Dr. Green

ANTI-INFLAMMATORY DRUGS

Many categories of drugs will be discussed.

1. **Non-narcotic analgesics/Nonsteroidal** Anti-inflammatory **drugs (NSAIDs**). Some compounds are used for analgesic action at low doses and anti-inflammatory action at higher doses. EX. acetylsalicylic acid-ASPIRIN. Some are analgesic only. EX acetaminophen-TYLENOL. Some are too toxic to be used for analgesic action and are used only for anti-inflammatory action. EX. phenylbutazone and indomethacin.

2. **Drugs used in the treatment of gout**

    a. colchicine
    b. Allopurinol
    c. uricosuric agents

3. **Disease arresting anti-inflammatory agents**. Gold-containing compounds, penicillamine, immunosuppressants

SALICYLATES (ASPIRIN)

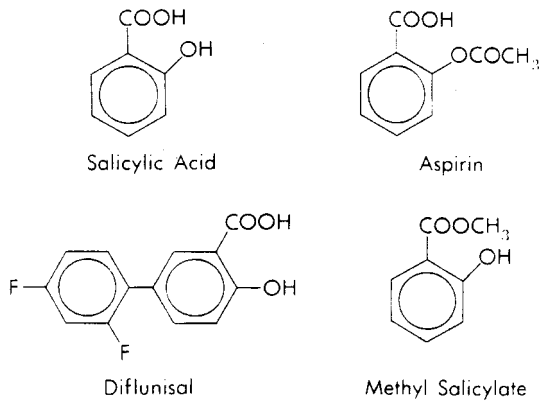
Drugs. Na Salicylate; acetylsalicylic acid (ASPIRIN), methyl salicylate (Oil of Wintergreen:topical only) and Diflunisal

Four major (therapeutically beneficial) actions.

1. Anti-inflammatory
2. Analgesic
3. Antipyretic
4. Uricosuric

Actions 1,2 and 3 due to inhibition of fatty acid cyclo-oxygenase.

STRUCTURAL FORMULAS OF THE SALICYLATES



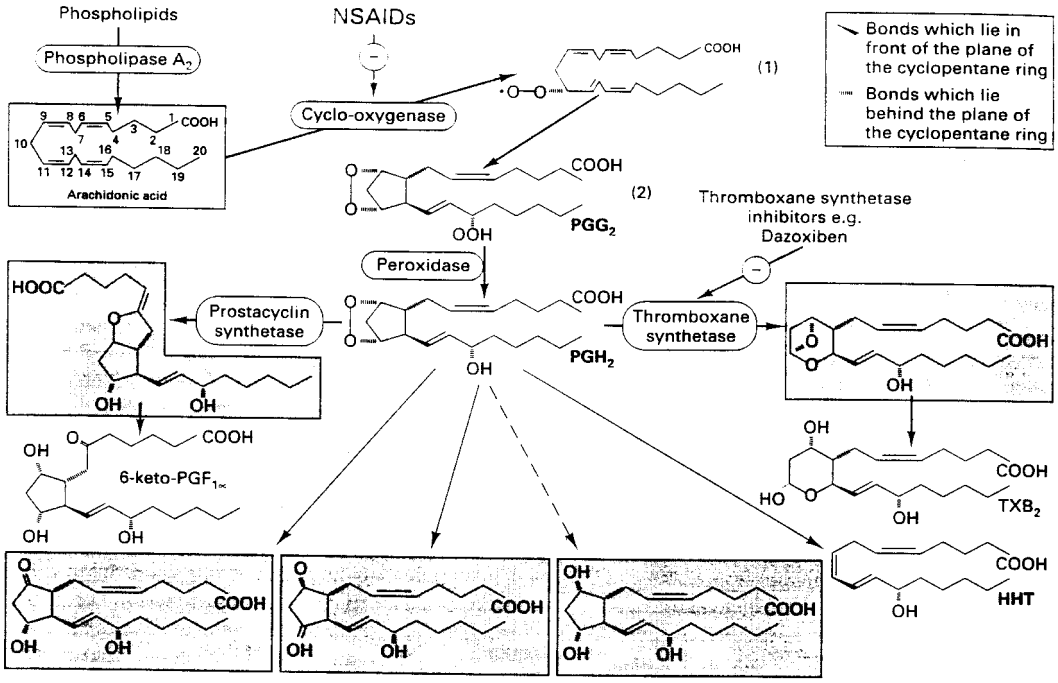


Fig. 11.8 The biosynthesis of prostaglandins, prostacyclin and thromboxane from arachidonate. Solid lines indicate known enzymic reactions, and dotted lines the transformations not known to be enzymic. Compounds with biological action are shown in boxes. There are two forms of cyclo-oxygenase (COX): one (COX–I) is constitutive and occurs in most cell types, and the other (COX–II) is induced in inflammatory cells by inflammatory stimuli. The current NSAIDs act mainly on COX-I. (PG = prostaglandin; TX = thromboxane; NSAIDs = non-steroidal anti-inflammatory drugs)

Not all agents inhibit cyclo-oxygenase by same mechanism

a.Irreversible inactivation. ASPIRIN-acetylates enzyme

b.Reversible competitive Inhibition. Ibuprofen

c.Reversible noncompetitive-involves antioxidant or free radical trapping properties. - Acetaminophen.

Metabolism-ASA

a.glycine conjugation ~75% ~~▲ SALICYLURIC ACID

b.phenolic (ether) glucuronide formation~10%

c.acetyl(ester) glucuronide formation ~5%

d.excretion unchanged~10%

Capacities of pathways 1 and 2 are limited and become saturated with high doses of ASA or salicylic acid. **Usually metabolize constant fraction of compound.i.e., metabolism substrate concentration: 1st ORDER. When exceed metabolic capacity, metabolize constant amount of substrate: ZERO ORDER. Consequences of going from 1st order to zero order:(1) other pathways become more important, (2) $t_{½}$ for decline in blood level increases:2-4 hours with low dose ➜ 15-30 hours with high doses. Takes longer to reach plateau level of drug. Do not increase doses too fast.**

Effects of salicylates on acid-base balance and electrolytes. Characteristic progression of changes in acid-base balance as plasma level of salicylate increases.

1. Direct stimulatory effect on respiratory center pCO_2: RESPIRATORY ALKALOSIS.
2. Increase excretion of HCO_3^- to lower blood HCO_3^- -COMPENSATED RESPIRATORY ALKALOSIS.(adult with intensive salicylate therapy)
3. Direct depression of respiratory center with higher blood level buildup of CO_2 RESPIRATORY ACIDOSIS. Blood pH falls rapidly because of low HCO_3^-.
4. At same time have metabolic acidosis due to impaired renal function (strong acids of metabolic origin accumulate) and derangements in carbohydrate metabolism.

Shared effects of cyclo-oxygenase (COX) inhibitors. Long realized that all of these agents tend to have the same side effects or problems. Now clear that the extent of these problems is not the same and is, in fact, very variable.

Reports of serious unwanted reactions to non-steroidal anti-inflammatory drugs*

Drug	Number of prescriptions (million)	Serious GIT reactions per million prescriptions	Other serious reactions per million prescriptions
Ibuprofen	5.47	6.6	6.6
Naproxen	4.67	32.8	8.4
Flurbiprofen	3.35	27.4	8.4
Fenbufen†	1.57	35.7	33.8
Ketoprofen	3.19	33.2	5.3
Indomethacin (slow-release type)	0.44	386.4	18.2
Sulindac	1.38	23.9	30.4
Piroxicam	9.16	58.7	9.4
Diflunisal	3.13	33.5	13.7
Azapropazone†	0.91	67.0	20.9

	CSM Ranking	Garcia Rodriguez		Langman et al	
		Ratio	95% CI	Ratio	B 95% CI
Overall		4·7	3·8–5·7	4·5	3·6–5·6
Ibuprofen	1	2·9	1·78–5·0	2·0	1·4–2·8
Diclofenac	2	3·9	2·3–6·5	4·2	2·6–6·8
Naproxen	5	3·1	1·7–5·9	9·1	5·5–15·1
Ketoprofen	6	5·4	2·6–11·3	23·7	7·6–74·2
Indomethacin	*	6·3	3·3–12·2	11·3	6·3–20·3
Piroxicam	11	18·0	8·2–39·6	13·7	7·1–26·3
Azapropazone	12	23·4	6·9–79·5	31·5	10·3–96·9

*Not ranked by CSM. Marketed before yellow card scheme.

Table: **Odds ratio and 95% CI for bleeding and perforation (Garcia Rodriguez) or acute gastrointestinal bleeding (Langman), and CSM rank order of serious reports of gut toxicity expressed per million prescriptions in the first 5 years of marketing**

COX isozymes: Now know that there is more than one COX isozyme.

COX-1. Isozyme isolated ~ 20 years ago. Constitutively expressed in most tissues including stomach, kidney and blood platelets. Involved in cellular "housekeeping" functions. Inhibition probably associated with many/most side effects.

COX-2. Recently discovered. Shares 63% amino acid identity with COX-1. Expressed only in inflamatory cells after cell activation. Believed to be responsible for the production of prostanoid mediators of inflamation.

Currently available COX inhibitors inhibit both COX-1 and COX-2 but with different potencies.

The potency of some NSAIDs on COX-1 and COX-2 (from two different studies, a and b), expressed as a ratio*: COX-2 IC_{50}/COX-1 IC_{50}

NSAID	a	b
Aspirin	166	—
Sulindac sulfide†	—	31
Indomethacin	60	22
Ibuprofen	15	1
Flurbiprofen	—	8
Piroxicam	—	10
Mefenamic acid	—	7
Diclofenac	1	—
Naproxen	1	—
Acetaminophen	7‡	No effect on either enzyme
6-MNA§	—	0.14
BF389¶	0.2	—

IC_{50} = the concentration which reduces activity of the enzyme to 50% of the initial value
* The higher the figure for the ratio, the less the effect on COX-2 and the more the effect on COX-1. The figures have been rounded up.
† The active metabolite of sulindac
‡ IC_{30} value because 50% inhibition was not achieved
§ 6-Methoxy-2-naphthylacetic acid, the active metabolite of nabumetone
¶ A new compound under test
Values from: (a) Mitchell et al. (1993) — measurements of inhibition of COX-1 in intact bovine aortic endothelial cells and of COX-2 in intact macrophages stimulated with endotoxin; (b) Meade et al. (1993) — measurements in microsomal membranes from murine cells to which the cDNA of the relevant isoenzyme had been transferred by vector

Selective pharmacology of NSAIDs

NSAIDs (0.001–100 μM) were preincubated with membranes containing COX-1 or COX-2 before addition of arachidonic acid (10 μM) for 10 min. COX activity was measured as PGE_2 formed: min per mg

IC_{50} (μM)	hCOX-1	hCOX-2
Indomethacin	0.1	0.9
Naproxen	1.1	36
Flurbiprofen	0.1	0.4
Flufenamic acid	2	29.5
Mefenamic acid	0.04	3
Ketoprofen	7.5	7.6
Ibuprofen	3.3	37.5
Piroxicam	13	> 100
Diclofenac	0.04	0.1
NS-398	> 100	0.1
Dup-697	0.8	0.01

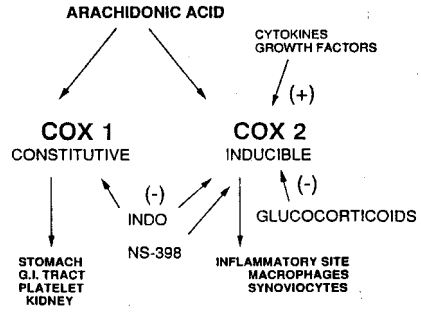


FIG. 6. Model for regulation of PG synthesis in normal and inflamed states. INDO, indomethacin; G.I., gastrointestinal.

1. **GI irritation**: Primarily stomach but also small intestine. Stomach:(1) direct irritant effect of organic acid responsible for superficial erosions, (2) **Deep ulcers in antral region are due to the inhibit synthesis of gastric prostaglandins that normally inhibit acid secretion and stimulate the secretion of cytoprotective mucus (COX-1).** Increased adhesion of leukocytes (primarily neutrophils) to vascular endothelium in gastric microcrculation also implicated. Not clear if pathogenesis in small intestine involves the same mechanisms.

Strategies to reduce NSAID gastropathy.

> Co-administration of stable PGE_1 analog, Misoprostol. Good results reported but not widely used due to:(1) side effects, mainly diarrhea, and (2) cost effectiveness.
>
> Development of COX inhibitors that selectively inhibit COX-2. Animal models promising.
>
> Development of NSAIDs that also generate nitric oxide (NO). NO is powerful vasodilator and inhibitor of neutrophil function. Current compounds have no selectively for COX-1 or COX-2 but are less ulcerogenic in animal models.

2. **Renal failure**. PGE_2 and PGI_2 are involved in the maintenance of renal blood flow dynamics. Appears to be important in maintaining renal function in conditions that favor a reduction in renal blood flow (congestive heart failure, hepatic cirrhosis, chronic renal disease or volume depletion). In these cases NSAIDs can lead to renal failure.

3. **Inhibition of platelet function**. Prevent formation of TBX_2, a potent aggregating agent. Tendency to increase bleeding time.

4. **Prolong gestation**

Specific problem of salicylates: Association with Reye's Syndrome (severe hepatic injury and encephalopathy) when children with febrile viral illness (chicken pox or influenza) are treated with salicylate. **Don't use salicylates when these conditions exist.**

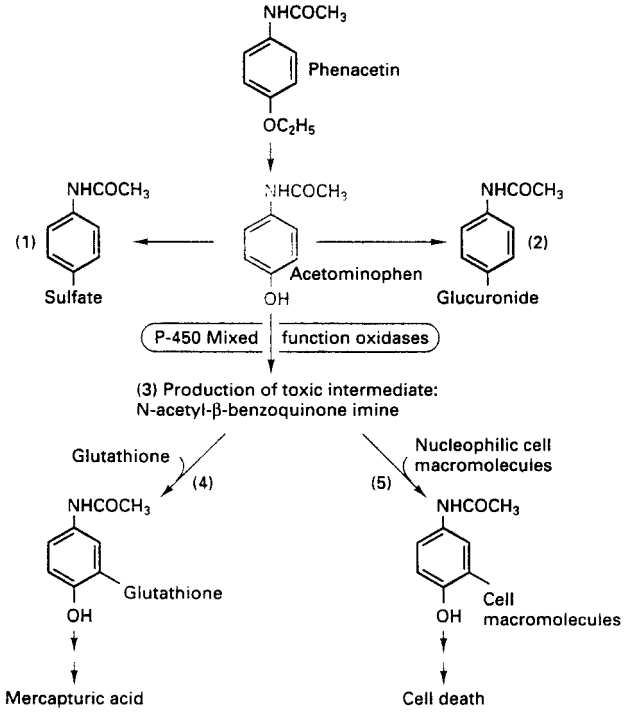
Acetaminophen (TYLENOL)

Analgesic and antipyretic: **WEAK ANTI-INFLAMMATORY ACTION ASA**. Also does not produce gastric irritation and prolonged bleeding times characteristic of salicylates.

Not clear why pharmacology is different from ASA. Two common explanations:(1) only blocks cyclo-oxygenases in environment low in peroxides and [peroxide] is high in area of inflammation, (2) selectively inhibits a CNS isozyme of cyclo-oxygenase.

Metabolism/toxicity

Conjugated in liver. With high doses form a highly reactive intermediate in the liver that reacts with -SH groups in proteins and glutathione. When glutathione is depleted only protein -SH HEPATIC NECROSIS-POTENTIALLY FATAL. Specific antidote: **mucomyst**. Must give soon after poisoning to be effective.



Use: analgesic/antipyretic when ASA contraindicated or not well tolerated.

Ibuprofen (Advil, Motrin)

analgesic, antipyretic and anti-inflammatory. Used for all actions. Became available over-the-counter because of effectiveness in dysmenorrhea and is now widely used both in low dosages as an ASA/tylenol alternative and in higher doses as an anti-inflammatory agent.

Related drugs: Naproxen, fenoprofen

Agents only available by prescription and used for their anti-inflammatory action.

Phenylbutazone

- # has all actions of salicylates
- # used only for short term therapy in rheumatoid arthritis or gout due to severe, potentially fatal, side effects
- # related: oxyphenbutazone and Apazone (reportedly less toxic). Sulfinpyrazone is also a related drug that is uricosuric but not anti-inflammatory (and not highly toxic).

Indomethacin

- # Used primarily for its anti-inflammatory action; too toxic to use for analgesic action
- # High incidence of side effects: gastric ulcerations, severe frontal headache, bone marrow suppression.
- # Other uses: (1) anti-pyretic in Hodgkin's disease, and (2) induce closure of patent ductus arteriosis. I.V. ~70% success
- # Sulindac:related prodrug

Tolmetin

potency between ASA and toxic agents such as phenylbutazone and indomethacin. May be better tolerated than ASA.

Piroxicam

distinguishing feature:long biological half-life single daily dose

Diclofenac: newer potent agent

Mefenamic acid and meclofenamate; related agents that have been around a while. Appear to also (in addition to inhibition cyclo-oxygenase) directly antagonize effects of prostaglandins, High incidence of GI problems and never became popular.

Disease-arresting anti-inflammatory drugs

Gold:Chrysotherapy

Use: Treatment of rheumatoid arthritis. Usually patients with rapidly progressing disease with inadequate response to other drugs. **Unlike other agents these drugs sometimes arrest the**

progress of the disease and induce an apparent remission.

Preparations: Aurothioglucose and gold sodium thiomalate (both given I.M) and Auranofin (oral)

Pharmacology: probably act by inhibiting functions of mononuclear phagocytes but exact mechanism is unknown. Little or no anti-inflammatory action in other circumstances.

Pharmacodynamics: initial plasma level half-life ~ 7 days but increases to weeks or months after prolonged therapy. **Takes a few months to detect a favorable response.** Reduce maintenance dose when get response.

Toxicity: mild cutaneous reactions to severe blood dyscrasias. If major toxic reaction may need to give -SH reagent DIMERCAPROL, which will chelate the gold.

Alternative drugs:

Penicillamine:metabolic product of penicillin with chelating action. Primarily used in poisoning with copper, mercury, or lead. Toxicity with chronic use.

Immunosuppressants such as cyclophosphamide. Effective but usefulness limited by toxicity.

Drugs used in the treatment of gout

Gout is a specific form of acute arthritis found only in humans. The cardinal biochemical feature is hyperuricemia,i.e., increased level of uric acid in the blood. The disease is caused by the deposition of crystals of Na urate in joints. If have hyperuricemia must have either overproduction or underexcretion of uric acid. Although it is often not clear which is the case, can treat the hyperuricemia with drugs that decrease uric acid production and drugs that increase uric acid excretion.

A deficiency in the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT), an important enzyme in the purine salvage pathway will increase the formation of uric acid and cause severe hyperuricemia. The Lesh-Nyhan Syndrome, a severe disease in newborns associated with self-mutilation and possible mental retardation (and gout if not treated) is caused by a severe, if not complete, deficiency in HGPRT. Less severe deficiencies in HGPRT can be associated with gout in adults.

Three drugs or classes of drugs are used to treat gout: (1) inhibitors of xanthine oxidase,i.e., inhibitors of uric acid production, (2) agents that promote uric acid excretion, URICOSURIC AGENTS, and (3) COLCHICINE, a drug that does not fit into either category.

COLCHICINE

Colchicine has been used in the treatment of gout for about 200 years, Its effectiveness in an arthritic state is diagnostic of gout. It is not an analgesic, does not affect plasma uric acid, and is anti-inflammatory only in gout. Its effect is apparently due to its well known ability to disrupt microtubule function. It is believed that this effect on microtubule function in neutrophils inhibits the infiltration of neutrophils into the inflamed area. Normally neutrophils migrate to the inflamed area where in the process of phagocytosis they release lactic acid which lowers the local pH and causes a further precipitation of Na urate and a further inflammatory response.

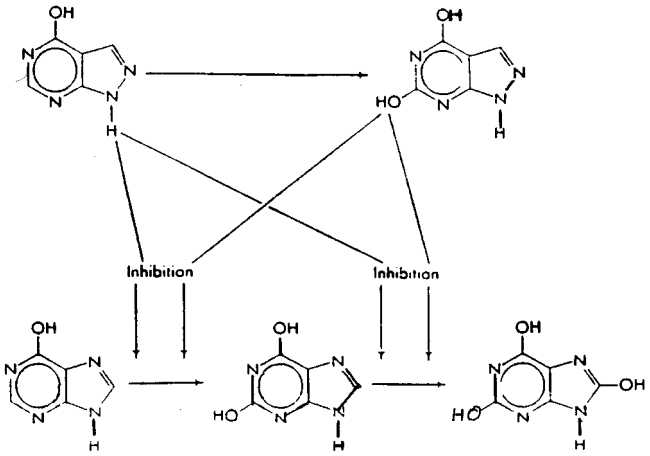
Toxicity: effect on microtubule function inhibits mitosis in all cells. This, of course, affects rapidly dividing cells the most. EFFECT ON GASTRIC MUCOSA CAUSES NAUSEA, VOMITING AND ABDOMINAL PAIN.

Use: Acute gout. Tablets (0.5 and 0.6 mg): give one tablet every 1-2 hours until pain disappears or GI symptoms appear. Can use indomethacin or phenylbutazone in patients that do not tolerate colchicine. Chronic gout: If given at a lower dose can be used chronically to decrease the intensity and frequency of acute episodes. Increase dose at first sign of acute attack.

ALLOPURINOL

Allopurinol is structurally similar to hypoxanthine and was developed as a potential chemotherapeutic agent. When given with the chemotherapeutic agent 6-mercaptopurine to treat leukemia it was found to increase the levels of the drug and to decrease the plasma levels of uric acid. This we due to the inhibition of the enzyme **xanthine oxidase.** This enzyme metabolizes the drug to an inactive product 6-thiouric acid, and catalyzes the last two steps converting purines to uric acid (hypoxanthine xanthine uric acid).

Mechanism. Allopurinol is a competitive inhibitor of xanthine oxidase at low concentrations and a noncompetitive inhibitor at higher concentrations. It is itself a substrate for xanthine oxidase and its metabolic product, **alloxanthine**, is also a noncompetitive xanthine oxidase inhibitor. Alloxanthine has a much longer plasma half-life and is probably the primary uric acid-lowering agent.



Toxicity: Minor. Can induce attack of gout when initiate therapy therefore colchicine can be co-administered at the initiation of therapy.

Use: Treat all forms of hyperuricemia, especially if renal problems due to uric acid deposition, if large TOPHI (uric acid deposits) are present, or if uricosuric agents give an inadequate response. Therapy can be for life.

URICOSURIC AGENTS

Renal handling of organic anions. The transport of organic anions across renal proximal tubules is studied with the anion, p-amino hippuric acid (PAH). Look at movement of PAH from plasma (interstitial) side to urine (luminal side).

a.PAH is transported from interstitial fluid into cell via a transporter in the basolateral membrane. This transport is associated with Na^+ transport and possibly an anion exchange mechanism.

b.PAH is transported from the cell into the luminal side via a specific transporter in the brush border membrane.

If there is a competition between organic anions for the secretory pathway, it occurs at the transporter at the basolateral membrane. **It is this site that uricosuric agents inhibit the tubular secretion of penicillin.**

The pharmacology of uricosuric agents is complicated because of the complicated (and species specific) way the body handles uric acid. Uric acid in not bound to plasma proteins. While

the filtered load is about 6-7 mg/min, the body excretes < 1 mg/min. This is because uric acid is actively reabsorbed in the proximal tubules. It is transported from the lumen across the brush border membrane via the same transporter that is involved in the secretion of organic anions. The transport mechanism for uric acid at the basolateral membrane is not clear. **It is the uricosuric agent in the lumen that competes with uric acid for transport by the brush border transporter that is responsible for the uricosuric effect.**

Paradoxical effect of uricosuric agents:Low doses decrease the excretion of uric acid while higher doses are uricosuric. Don't worry about possible explanations.

Specific agents:

PROBENECID

Developed to prolong the biological half-life of penicillin when penicillin very expensive. As mentioned earlier blocks secretory mechanism at the basolateral membrane. Highly lipid soluble benzoic acid derivative. Highly bound to plasma proteins but actively secreted in proximal tubule and passively reabsorbed by back diffusion. Can increase excretion if alkalinize urine.

Effective in treatment of gout. Also can be used in one-dose treatment of gonococcal infections if patient unlikely to return.

SULFINPYRAZONE

related to phenylbutazone but not anti-inflammatory and toxic.98% bound to plasma proteins but actively secreted and little back diffusion short plasma half-life.

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Important interactions

1.Probenecid and sulfinpyrazone can give additive effect. Probenecid prolong half-life of sulfinpyrazone?

2.**Salicylates inhibit uricosuric effects of probenecid and sulfinpyrazone (even though salicylates can be uricosuric). Important that patients taking these agents not take a salicylate such as aspirin. Use acetaminophen or iboprofin.**

3.Since these agents are highly bound to plasma proteins you must be aware that they can affect the plasma levels of other drugs that are also highly bound to plasma proteins.

PURINE METABOLISM IN MAN