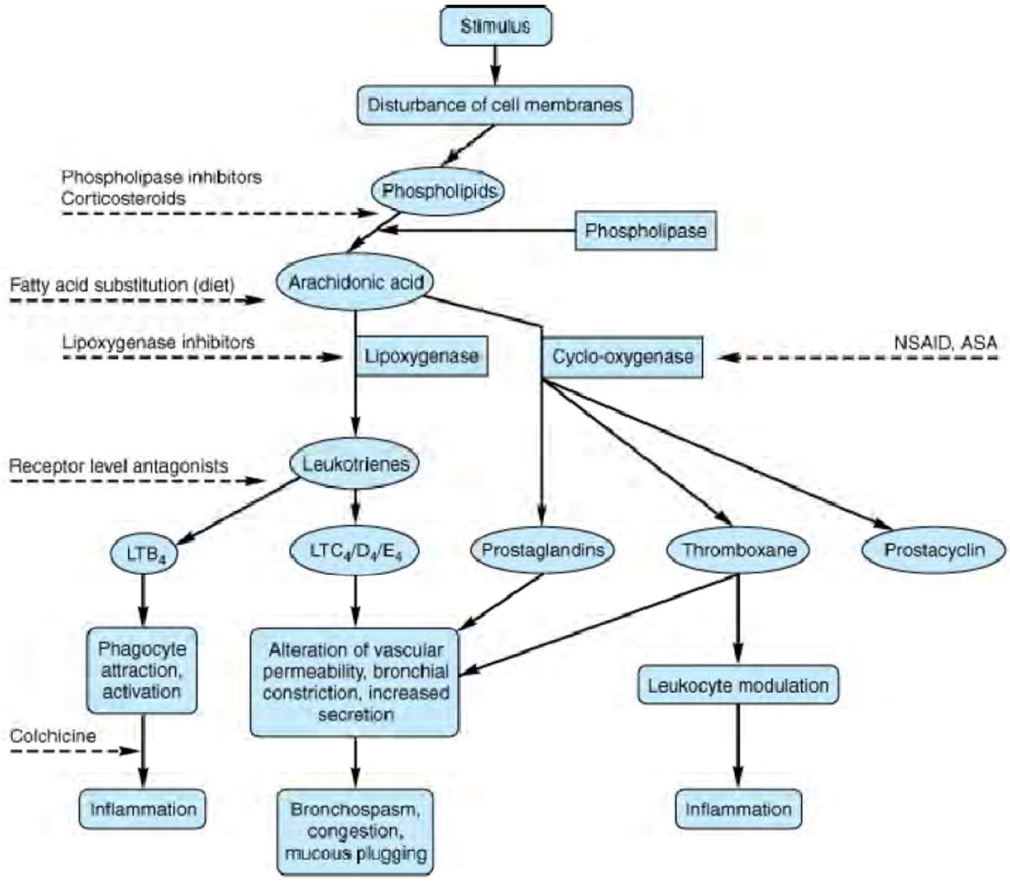
2
3
Phospholipase A1
Phospholipase D
Phospholipase A2
Phospholipase C



The term *prostanoids* encompasses the prostaglandins and the thromboxanes.

- PGI_2 **(prostacyclin)**, predominantly from **vascular endothelium**, acts on IP receptors, producing vasodilatation and inhibition of platelet aggregation.
- Thromboxane (TX) A_2, predominantly from platelets, acts on TP receptors, **causing platelet aggregation and vasoconstriction.**
- PGE_2 is prominent in inflammatory responses and is a mediator of fever. Main effects are:
    - EP_1 receptors: contraction of bronchial and gastrointestinal tract (GIT) smooth muscle
    - EP_2 receptors: relaxation of bronchial, vascular and GIT smooth muscle
    - EP_3 receptors: inhibition of gastric acid secretion, **increased gastric mucus secretion**, contraction of pregnant uterus and of GIT smooth muscle, inhibition of lipolysis and of autonomic neurotransmitter release.
- $PGF_{2\alpha}$ acts on FP receptors, found in uterine (and other) smooth muscle, and corpus luteum,

producing **contraction of the uterus** and luteolysis (in some species).

- PGD_2 is derived particularly from mast cells and acts on DP receptors, causing vasodilatation and inhibition of platelet aggregation.

Prostaglandins of the E series are also pyrogenic (i.e. they induce fever). High concentrations are found in cerebrospinal fluid during infection, and there is evidence that the increase in temperature (attributed to cytokines) is actually finally mediated by the release of PGE_2. NSAIDs exert antipyretic actions by inhibiting PGE_2 synthesis in the hypothalamus.

Clinical uses of prostanoids

- Gynecological and obstetric
  - termination of pregnancy: **Gemeprost** or **misoprostol** (a metabolically stable prostaglandin (PG)
    (PG E analogue)
  - induction of labour: **Dinoprostone (PGE₂ analogue)** or **misoprostol**
  - Postpartum haemorrhage: **Carboprost (15-α methyl PGF2α analogue)**
- Gastrointestinal
  - to prevent ulcers associated with non-steroidal anti-inflammatory drug use: **misoprostol**
- Cardiovascular
  - to maintain the patency of the ductus arteriosus until surgical correction of the defect in babies with certain congenital heart malformations: **Alprostadil** (PGE_1)
  - to inhibit platelet aggregation (e.g. during haemodialysis): **Epoprostenol** or **Cicaprost (PGI_2 analogue),** especially if heparin is contraindicated
  - Primary pulmonary hypertension: **Epoprostenol**.
- Ophthalmic
  - Open-angle glaucoma: **latanoprost ($PGF_{2\alpha}$ analogue)** eye drops.

Dinoprostone (PGE_2 analogue)

Carboprost(15-αmethylPGF2α

latanoprost ($PGF_{2\alpha}$ analogue)

Misoprostol (PGE_1 analogue)

Misoprostol is approved for **use in the prevention of** NSAID**-induced gastric ulcers.** It acts upon gastric parietal cells, inhibiting the secretion of gastric acid via G-protein coupled receptor-mediated inhibition of adenylate cyclase, which leads to decreased intracellular cyclic AMP levels and decreased proton pump activity at the apical surface of the parietal cell.

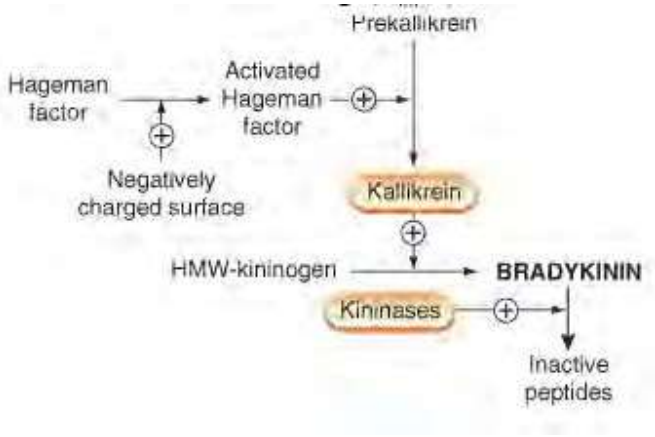
Because other classes of drugs, especially H2-receptor antagonists and proton pump inhibitors, are more effective for the treatment of acute peptic ulcers, Misoprostol is only indicated for use by people who are both taking NSAIDs and are at high risk for NSAID-induced ulcers, including the elderly and people with ulcer complications.

Misoprostol is sometimes co-prescribed with NSAIDs to prevent their common adverse effect of gastric ulceration (e.g. with Diclofenac in Arthrotec). Misoprostol may stimulate **increased secretion of the protective** mucus that lines the gastrointestinal tract and increase mucosal blood flow, thereby increasing mucosal integrity—however, these effects are not pronounced enough to warrant prescription of misoprostol at doses lower than those needed to achieve gastric acid suppression

BRADYKININ

BK is a nonapeptide 'clipped' from a plasma α-globulin, *kininogen*, by *kallikrein*.

- It is converted by *kininase I* to an octapeptide, BK_{1-8} (des-Arg^9-BK), and inactivated by *kininase II* (angiotensin-converting enzyme) in the lung.
- Pharmacological actions:
  - **vasodilatation (largely dependent on endothelial cell nitric oxide and prostaglandin I_2)**
  - increased vascular permeability
  - **stimulation of pain nerve endings**
  - stimulation of epithelial ion transport and fluid secretion in airways and gastrointestinal tract
  - Contraction of intestinal and uterine smooth muscle.
- There are two main subtypes of BK receptors: B_2, which is constitutively present, and B_1, which is induced in inflammation.



Leukotrienes

- 5-Lipoxygenase oxidises arachidonate to give 5-hydroperoxyeicosatetraenoic acid (5-HPETE), which is converted to leukotriene (LT) A_4. This, in turn, can be converted to either LTB_4 or to a series of glutathione adducts, the cysteinyl-leukotrienes LTC_4, LTD_4 and LTE_4.
- **LTB_4 mainly involves in inflammatory cells,** acting on specific receptors, causes adherence, **chemotaxis** and activation of polymorphs and monocytes, and stimulates proliferation and cytokine production from macrophages and lymphocytes.
- The cysteinyl-leukotrienes cause:
  - **Contraction of bronchial muscle mainly LTC_4, LTD_4**

- Vasodilatation in most vessels, but coronary vasoconstriction.
- LTB_4 is an important mediator in all types of inflammation; the cysteinyl-leukotrienes are of particular importance in asthma.
- **The CysLT-receptor or leukotriene antagonist** zafirlukast **and montelukast** are now in use in the treatment of asthma. Cysteinyl-leukotrienes may mediate the cardiovascular changes of acute anaphylaxis.

ASTHMA

Asthma is defined as recurrent reversible airway obstruction, with attacks of wheeze, shortness of breath and often nocturnal cough. Severe attacks cause hypoxaemia and are life-threatening. Essential features include: airways inflammation, which causes bronchial hyper-responsiveness, which in turn results in recurrent reversible airway obstruction. Pathogenesis involves exposure of genetically disposed individuals to allergens; activation of Th2 lymphocytes and cytokine generation promote:

- Differentiation and activation of eosinophils
- IgE production and release
- Expression of IgE receptors on mast cells and eosinophils.
- Important mediators include leukotriene B_4 and cysteinyl leukotrienes (C_4 and D_4); interleukins IL- 4, IL-5, IL-13; and tissue-damaging eosinophil proteins.

DRUGS USED TO TREAT ASTHMA

There are two categories of antiasthma drugs: *bronchodilators* and *anti-inflammatory agents*. Bronchodilators reverse the bronchospasm of the immediate phase; anti-inflammatory agents inhibit or prevent the inflammatory components of both phases.

Theophylline and *leukotriene antagonists*, such as **montelukast**, also exert a corticosteroid-sparing effect **Cromoglicate** (see below) has only a weak effect and is now seldom used.

BRONCHODILATORS

The main drugs used as bronchodilators are β_2-*adrenoceptor agonists*; others include xanthines, cysteinyl leukotriene receptor antagonists and muscarinic receptor antagonists.

β-Adrenoceptor agonists

Two categories of β_2-adrenoceptor agonists are used in asthma.

- Short-acting agents: **Salbutamol** and **Terbutaline**, duration of action is 3-5 hours.
- Longer-acting agents: e.g. **Salmeterol** and **Formoterol**, the duration of action is 8-12 hours.
- Others are **Adrenaline, Ephedrine, Isoprenaline**

Xanthine drugs

There are three pharmacologically active, naturally occurring methylxanthines: *theophylline* , *theobromine* and *caffeine* . Theophylline (1,3-dimethylxanthine), which is also used as theophylline ethylenediamine (known as aminophylline), is the main therapeutic drug of this class.

Actions

Antiasthmatic. Methylxanthines have long been used as **bronchodilators**.

Central nervous system. Methylxanthines **stimulate** the CNS, increasing alertness. They can cause tremor and nervousness, and can interfere with sleep and have a stimulant action on respiration. This may be useful in patients with COPD and reduced respiration evidenced by a tendency to retain CO_2 (see below).

Cardiovascular. Methylxanthines **stimulate** the heart having **positive chronotropic and inotropic actions**, while relaxing vascular smooth muscle. They cause generalised vasodilatation but constrict cerebral blood vessels.

Kidney. Methylxanthines are **weak diuretics**, although this effect is not therapeutically useful.

Mechanisms of action

The relaxant effect on smooth muscle has been attributed to inhibition of the phosphodiesterase (PDE) isoenzymes, with resultant increase in cAMP and/or cGMP . However, the concentrations necessary to inhibit the isolated enzymes exceed the therapeutic range of plasma concentrations.

Competitive antagonism of *adenosine* at adenosine A_1 and A_2 receptors may contribute, but the PDE inhibitor **enprofylline**, which is a potent bronchodilator, is **not** an adenosine antagonist.

Type IV PDE is implicated in inflammatory cells and non-specific methylxanthines may have some anti-inflammatory effect. (**Roflumilast**, a type IV PDE inhibitor.

Clinical use of theophylline

- As a second-line drug, in addition to steroids, in patients whose *asthma* does not respond adequately to β_2-adrenoceptor agonists.
- Intravenously (as aminophylline , a combination of theophylline **with ethylenediamine** to increase its solubility in water) in *acute severe asthma.*

Muscarinic receptor antagonists

The main compound used as a bronchodilator is **ipratropium,** is a quaternary derivative of *N*-isopropylatropine.

Cysteinyl leukotriene receptor antagonists

All the cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4) act on the same high-affinity cysteinyl leukotriene receptor termed *CysLT*$_1$. Two receptors have been cloned, $CysLT_1$ and $CysLT_2$, and both are expressed in respiratory mucosa and infiltrating inflammatory cells, but the functional significance of each is unclear. The **'lukast' drugs** (**montelukast** and zafirlukast) **antagonise only $CysLT_1$.**

Used for some patients with *chronic obstructive pulmonary disease,* especially long-acting drugs (e.g.

tiotropium). **ANTI-INFLAMMATORY AGENTS**

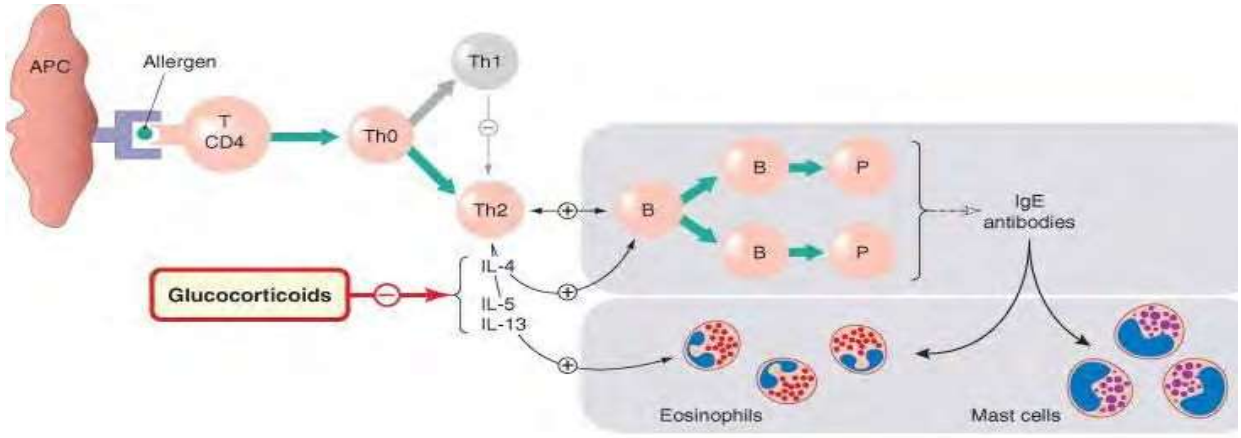
The main drugs used for their anti-inflammatory action in asthma are the

glucocorticoids. **Glucocorticoids**

Systemic : Prednisolone, Hydrocortisone

Inhalational: Triamcinolone, Beclomethasone

They are not bronchodilators but prevent the progression of chronic asthma and are effective in acute severe asthma.



Actions and mechanism

The basis of the anti-inflammatory action of glucocorticoids . An important action, of relevance for asthma, is that they **decrease formation of cytokines**), in particular the Th_2 cytokines that recruit and activate eosinophils and are responsible for promoting the production of IgE and the expression of IgE receptors . Glucocorticoids also **inhibit** the generation of the vasodilators PGE_2 and PGI_2, by **inhibiting phospholipase A_2**. **By inducing *annexin 1*, they could inhibit production of leukotrienes and platelet-activating factor**, although there is currently no direct evidence that the release of this protein is involved in the antiasthma effects of glucocorticoids. The main compounds used are **beclometasone**, budesonide , **fluticasone**, **mometasone** and **ciclesonide**.

Cromoglicate and nedocromil ('mast cell stabiliser')

These drugs are now hardly used for the treatment of asthma. Cromoglicate is a **'mast cell stabiliser'**,

preventing hista release from mast cells.

Anti-IgE treatment

Omalizumab is a humanised monoclonal anti-IgE antibody. It is effective in patients with allergic as allergic rhinitis.

COUGH

Cough is a protective reflex that removes foreign material and secretions from the bronchi and bronchioles. It is a very common adverse effect of *angiotensin-converting enzyme inhibitors.*

Drugs for cough

Codeine (methylmorphine) is a weak opioid. **Dextromethorphan** and **pholcodine** are believed to have fewer adverse effects.

NSAIDS

They provide symptomatic relief from pain and swelling in chronic joint disease such as occurs in osteo- and rheumatoid arthritis, and in more acute inflammatory conditions such as sports injuries, fractures, sprains and other soft tissue injuries. They also provide relief from postoperative, dental and menstrual pain, and from the pain of headaches and migraine.

COX-1 is a constitutive enzyme expressed in most tissues, including blood platelets. It has a 'housekeeping' role in the body, being involved in tissue homeostasis, and is responsible for the production of prostaglandins involved in, for example, gastric cytoprotection platelet aggregation renal blood flow auto regulation and the initiation of parturition.
In contrast, **COX-2 is induced in inflammatory cells when they are activated, and the primary inflammatory cytokines-interleukin (IL)-1 and tumour necrosis factor (TNF)-α** are important in this regard. Thus the COX-2 isoform is responsible for the production of the prostanoid mediators of inflammation although there are some significant exceptions. For example, there is a considerable pool of 'constitutive' COX-2 present in the central nervous system (CNS) and some other tissues, although its function is not yet completely clear.

Most 'traditional' **NSAIDs are inhibitors of both isoenzymes of COX by inhibiting dioxygenation step.** although they vary in the degree to which they inhibit each isoform. It is believed that the anti-inflammatory action (and probably most analgesic actions) of the NSAIDs is related to their inhibition of COX-2, **while their unwanted effects-particularly those affecting the gastrointestinal tract-are largely a result of their inhibition of COX-1.** Compounds with a selective inhibitory action on COX-2 are now in clinical use, but expectations that these inhibitors would transform the treatment of inflammatory conditions have received a setback **because of an increase in cardiovascular risk (Rolecoxib)**

Normal body temperature is regulated by a centre in the hypothalamus that controls the balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat', which leads to the set point of body temperature being raised. NSAIDs 'reset' this thermostat. **The NSAIDs exert their antipyretic action largely through inhibition of prostaglandin production in the hypothalamus.** During an inflammatory reaction, bacterial endotoxins cause the release from macrophages of a pyrogen-IL-1 which stimulates the generation, in the hypothalamus, of **E-type**

prostaglandins that elevate the temperature set point. COX-2 may have a role here, because it is induced by IL-1 in vascular endothelium in the hypothalamus.

So NASIDS have following actions:

- **Anti-inflammatory action:** the **decrease in prostaglandin E_2 and prostacyclin reduces** vasodilatation and, indirectly, oedema. Accumulation of inflammatory cells is not reduced.

- **An analgesic effect:** decreased prostaglandin generation means less sensitisation of nociceptive nerve endings to inflammatory mediators such as bradykinin and 5-hydroxytryptamine. Relief of headache is probably a result of decreased prostaglandin-mediated vasodilatation.
- **An antipyretic effect:** interleukin-1 releases prostaglandins in the central nervous system, where they elevate the hypothalamic set point for temperature control, thus causing fever. NSAIDs prevent this.

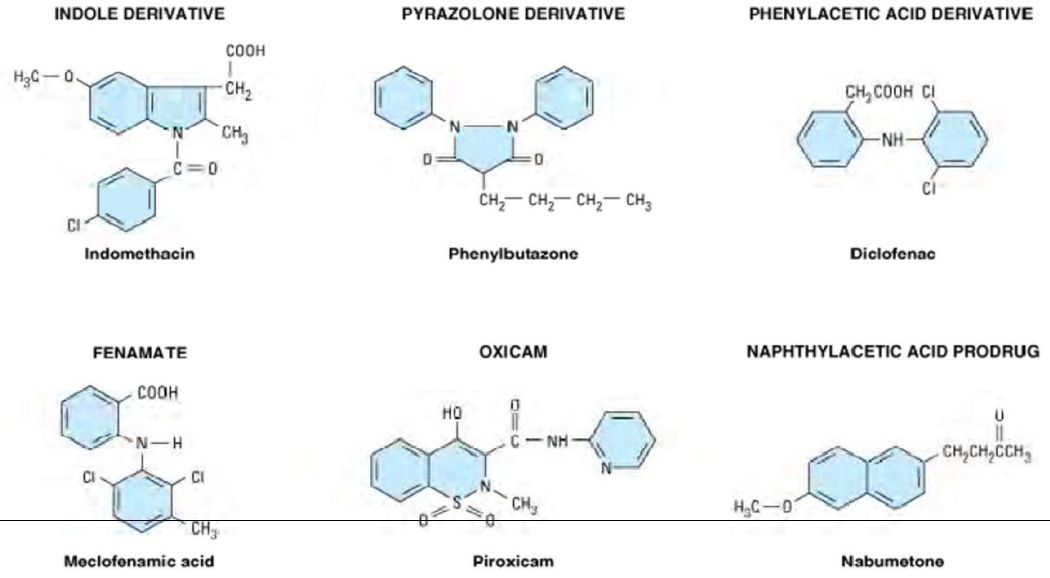
Classification

A. **Nonselective COX inhibitors**
   1. **Salicylates:** Aspirin, Diflunisal
   2. **Pyrazolone derivatives:** Phenylbutazone, Oxyphenbutazone
   3. **Anthranilic acid derivatives:** Mephenamic acid
   4. **Aryl acetic acid derivatives:** Diclofenac
   5. **Indole derivatives:** Indomethacin, Sulindac
   6. **Propionic acid derivatives:** Ibuprofen, Naproxen, Ketoprofen, Flubiprofen
   7. **Oxicam derivatives:** Piroxicam, Tenoxicam
   8. **Pyrrolo-pyrrole derivatives:** Ketorolac

B. **Preferential COX-2 inhibitors:** Nimesulide, Meloxicam, Nabumetone

C. **Selective COX-2 inhibitors:** Celecoxib, Rofecoxib, Valdecoxib, Parecoxib (Prodrug of valdecoxib)

D. **Analgesic-antipyretic with poor anti-inflammatory: Paracetamol**
   1. **Pyrozolone derivatives:** Metamizole (Dipyrone), Propiphenazone
   2. **Benzoxazocine derivatives:** Nefopam



Some important points:

1. **NSAIDS which are prodrugs: Sulindac, Fenoprofen, Nabumetone**
2. **NSAIDS which reduce chemotaxis of leukocytes and useful in acute gout: Indomethacin, Naproxen, Piroxicam**
3. **Drugs for post-operative pain: Ketorolac, Nefopam, Etodolac**
4. **Gastric intolerance to conventional NASIDS uses Rofecoxib or selective COX-2 inhibitors.**
5. **Patients with history of asthma or anaphylaxis:**

Nimesulide Some adverse effects of NASIDS:

- **Aspirin cause local damage to the gastric mucosa directly or some gastric bleeding.** Oral administration of prostaglandin analogues such as misoprostol (PGE1 analogue) can diminish the gastric damage produced by these agents.
- **Severe rashes or** idiosyncratic reaction are common with **Mefenamic acid and Sulindac**.
- Analgesic **nephropathy characterised by chronic nephritis** and renal papillary necrosis is caused by chronic NSAID consumption i.e. **Phenacetin (Prodrug of Paracetamol)** one of its metabolite but paracetamol is safe.
- **Paracetamol over dose can cause liver toxicity.** This occurs when the liver enzymes catalysing the normal conjugation reactions are saturated, causing the drug to be metabolised instead by mixed function oxidases. The resulting toxic metabolite, **N-acetyl-p-benzoquinone imine**, is inactivated by conjugation with glutathione, but when glutathione is depleted the toxic intermediate accumulates and reacts with nucleophilic constituents in the cell. This causes necrosis in the liver and also in the kidney tubules. **The liver damage can be prevented by giving agents that increase glutathione formation in the liver (N-**acetylcysteine **intravenously, or** methionine **orally).**
- **Rolecoxib severe cardiovascular toxicity** and hence banned.
- **Phenylbutazone severe agranulocytosis and fluid retention.**

Aspirin

Aspirin is rapidly hydrolysed by esterases in the plasma and the tissues-particularly the liver-yielding **salicylate.** Salicylate is oxidized, some is conjugated to give the **glucuronide or sulfate before excretion. Aspirin cause Salicylism and Reye's syndrome** (a rare disorder of children that is characterised by hepatic encephalopathy following an acute viral illness).

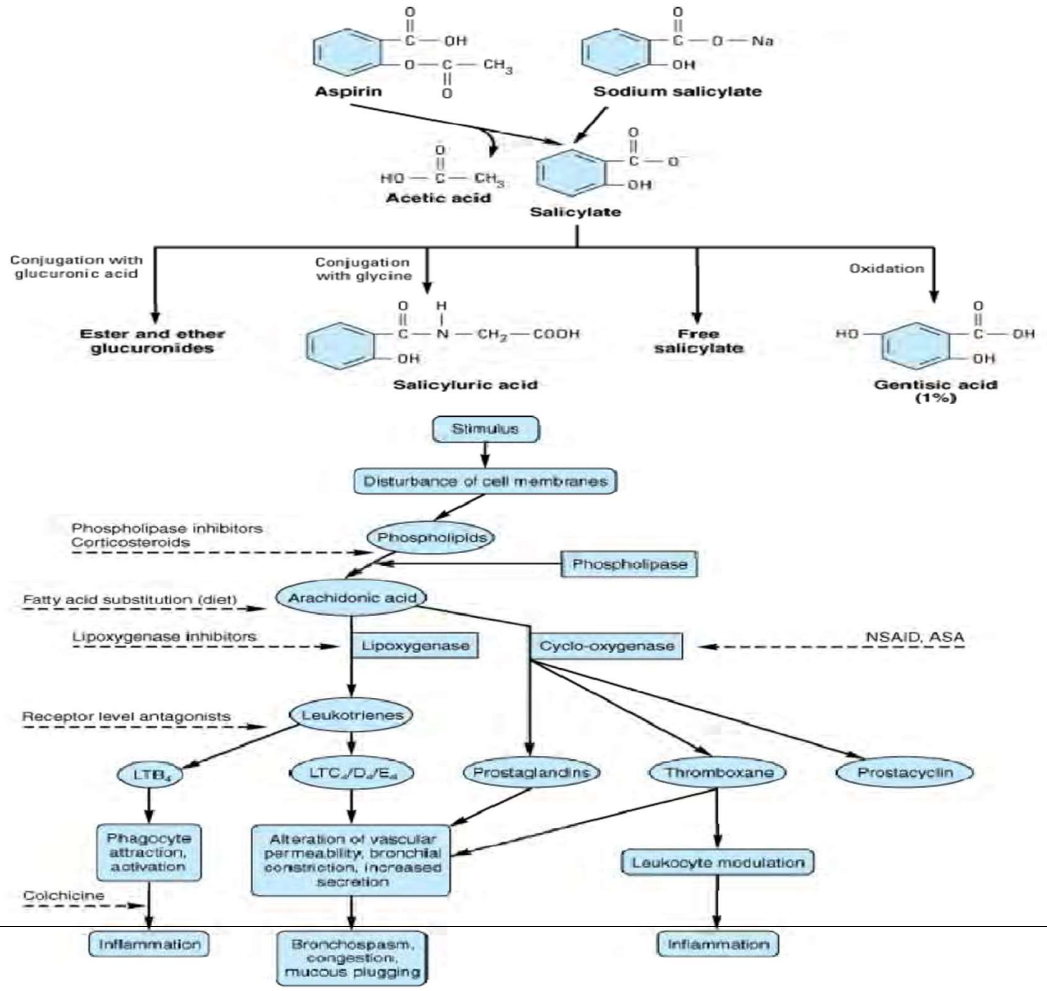
Salicylate poisoning is a result of disturbances of the acid-base and the electrolyte balance that may be seen in patients treated with high doses of salicylate-containing drugs and in attempted suicides. **These drugs can uncouple oxidative phosphorylation** (mainly in skeletal muscle), leading to increased oxygen consumption and thus increased production of carbon dioxide. This stimulates respiration, which is also stimulated by a direct action of the

drugs on the respiratory centre. The resulting hyperventilation causes a **respiratory alkalosis** that is normally compensated by renal mechanisms involving increased bicarbonate excretion. Larger doses can cause a depression of the respiratory centre, which leads eventually to retention of carbon dioxide and thus an increase in plasma carbon dioxide. Because this is superimposed on a reduction in plasma bicarbonate, an uncompensated respiratory acidosis will occur. This may be complicated by a metabolic acidosis, which results from the accumulation of metabolites of pyruvic, lactic and acetoacetic acids (an indirect consequence of interference with carbohydrate metabolism)

- Aspirin causes a potentially hazardous increase in the effect of **warfarin**, **partly by displacing it from plasma proteins so** increase the risk of bleeding.
- Aspirin being a weak acid also interferes with the effect of uricosuric agents such as probenecid and sulfinpyrazone , and because low doses of aspirin may, on their own, **reduce urate excretion, so** aspirin

should not be used in gout.

- Aspirin **potentiates the hypoglycemic** effect of oral hypoglycemic drugs like Tolbutamide, Glibenclamide



Meloxicam: The drug is popular in Europe and many other countries for most rheumatic diseases and has recently been approved for treatment of osteoarthritis in the USA. **Meloxicam is known to inhibit synthesis of thromboxane A_2**; it appears that even at supratherapeutic doses its blockade of thromboxane A2 does not reach levels that result in decreased in vivo platelet function.

Valdecoxib has no effect on platelet aggregation or bleeding time. Valdecoxib was withdrawn from the market in the USA in early 2005 in response to FDA concerns about **cardiovascular risks and Stevens-Johnson syndrome,** but the drug is still available in other countries.

Diflunisal is derived from salicylic acid, it is not metabolized to salicylic acid or salicylate. It undergoes an enterohepatic cycle with reabsorption of its glucuronide metabolite followed by cleavage of the glucuronide to again release the active moiety.

Etodolac provides **good postoperative pain** relief after coronary artery bypass operations, although transient impairment of renal function has been reported.

Ketorolac drug is an effective analgesic and has been used successfully **to replace morphine** in some situations involving mild to moderate postsurgical pain. It is most often given intramuscularly or intravenously.

Nefopam is **a nonopioid analgesic which does not inhibit PG synthesis. It also has anticholinergic activity. It** provides **good postoperative pain** relief

Indomethacin is an indole derivative. It is a potent nonselective COX inhibitor **and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T cell and B cell proliferation. Indomethacin is more effective in relieving inflammation than is aspirin or any of the other NSAIDs.** Indomethacin is indicated for use in rheumatic conditions and is particularly popular for gout and ankylosing spondylitis. In addition, it has been used to **treat patent ductus arteriosus.** Indomethacin can cause CNS effects are dizziness, vertigo, light-headedness, and mental confusion and hence **avoided during the driving of vehicles.**

Piroxicam an oxicam is a nonselective COX inhibitor that at high concentrations **also inhibits polymorphonuclear leukocyte migration or chemotaxis of leukocytes,** decreases oxygen radical

production, and inhibits lymphocyte function. Its long half-life permits once-daily dosing.

Naproxen is potent particularly **inhibiting leukocyte migration and hence suitable for acute gout. Ketoprofen is a propionic acid derivative that inhibits both COX (nonselectively) and lipoxygenase.**

Nabumetone is prodrug and the **only nonacid NSAID** in current use; it is converted to the active acetic acid derivative in the body. It is given as **a ketone prodrug** that resembles naproxen in structure.

Sulindac is a sulfoxide prodrug. It is reversibly metabolized to the active **sulfide metabolite**, which is excreted in bile and then reabsorbed from the intestine. The enterohepatic cycling prolongs the duration of action. In addition to its rheumatic disease indications, sulindac suppresses familial intestinal polyposis; it may inhibit the development of colon, breast, and prostate cancer in humans.

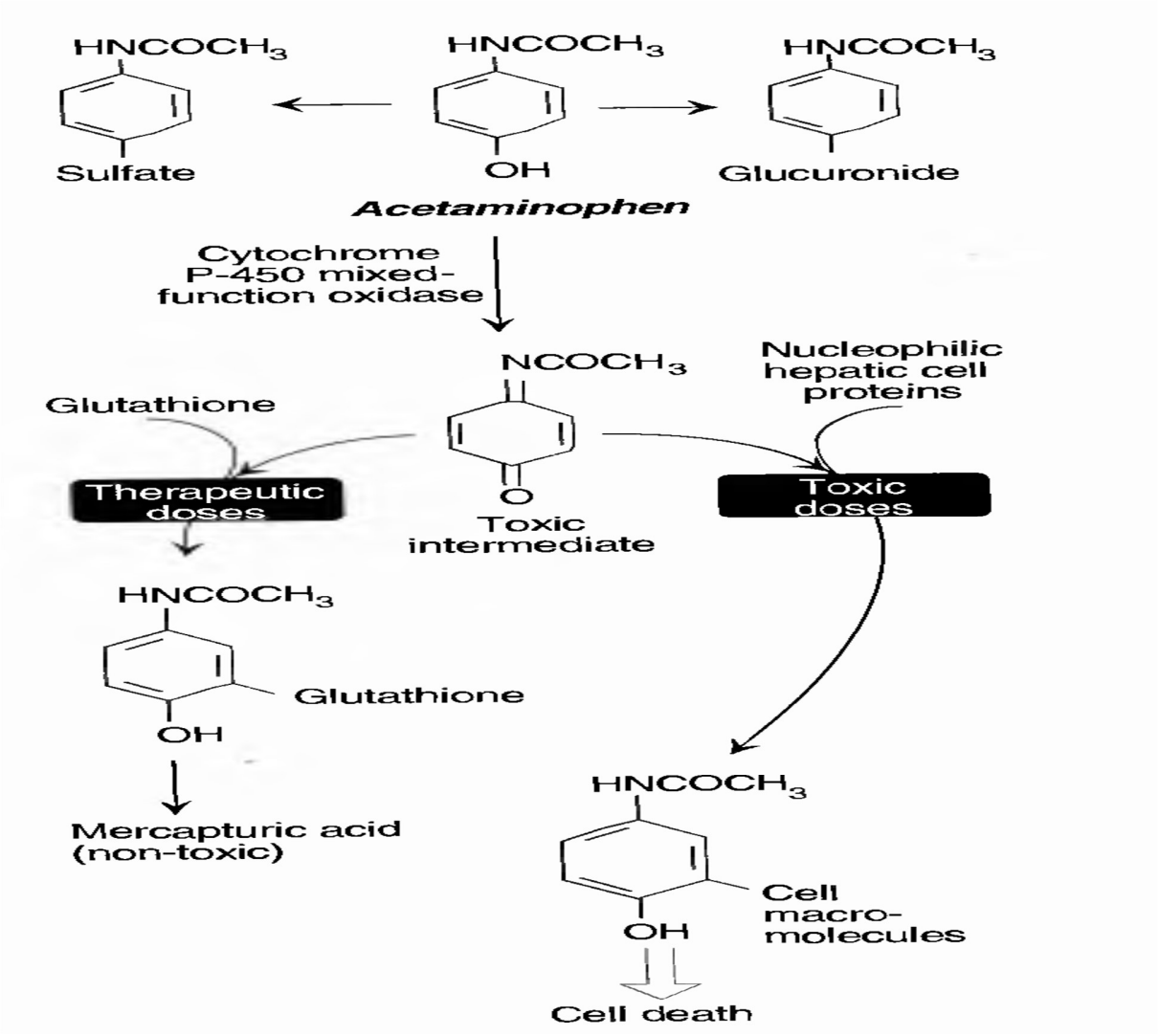
Phenylbutazone has powerful anti-inflammatory effects but **weak analgesic and antipyretic activities.** Phenylbutazone is prescribed chiefly in short term therapy of acute gout and in acute rheumatoid arthritis when **other** NSAID agents have failed. Phenylbutazone is extensively bound to plasma proteins. This property causes displacement of warfarin, oral hypoglycemics and sulfonamides from binding sites on plasma proteins, causing transient elevations in the free fraction of these drugs. **The most serious adverse effects are agranulocytosis and aplastic anemia.** Other side effects include fluid and electrolyte (sodium and chloride) retention, with resulting edema and decreased urine volume. Phenylbutazone **reduces the uptake of iodine by the thyroid gland**, sometimes resulting in goiter and myxedema.

Diclofenac is approved for **long-term use in the treatment of rheumatoid arthritis**, osteoarthritis and ankylosing spondylitis. It is more potent than indomethacin or naproxen. Diclofenac accumulates in synovial fluid.

Acetaminophen or Paracetamol and Phenacetin act by **inhibiting prostaglandin synthesis in the CNS.** This explains their antipyretic and analgesic properties. They have less effect on cyclooxygenase in peripheral tissues, which accounts for their weak anti-inflammatory activity. Acetaminophen and phenacetin do not affect platelet function or increase blood clotting time, and they lack many of the side-effects of aspirin. **Phenacetin can no longer be prescribed in the United States because of its potential for renal toxicity.** Acetaminophen is the analgesic-antipyretic of choice for children with viral infections or chicken pox (aspirin increases the risk of Reye's syndrome). Acetaminophen does not antagonize the uricosuric agent probenecid and therefore may be used in patients with gout taking that drug. Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin in those patients with gastric complaints and in those for whom prolongation of bleeding time would be a disadvantage or who do not require the anti- inflammatory action of aspirin.

Under normal circumstances, acetaminophen is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form **N-acetyl-benzoquinoneimine**--a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups. At normal doses of acetaminophen, the N- acetyl-benzoquinoneimine reacts with the sulfhydryl group of glutathione, forming a nontoxic substance. Acetaminophen and its metabolites are excreted in the urine. With large doses of acetaminophen, the available glutathione in the liver becomes depleted **and N-acetyl-benzoquinoneimine reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds**. Hepatic necrosis, a very serious and potentially life-threatening

condition, can result. Administration of **N-acetylcysteine,** which contains sulfhydryl groups to which the toxic metabolite can bind, can be life-saving if administered within 10 hours of the overdose.



Ibuprofen is safest NASIDS among the conventional NASIDS. **Flurbiprofen is mostly used as ocular anti- inflammatory.**

ANTI-GOUT DRUGS

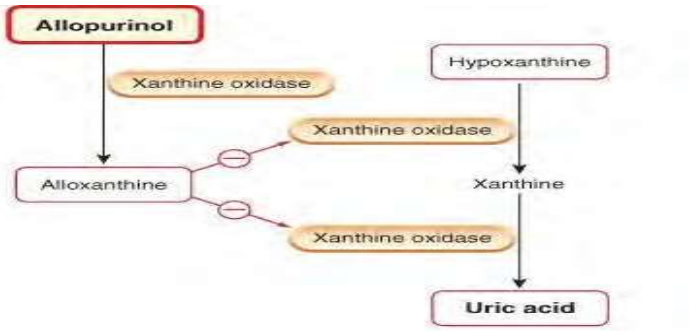
Gout is a metabolic disease in which plasma uriate concentration is raised because of overproduction (sometimes linked to indulgence in alcoholic beverages, especially beer, or purine-rich foods such as offal, or increased cell turnover as in haematological malignancies, particularly when treated with cytotoxic drugs) or impaired excretion of uric acid. It is characterised by very painful intermittent attacks of acute arthritis produced by the **deposition of crystals of sodium urate (a product of purine metabolism) in the synovial tissue of joints and elsewhere**.

When an inflammatory response is evoked, involving activation of the kinin, complement and plasmin systems, generation of lipoxygenase products such as **leukotriene B_4** and **local accumulation of neutrophil granulocytes. These engulf the crystals by phagocytosis, releasing tissue-damaging toxic oxygen metabolites and subsequently causing lysis of the cells with release of proteolytic enzymes. Urate crystals also induce the production of IL-1 and possibly other cytokines too.**

Drugs used to treat gout may act in the following ways:

- By inhibiting uric acid synthesis: **Allopurinol** (**Main prophylactic drug)**
- By increasing uric acid excretion (uricosuric agents: **Probenecid , Sulfinpyrazone** both are also used as **prophylactic drug**)
- By inhibiting leucocyte migration into the joint (**Colchicine for acute attack**)
- By a general anti-inflammatory and analgesic effect (NSAIDs).

Allopurinol is an **analogue of hypoxanthine** and reduces the synthesis of uric acid by **competitive inhibition of xanthine oxidase**. Some **inhibition of de novo purine synthesis** also occurs. Allopurinol is converted to **alloxanthine** by xanthine oxidase, and this metabolite, which remains in the tissue for a considerable time, is an effective non-competitive inhibitor of the enzyme. The **pharmacological action of** allopurinol **is largely due to alloxanthine.** Allopurinol reduces the concentration of the relatively insoluble urates and uric acid in tissues, plasma and urine, while increasing the concentration of their more soluble precursors, the xanthines and hypoxanthines. The deposition of urate crystals in tissues (*tophi*) is reversed, and the formation of renal stones is inhibited. Allopurinol is the drug of choice in the long-term treatment of gout, but it is ineffective in the treatment of an acute attack and may even exacerbate the inflammation.



Allopurinol can cause potentially fatal skin diseases (Stevens-Johnson syndrome and toxic epidermal necrolysis-a horrible disorder where skin peels away in sheets as if scalded) are rare but devastating.

- Allopurinol increases the effect of mercaptopurine , an antimetabolite used in cancer chemotherapy and also that of azathioprine (an immunosuppressant used to prevent transplant rejection which is metabolised to mercaptopurine) . Allopurinol also enhances the effect of another anticancer drug, cyclophosphamide

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Colchicine:

Colchicine is drug choice for acute attack. Colchicine an alkaloid extracted from the autumn crocus. It has a specific effect in gouty arthritis and can be used both to prevent and to relieve acute attacks.

It prevents migration of neutrophils into the joint, apparently by binding to tubulin, resulting in the depolymerisation of the microtubules and reduced cell motility.

Colchicine-treated neutrophils develop a 'drunken walk'. Colchicine may also **prevent the production of a putative inflammatory glycoprotein by neutrophils** that have phagocytosed urate crystals, and other mechanisms may also be important in bringing about its effects.

References:

1. Conceptual Review of Pharmacology for NBE, Ranjan Kumar Patel, Fourth Edition,CBS Publication

2. KD Tripathi,Essentials of Medical pharmacology,8th Edition.

3. Lippincott Illustrated Reviews Pharmacology, Karen Whalen,6th Edition.

4.Pharmacology for Medical graduates,Tara V Shanbhag,3rd Edition.

5.Medical Pharmacology,Padmaja Udayakumar,5th Edition.

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