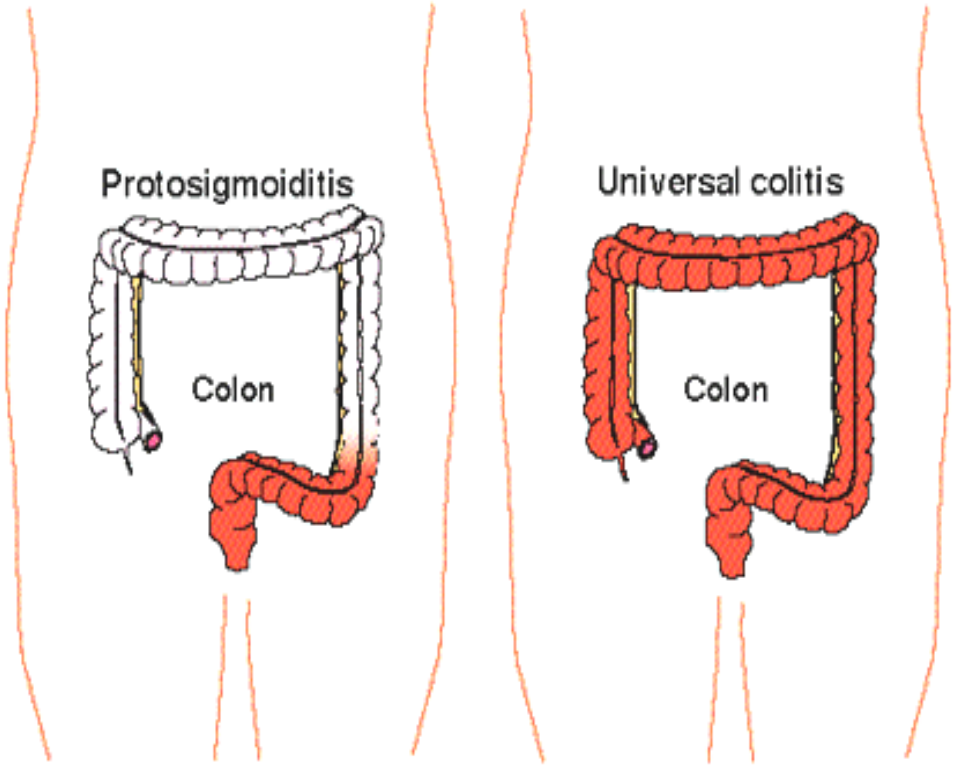
Drugs used in inflammatory bowel disease

Chronic inflammatory bowel diseases (IBD)

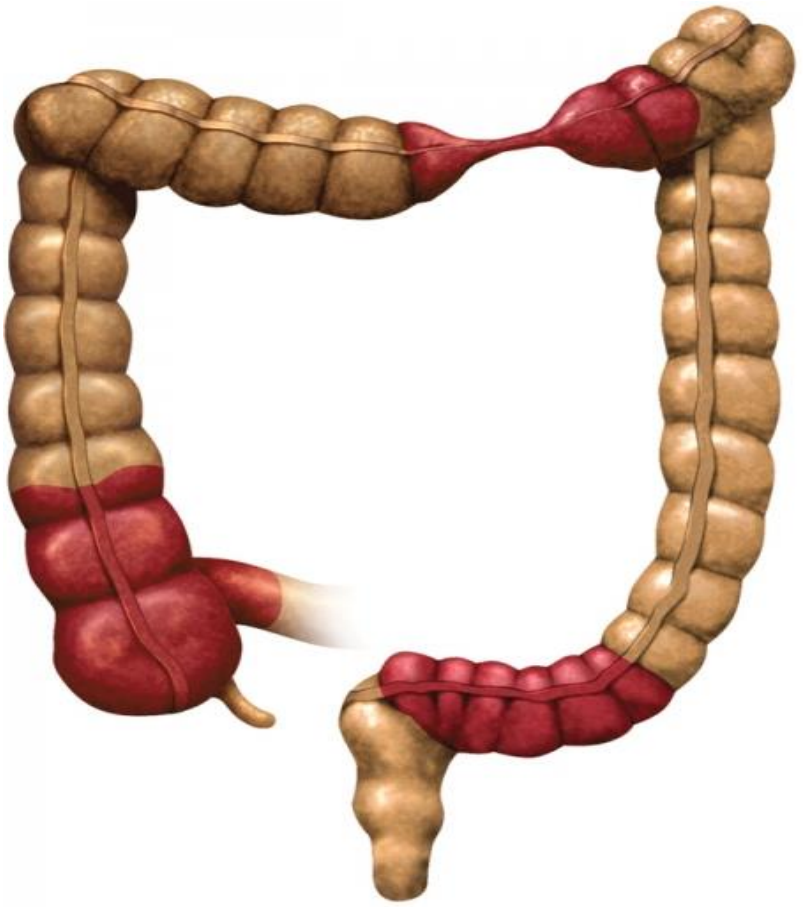
- IBD is **is a group of inflammatory conditions of the colon and small intestine.**
- **auto-immune disorders**
- **The major types of IBD are Crohn's disease and ulcerative colitis (UC).**

Differences between Crohn's disease and UC

	Crohn's disease	Ulcerative colitis
Location	affect any part of the GIT, from mouth to anus	Restricted to colon & rectum
Distribution	Patchy areas of inflammation *(Skip lesions)*	Continuous area of inflammation
Depth of inflammation	deep into tissues	Shallow, mucosal
Complications	Strictures, Obstruction Abscess, Fistula	Toxic mega colon Colon cancer



Ulcerative colitis



Crohn's disease

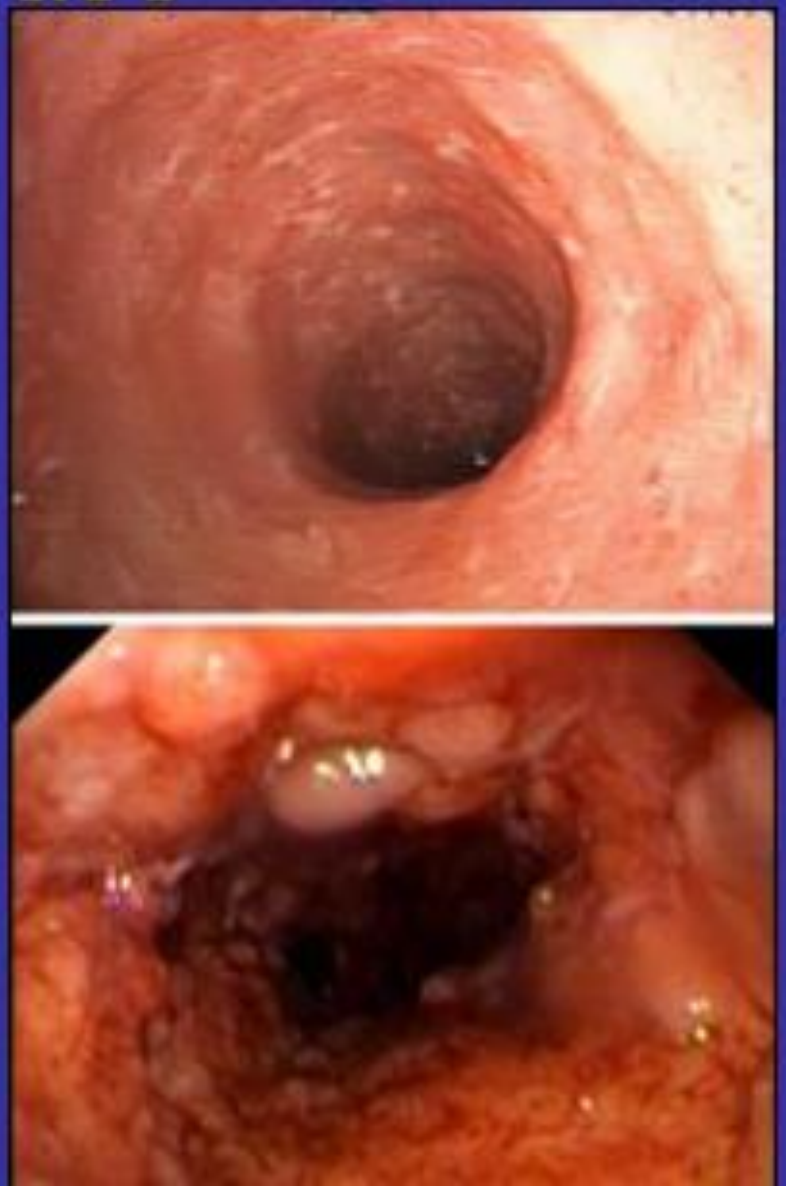

Normal Colon Lining
Ulcerative Colitis

Crohn's disease

- patchy transmural inflammation

- fistulae, strictures

- any part of GI tract



Causes of IBDs

- **Not known.**
- **Abnormal activation of the immune system.**
- **The susceptibility is genetically inherited.**

Symptoms

- **Vomiting**
- **Abdominal pain**
- **Diarrhea**
- **Rectal bleeding.**
- **Weight loss**

Complications

1. **Anemia**
2. **Abdominal obstruction (Crohn’s disease)**
3. **Mega colon**
4. **Colon cancer**

Treatment of IBD

There is no cure for IBDs but treatment options are restricted to controlling symptoms, maintaining remission, and preventing relapse.

Treatment of IBD

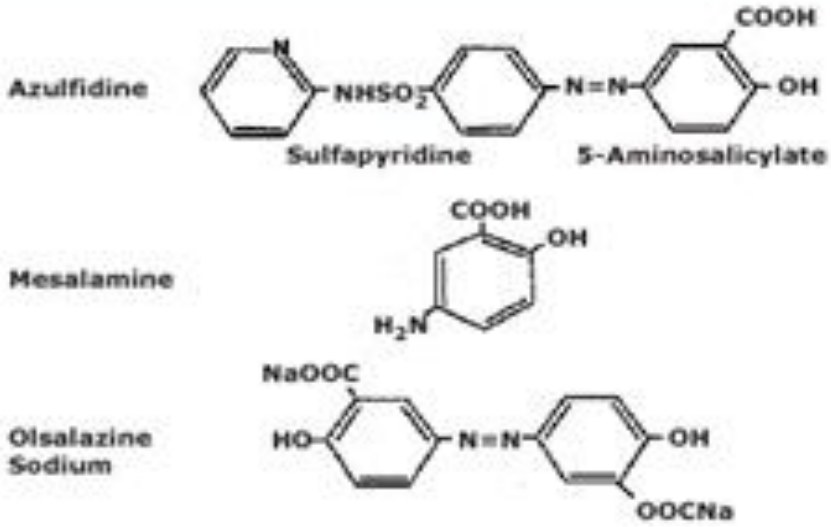
1. **5-amino salicylic acid compounds (5-ASA).**
2. **Glucocorticoids**
3. **Immunomodulators**
4. **Biological therapy (TNF-α inhibitors).**
5. **Surgery in severe condition**

5-amino salicylic acid compounds (5-ASA)
Aminosalicylates

- **Topical anti-inflammatory drugs**
- **5-ASA itself is absorbed from small intestine.**
- **Different formulations are used to overcome rapid absorption of 5-ASA from the proximal small intestine**

  - **Azo compounds**
  - **Mesalamine compounds**

Structures of sulfasalazine, mesalamine, and olsalazine



Sulfasalazine is a composite molecule composed of 5-aminosalicylic acid (5-ASA) linked by an azo bond to sulfapyridine. Mesalamine is the 5-ASA moiety alone, while olsalazine consists of two 5-ASA molecules joined by an azo bond.

The mechanism of action of 5-ASA is not certain.

Several mechanisms were proposed, including:

1- Inhibition of cytokine synthesis

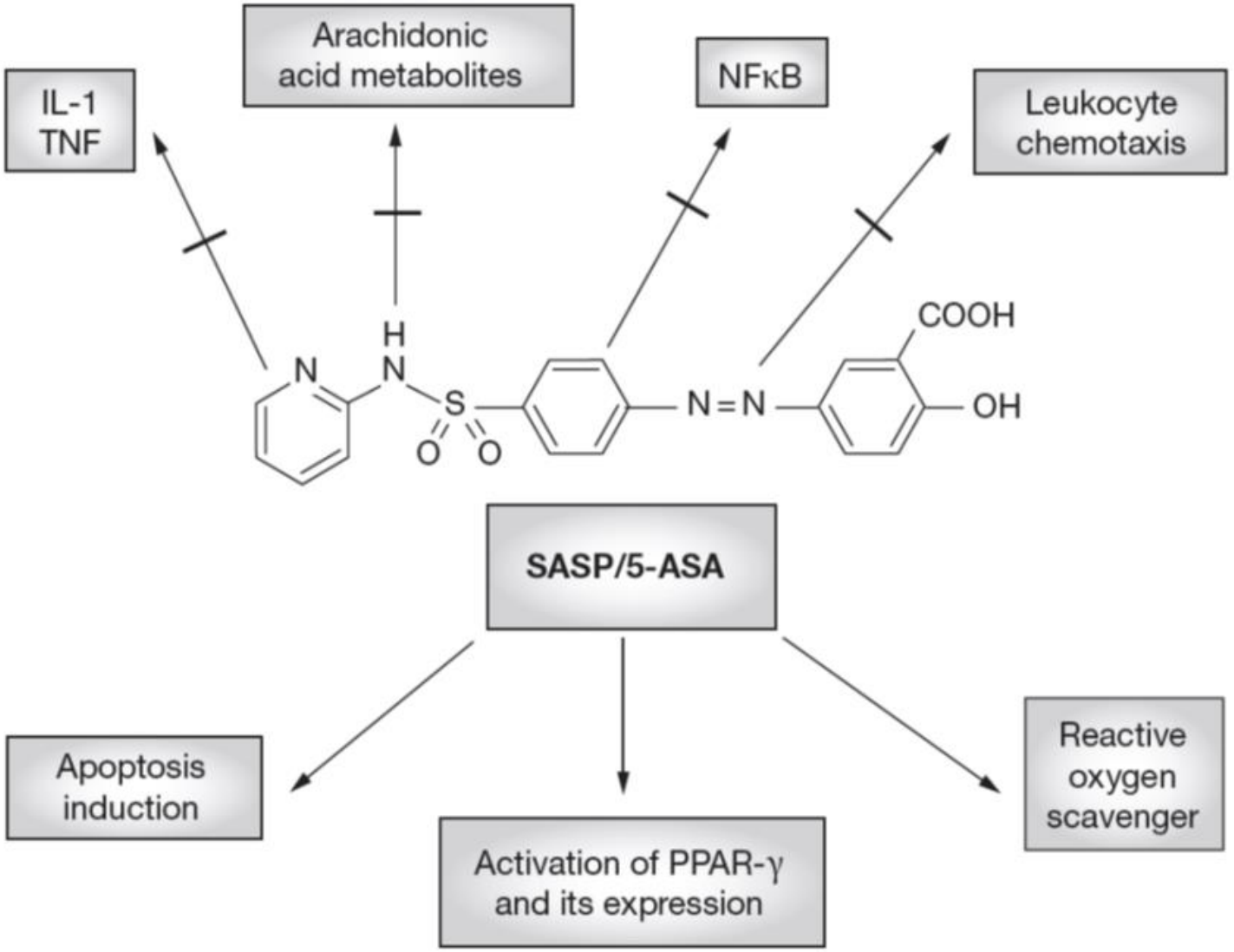
2- Inhibition of prostaglandin and leukotriene synthesis

3- Free radical scavenging

4- Immunosuppressive activity

5-ASA inhibits both T-cell proliferation and subsequent activation and differentiation.

5- Impairment of white cell adhesion and function.


IL-1
TNF
Arachidonic
acid metabolites
NFκB
Leukocyte
chemotaxis
COOH
OH
N=N
H
N
N
S
O
O
SASP/5-ASA
Apoptosis
induction
Activation of PPAR-γ
and its expression
Reactive
oxygen
scavenger

Azo compounds

Compounds that contain 5-ASA and connected by azo bond (N=N) to sulfapyridine moiety, another molecule of 5-ASA or to inert compound.

Sulfasalazine: 5-ASA + sulphapyridine

Olsalazine: 5-ASA + 5-ASA

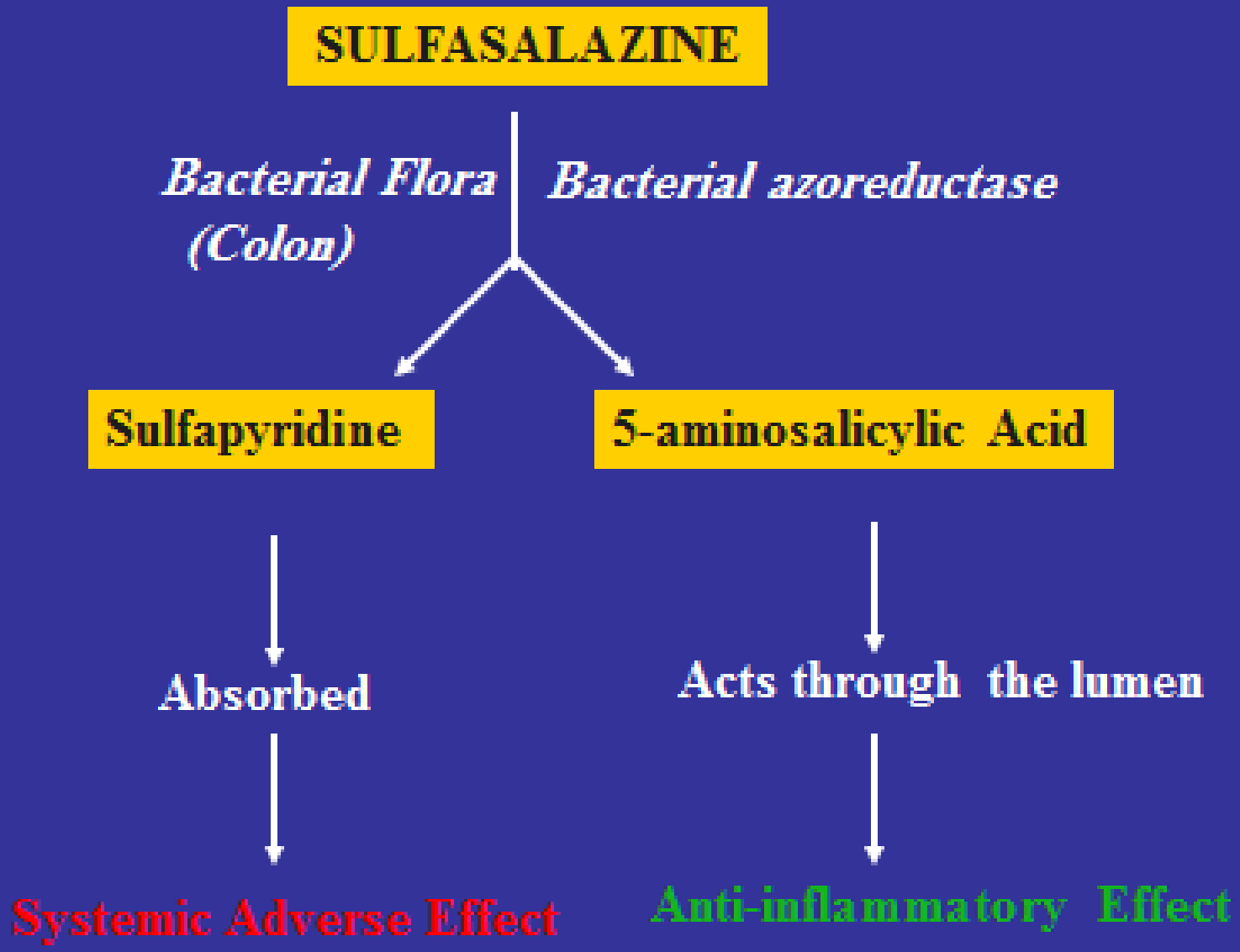
Balsalazide: 5-ASA + inert carrier

Azo compounds

- **Azo structure reduces absorption in small intestine**
- ***In the terminal ileum and colon*, bacterial flora release azoreductase that cleaves the azo bond (N=N) and releases 5-ASA.**

Sulfasalazine

- **Pro-drug**
- **A combination of 5-ASA and sulfapyridine**
- **Is given orally.**
- **Little amount is absorbed (10%)**
- ***In the terminal ileum and colon*, sulfasalazine is broken by azoreductase into:**
- **5-ASA (not absorbed, active moiety)**
- **Sulphapyridine (absorbed, side effects)**


SULFASALAZINE
Bacterial Flora (Colon)
Bacterial azoreductase
Sulfapyridine
5-aminosalicylic Acid
Absorbed
Acts through the lumen
Systemic Adverse Effect
Anti-inflammatory Effect

Adverse effects

- Dose-related

- Idiosyncratic (rare)

  - blood disorders

  - skin reactions – lupus like syndrome; Stevens-Johnson syndrome; alopecia

Side effects of sulfasalazine and aminosalicylates

	Common (>10 percent)	Uncommon (1 to 10 percent)	Rare (<1 percent)
Sulfasalazine	Nausea/headache Rash Male infertility Headache	Abdominal pain Hemolytic anemia Leukopenia Thrombocytopenia	Hepatitis Pneumonitis Neutropenia Pancreatitis Agranulocytosis Otalgia
Aminosalicylates	Watery diarrhea Abdominal pain Headache Nausea	Pancreatitis Colitis exacerbation Fever/rash Rash	Pneumonitis Pericarditis Nephritis Thrombocytopenia

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Blood disorders

- Agranulocytosis; aplastic anaemia; leucopenia; neutropenia; thrombocytopenia; methaemoglobinemia

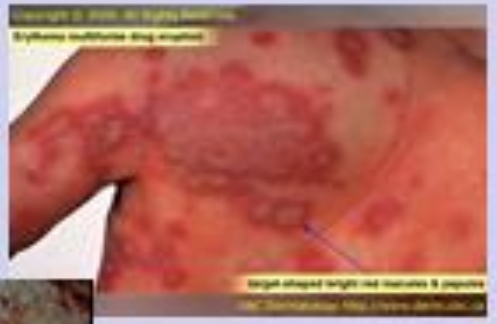
- Patients should advised to report any unexplained bleeding; bruising; purpura; sore throat; fever or malaise

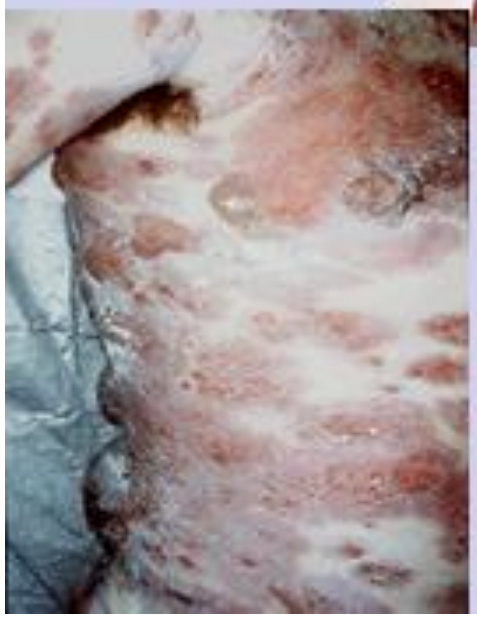
- **Folic acid deficiency (should be provided).**
- **Impairment of male fertility (*Oligospermia*).**
- **Interstitial nephritis due to 5-ASA.**

Contraindications /cautions

- 5-ASA
  - Salicylate hypersensitivity
- Sulfapyridine
  - G6PD deficiency (haemolysis)
  - Slow acetylator status (↑ risk of hepatic and blood disorders)

Steven's Johnson syndrome





- immune-complex–mediated hypersensitivity
- erythema multiforme
- target lesions, mucosal involvement

Mesalamine compounds

Formulations designed to deliver 5-ASA in terminal small bowel & large colon

Mesalamine formulations are

- **Sulfa free**
- **well tolerated**
- **have less side effects**
- **useful in patient sensitive or allergic to sulfa drugs.**

Mesalamine compounds

Oral formulations

Asacol: 5-ASA coated in pH-sensitive resin that dissolved at pH 7 (*controlled release*).

Pentasa: time-release microgranules that release 5-ASA throughout the small intestine (*delayed release*).

Rectal formulations

Canasa (suppositories)

Rowasa (enema)

Clinical uses of 5-amino salicylic acid compounds

- **Induction and maintenance of remission**

in mild to moderate ulcerative colitis (First line of treatment).

- **Rheumatoid arthritis *(Sulfasalazine only)***
- **Rectal formulations are used in active distal**

UC *ulcerative* proctitis and proctosigmoiditis.

Glucocorticoids

Prednisone, prednisolone (orally)

- **Higher rate of absorption**
- **More adverse effects compared to rectal administration**

Budesonide:

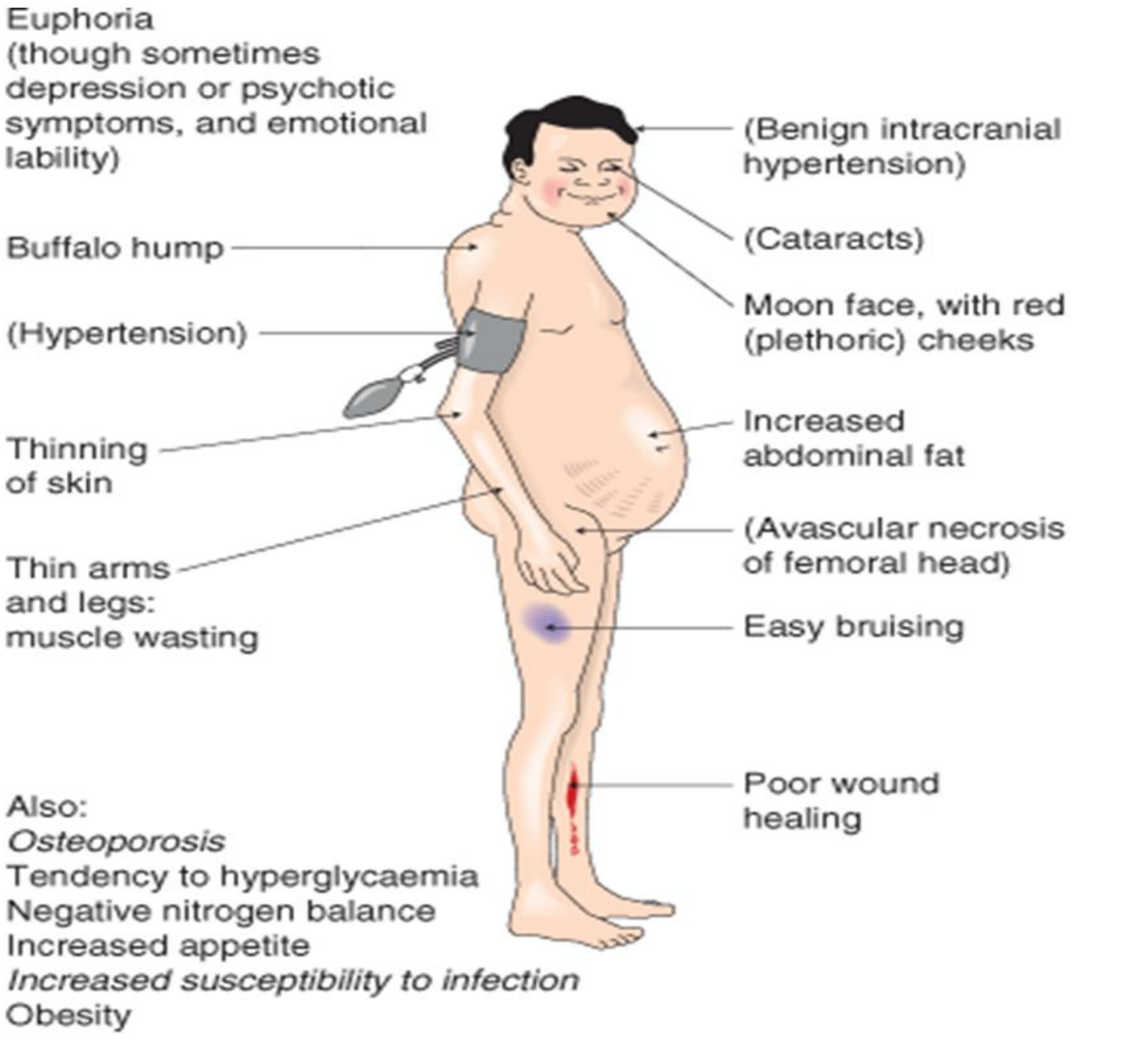
- **A potent synthetic compound**
- **Given orally *(controlled release tablets)* so release drug in ileum and colon.**
- **Low oral bioavailability (10%).**
- **Is subject to *first pass metabolism***
- **Used in treatment of active forms of moderate to severe UC & Crohn's disease involving ileum and proximal colon.**

Mechanism of action of glucocorticoids

- **Inhibits phospholipase A2**
- **Inhibits gene transcription of NO synthase, cyclooxygenase-2 (COX-2)**
- **Inhibit production of inflammatory cytokines**
- **Decrease antigen-antibody reaction**

Uses of glucocorticoids

- **Induction of remission in moderate & severe active IBD.**
- **Not used for maintaining remission.**
- **Oral glucocorticoids is commonly used in active condition.**
- **Rectal glucocorticoids are preferred in IBD involving rectum or sigmoid colon**



Immunomodulators

Are used to induce remission in IBD in active, severe conditions or steroid resistant patients.

Immunomodulators include:

- **Methotrexate**
- **Purine analogs:**
  (azathioprine & 6-mercaptopurine).

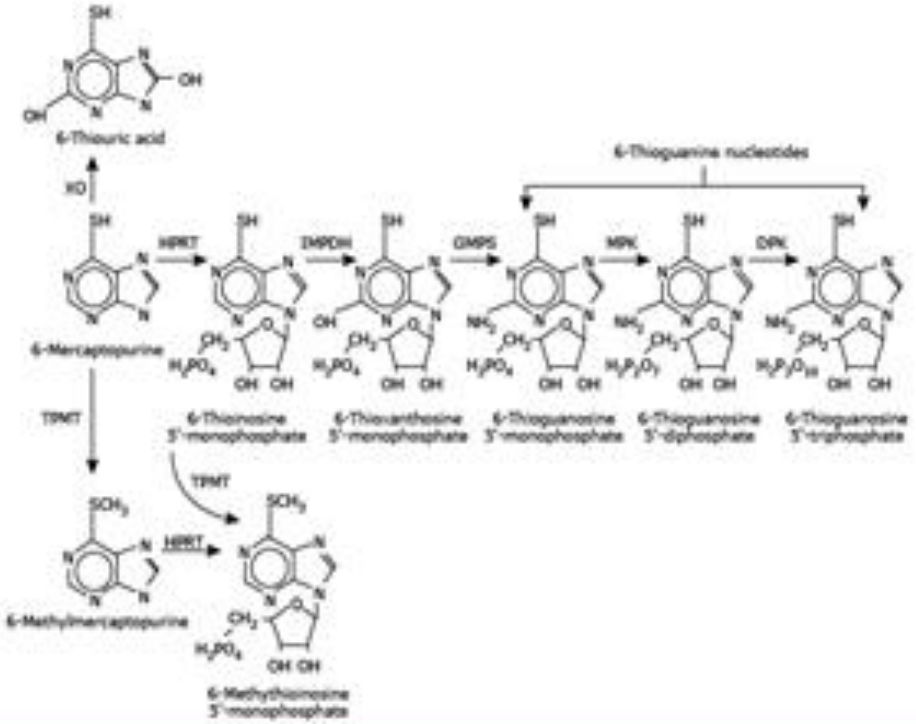
Purine analogs (azathioprine & 6-mercaptopurine)

Azathioprine

- **is a pro-drug of 6-mercaptopurine**
- **Inhibits purine synthesis**
- **Induction and maintenance of remission in IBD**

Inhibit purine nucleotide metabolism and DNA synthesis and repair, resulting in inhibition of cell division and proliferation and may promote T-lymphocyte apoptosis.

6-mercaptopurine metabolism



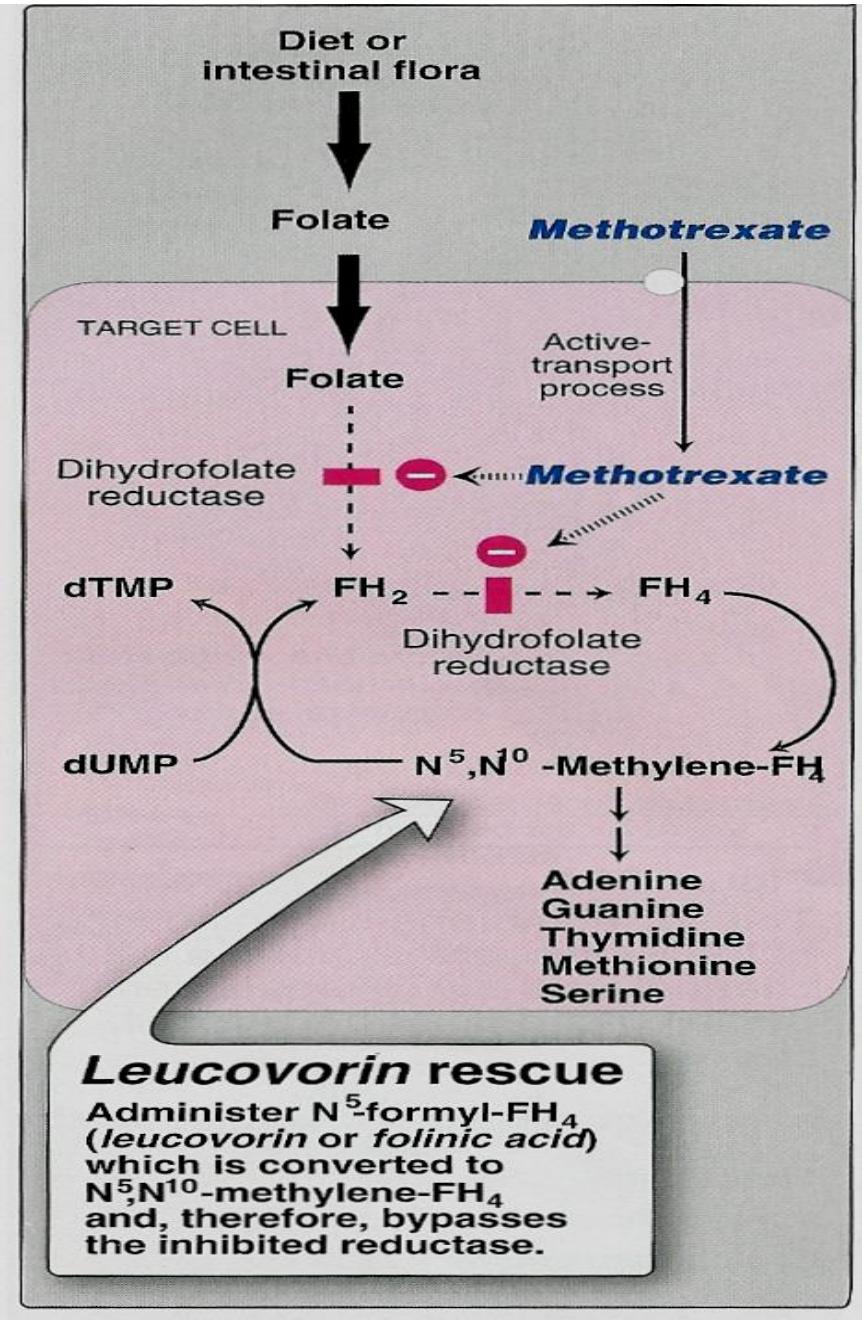
The initial metabolism of 6-mercaptopurine occurs along the competing routes catalyzed by thiopurine methyltransferase (TPMT), xanthine oxidase (XO), and hypoxanthine phosphoribosyltransferase (HPRT). Further metabolism of the thionucleotide is catalyzed by inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS). The diphosphates and triphosphates are formed by their respective monophosphate (MPK) and diphosphate (DPK) kinases.

Adverse effects:

- **Bone marrow depression: leucopenia, thrombocytopenia. –** myelotoxicity is determined by TPMT activity
  - **Gastrointestinal toxicity.**
  - **Hepatic dysfunction.**
  - **Pancreatitis.**
  - **Complete blood count & liver function tests are required in all patients**

Methotrexate

- a folic acid antagonist
- Inhibits dihydrofolate reductase required for folic acid activation
- Orally, S.C., I.M.
- Used to induce and maintain remission in inflammatory bowel diseases.
- Rheumatoid arthritis
- Cancer

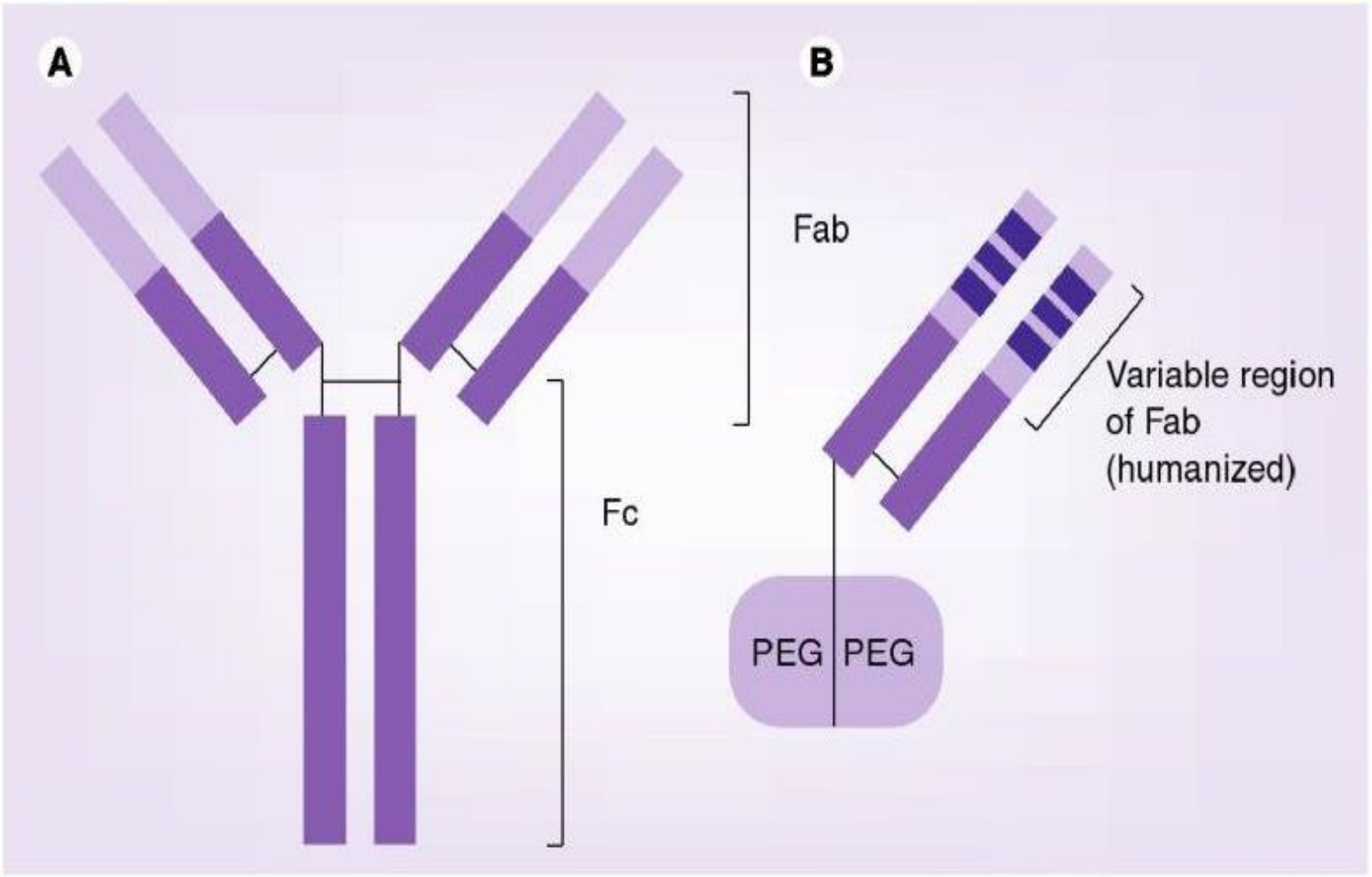

Diet or intestinal flora
Folate
Methotrexate
TARGET CELL
Folate
Active-transport process
Dihydrofolate reductase
Methotrexate
dTMP
FH2
FH4
Dihydrofolate reductase
dUMP
N5,N10-Methylene-FH4
Adenine
Guanine
Thymidine
Methionine
Serine
Leucovorin rescue
Administer N5-formyl-FH4 (leucovorin or folinic acid) which is converted to N5,N10-methylene-FH4 and, therefore, bypasses the inhibited reductase.

Adverse effects of methotrexate

- **Bone marrow depression**
- **Megaloblastic anemia**

Monoclonal antibodies used in IBD (TNF-α inhibitors)

- **Infliximab**
- **Adalimumab**
- **Certolizumab**



Infliximab

- a chimeric mouse-human monoclonal antibody
- 25% murine – 75% human.
- TNF-α inhibitors
- Inhibits soluble or membrane –bound TNF-α located on activated T lymphocytes
- Given intravenously as infusion (5-10 mg/kg).
- has long half life (8-10 days)
- 2 weeks to give clinical response

Uses of infliximab

- **In moderate to severe active Crohn's disease and ulcerative colitis**
- **Patients not responding to immunomodulators or glucocorticoids.**
- **Treatment of rheumatoid arthritis**
- **Psoriasis**

Side effects

- **Acute or early adverse infusion reactions *(Allergic reactions or anaphylaxis in 10% of patients).***
- **Delayed infusion reaction *(serum sickness-like reaction, in 5% of patients).***
- **Pretreatment with diphenhydramine, acetaminophen, corticosteroids is recommended.**

Side effects (Cont.)

- **Infection complication *(Latent tuberculosis, sepsis, hepatitis B).***
- **Loss of response to infliximab over time *due to the development of antibodies to infliximab***
- **Severe hepatic failure.**
- **Rare risk of lymphoma.**

Adalimumab (HUMIRA)

- **Fully humanized IgG antibody to TNF-α**
- **Adalimumab is TNFα inhibitor**
- **It binds to TNFα, preventing it from activating TNF receptors**
- **Has an advantage that it is given by subcutaneous injection**
- **is approved for treatment of, moderate to severe Crohn's disease, rheumatoid arthritis, psoriasis.**

Certolizumab

Polyethylene glycol Fab fragment of humanized anti- TNF-α, also given SC.

immunogenicity appears to be less of a problem than with infliximab.

Summary for drugs used in IBD

5-aminosalicylic acid compounds

- **Azo compounds:**
  sulfasalazine, olsalazine, balsalazide
- **Mesalamines:**
  Pentasa, Asacol, Rowasa, Canasa

Glucocorticoids

prednisone, prednisolone, hydrocortisone, budesonide

Immunomodulators

- **Methotrexate**
- **Purine analogues:**
  - **Azathioprine &6-mercaptopurine**

TNF-alpha inhibitors (monoclonal antibodies)

- **Infliximab – Adalimumab - Cetrolizumab**

Questions ?