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"And should there be a sudden loss of consciousness during this **class** oxygen masks will drop from the ceiling."

## Salicylates

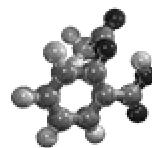
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**Learning Objectives:** After studying this material, the student should:

1. Know the **four** basic therapeutic uses for aspirin.
2. Know the major routes of absorption for salicylates and the **plasma half-life of aspirin** and of **salicylic acid**.
3. Know the **basic reaction by which aspirin is inactivated**.
4. Understand how **urine pH** can affect the excretion of free salicylic acid.
5. Understand the **basic mechanisms** or proposed mechanisms by which salicylates produce their four therapeutic activities.

6. **Understand how aspirin and salicylates can produce effects on respiration, electrolyte and acid/base balance, especially know the difference in these factors as the dose increases from normal therapeutic to toxic levels.**
7. Know the most predominant undesirable **side-effects** of salicylates.
8. Be able to define the term "**salicylism**".
9. Understand the possible implications of aspirin use in those with **hypersensitivity** responses or **in children who have chicken pox or flu**.

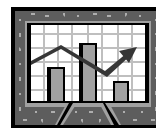


### I. Introduction

A. Use - anti-inflammatory, anti-pyretic, analgesic - non-narcotic, anti-thrombotic

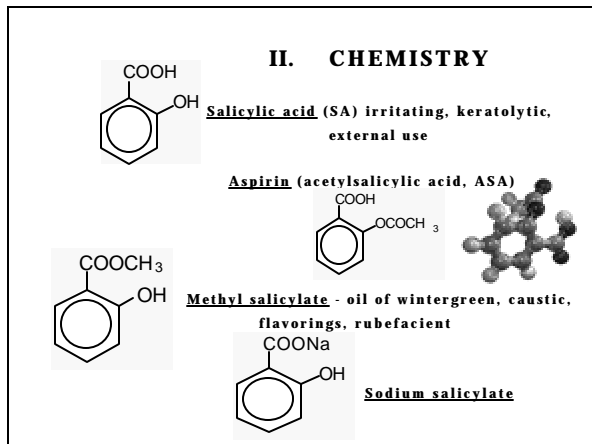
B. Prevalence - estimated U.S. annual consumption as high as 25-50 million lbs., **over 200 drug products contain aspirin**

8 million people consult GPs each year with some form of arthritic disorder




Between 2 and 4% of the GP registered population receive intermittent or maintenance long-term NSAIDs

C. History - **Salicin** - from the willow and the rose-like spirea



## III. ASPIRIN Absorption, Distribution, Biotransformation, Excretion



### A. Absorption - passive diffusion

- stomach and upper sm. intestine, generally rapid ( $t_{1/2} = 20-30 \text{ min}$ ), influenced by disintegration, dissolution, gastric emptying time and especially gastric pH.

Ionization increases ASA solubility in watery stomach contents but slows transport across GI membranes. Ionization of aspirin in mucosal cells causes concentrating effect and damage to cells.

- rectal absorption - poor
- skin - salicylic acid - rapid, methylsalicylate - rapid


### B. Distribution - 160 ml/kg

- extracellular distribution - rapid, thorough, slow across blood brain barrier
- intracellular distribution - variable
- 50-90% SA bound to plasma protein  
**!! Effects binding of other drugs**
- little ASA bound to plasma protein

### C. Biotransformation -

plasma ASA rapidly deacetylated to salicylic acid by liver and blood

- ASA + HOH  $\rightarrow$  SA + acetic acid
- plasma ASA  $t_{1/2} = 20-30 \text{ min}$ , plasma SA  $t_{1/2} = \text{hrs}$  (increases with dose)
- ASA acetylates some proteins
- SA does not acetylate protein, including cyclooxygenase, therefore no platelet effect




### D. Excretion in urine -

form influenced by urine pH

- normal urine pH
  - free SA - 10%
  - salicyluric acid (a glycine conjugate) - 75%
  - other metabolites - 15%
- alkaline urine pH - up to 30% free SA
- acidic urine pH - as low as 2% free SA

## IV. Pharmacologic Activity

### Anti-inflammatory -

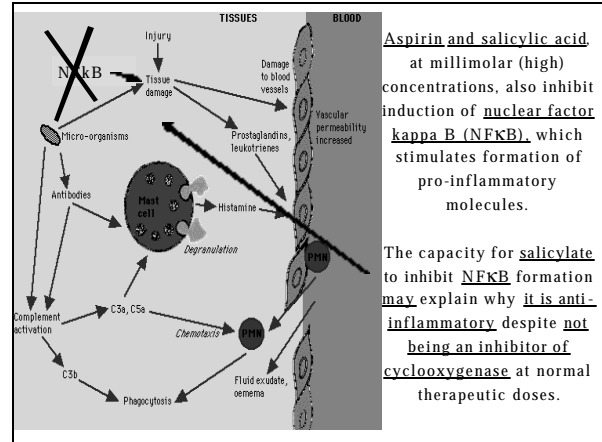
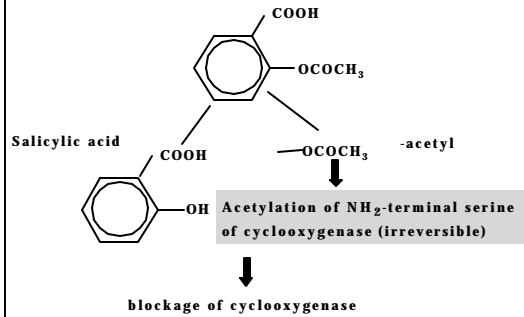


likely due to ASA's acetylation of cyclooxygenase, the enzyme necessary for the synthesis of prostaglandins (PGs) and thromboxanes.

PGs are produced by inflamed tissue and can cause hyperemia, increase capillary permeability and leukocyte migration.

Potency and efficacy to inhibit PG synthesis correlates with clinical potency and efficacy.

## Aspirin (acetyl salicylic acid)



Aspirin and salicylic acid at millimolar (high) concentrations, also inhibit induction of nuclear factor kappa B (NFκB), which stimulates formation of pro-inflammatory molecules.

The capacity for salicylate to inhibit NFκB formation may explain why it is anti-inflammatory despite not being an inhibitor of cyclooxygenase at normal therapeutic doses.

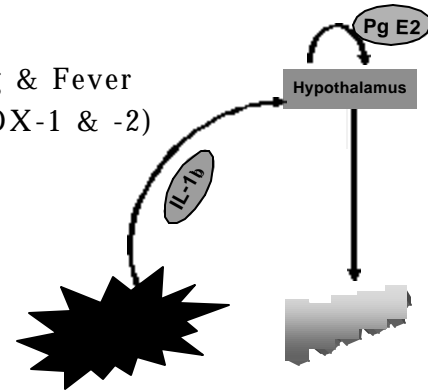
## B. Antipyretic -

lowers body temp. only if body temp. abnormally high.

Mechanisms may include:

- 1) resetting hypothalamic temp. reg. center
- 2) competing with pyrogens for receptor sites
- 3) inhibition of synthesis of pyrogenic prostaglandins

## Pg & Fever (COX-1 & -2)



## C. Analgesia -

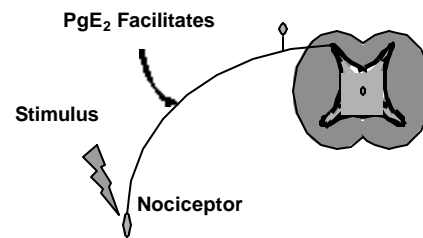
relieves mild-moderate intensity pathological pain arising mainly from integumental structures, but not hollow organs.

Mechanism uncertain but may involve peripheral and central neural actions.

May include inhibition of PGs, which sensitize pain receptors to cause hyperalgesia.


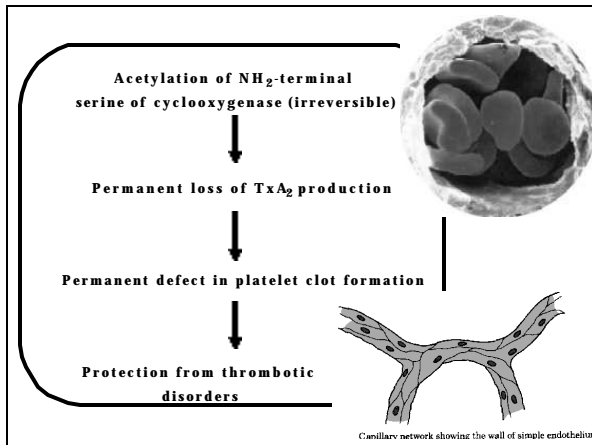
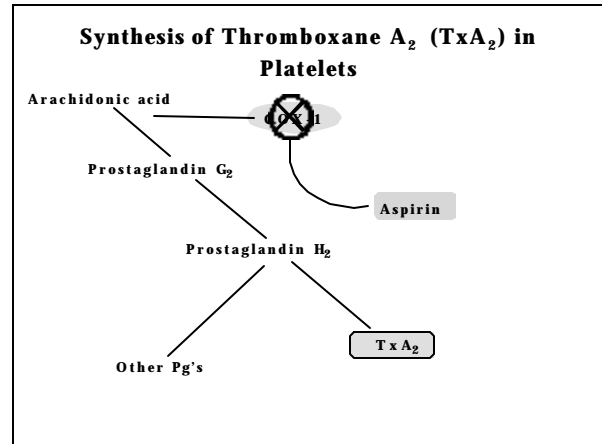
Central actions may also be via salicylic acid

## Prostaglandins & Pain (COX-1 & -2)



**D. Anti-thrombotic -**

prolongs bleeding time by decreasing platelet aggregability, works via inactivation of platelet cyclooxygenase and thus prevents formation of the platelet aggregator substance, thromboxane.





**E. Respiration, Electrolyte, Acid-base balance**


1. Metabolic effect (low dose ASA) -

uncouple ox. phos., get - O<sub>2</sub> use, - CO<sub>2</sub> prod.

therefore - ventilation depth



**E. Respiration, Electrolyte, Acid-base balance**



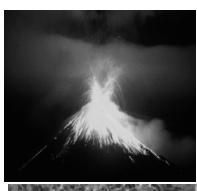
2. Central neural effects - dose dependent, in toxic range

a. Stimulation (higher dose) - - ventilation depth and rate, therefore resp. alk. - *MORE CO<sub>2</sub> than you can exhale* and compensatory - bicarb., Na & K excretion (compensated resp. alk.)

b. Depression (highest dose) - - vent. depth and rate therefore resp. acidosis

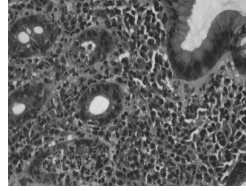
3. Metabolic acidosis (highest dose) due to decreased renal function, increase production of organic acids, salicylic acid itself

**F. Gastrointestinal -**



most predominant side effect of salicylates is epigastric distress.


Also nausea and vomiting.




ASA can cause gastric ulceration and - tendency toward ulcers.

Minor to major gastric bleeding. Effects may be due to - formation of cytoprotective PGs.


**Other Adverse Effects**



**Renal Failure**



**Congestive Heart Failure**



**Raised Blood Pressure**

**G. Hepatic and Renal -**

Salicylates may exacerbate problems in those with existing liver or renal problems.

In 1980 epidemiological evidence showed that salicylates were a factor in the severe hepatic injury and encephalopathy observed in childhood **Reyes Syndrome**, a rare but often fatal consequence of infection with chicken pox and various influenza strains.

While there is strong association, the mechanism of causality by salicylates has not been established. It is now standard practice to not use salicylates in children with chicken pox or influenza and many completely avoid aspirin use in children. The generally used alternative to aspirin is acetaminophen.

- *Reye's Syndrome*
  - children with acute febrile viral illnesses
  - aspirin for fever
  - fulminant hepatic failure
  - very high mortality
  - Particular risk of bronchospasm

Since 1980 the incidence of Reyes Syndrome in those under 18 years old has decreased precipitously and is now a rare occurrence (N. Engl. J. Med. 340: 1377, 1999).

**V. Salicylate Intoxication**

**Salicylism** - mild chronic salicylate intoxication.

Syndrome consists of:

headache, dizziness, tinnitus, difficulty hearing, dim vision, mental confusion, lassitude, drowsiness, sweating, thirst, hyperventilation, nausea, vomiting and occasionally diarrhea.

These symptoms subside upon stopping or lowering salicylate dose.

**VI. Aspirin Hypersensitivity**

Uncommon but may be severe or fatal.

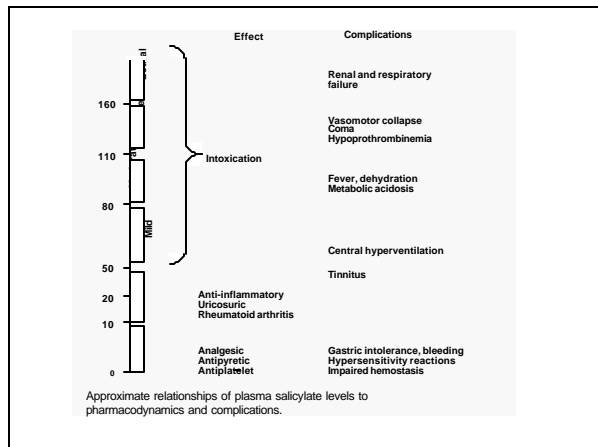
Occurs mostly in middle aged and females.

Warning signs are previous history of hypersensitivity to chemicals, asthma or especially nasal polyps.

May occur with small dose of ASA or other PG synthesis inhibs.

Effects include rhinorrhea, urticaria, bronchospasm, hypotension, and vasomotor collapse.

Treat with epinephrine.



## VII. Therapeutic Uses

analgesia

antipyresis

colds - symptomatic relief

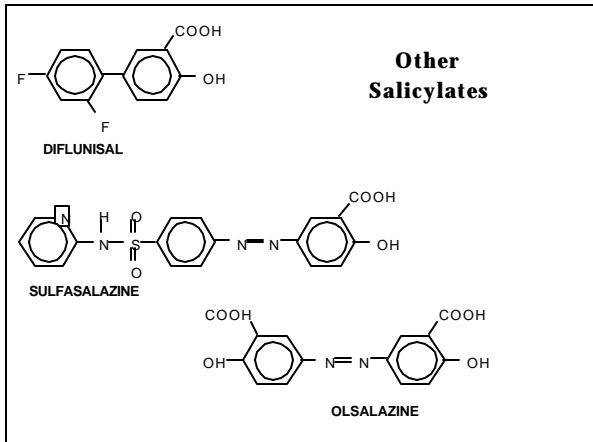
rheumatoid arthritis

acute rheumatic fever

keratolytic agent - salicylic acid

counter-irritant - methylsalicylic acid, sprains

anti-thrombotic - antiplatelet, TIAs, angina, as little as 80 mg (1/4 of 1 ASA tablet) per day is effective VIII.



### Other Salicylates

#### A. Diflunisal -

difluorophenyl derivative of salicylic acid.

**Competitive inhibitor of cyclooxygenase.**

**Not converted to salicylic acid in vivo.**

More potent anti-inflammatory agent than aspirin has **no anti-pyretic effects**, perhaps due to poor CNS penetration.

Used for sprains, osteoarthritis, rheumatoid arthritis (RA).

No auditory side effects (unlike ASA)

**Less GI upset and less anti-platelet effects than aspirin.**

#### B. Sulfasalazine -

sulfonamide anti-microbial

used for ulcerative colitis and regional enteritis.

Poorly absorbed in GI tract.

Broken down by intestinal bacteria to **sulfapyridine, an active sulfonamide, and 5-aminosalicylate, which is thought to be the effective anti-inflammatory agent when used to treat inflammatory bowel disease.**

Sulfasalazine has been empirically found to be helpful in RA and ankylosing spondylitis.

#### C Olsalazine -

**a dimer of 5-aminosalicylate, which is the active anti-inflammatory agent produced by metabolism of sulfasalazine.**

#### Learning Resources:

##### Drugs to Remember:

1. Salicylic acid
2. Aspirin
3. Methyl salicylate
4. Sodium salicylate
5. Diflunisal

##### Recommended Reading:

1. **Basic and Clinical Pharmacology**, B.G. Katzung (ed), 8th ed., 2001.

