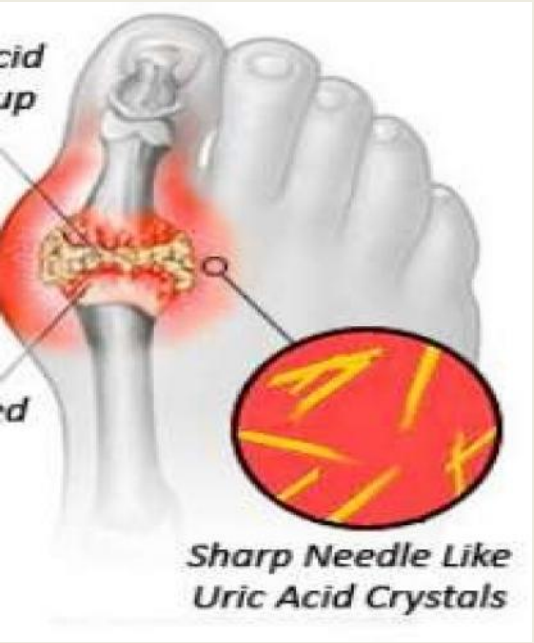
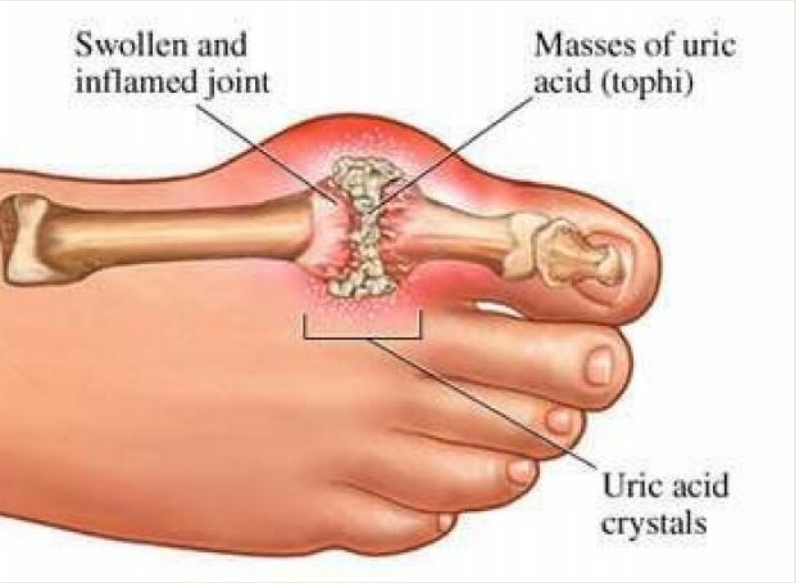


Catabolism of Purines & GOUT



cleotides of cell undergo continual turnover.

Nucleotides

↓ Nucleotidase

Nucleosides

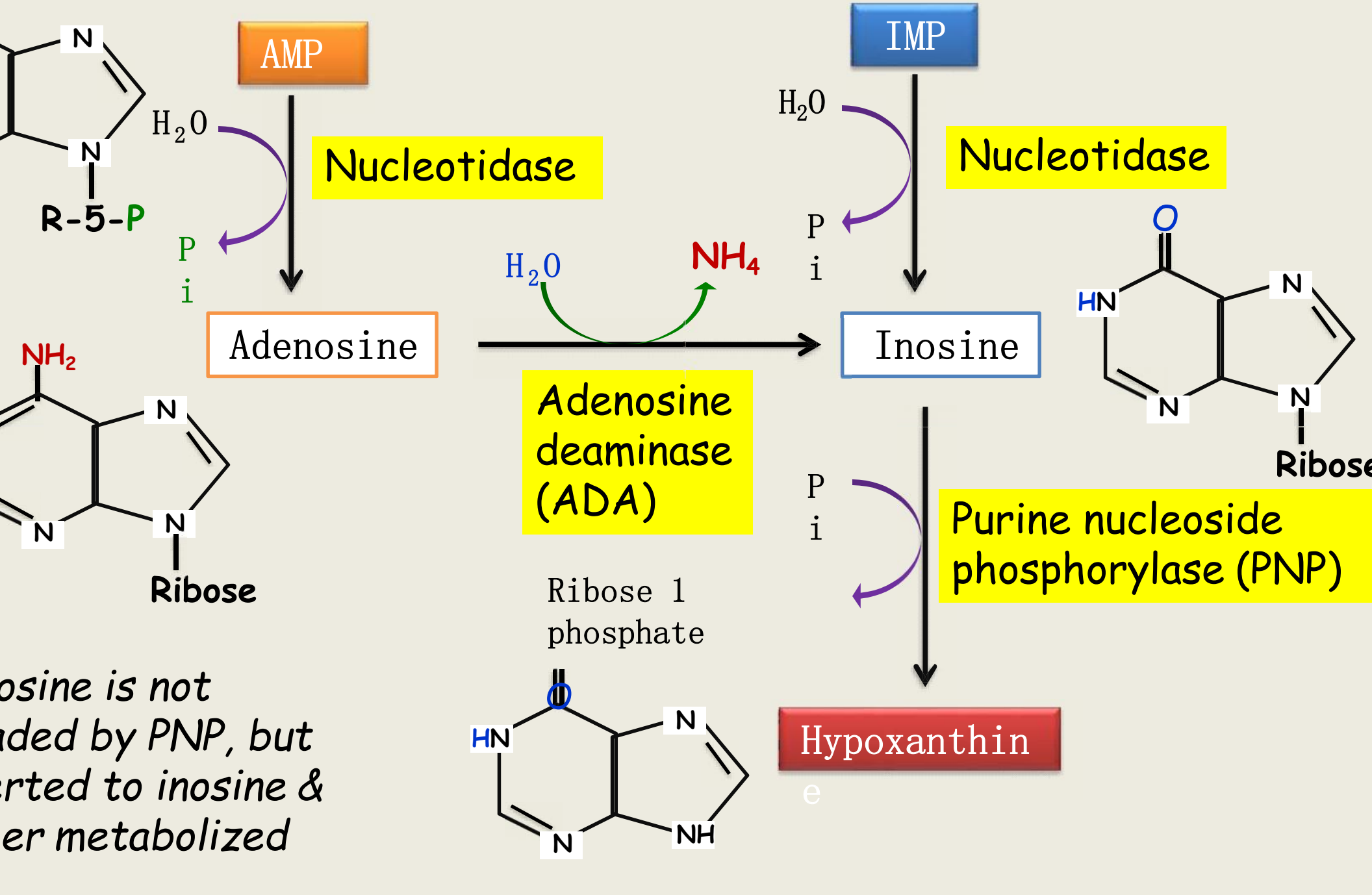
↓ Nucleoside Phosphorylase

Free bases + R-1-P

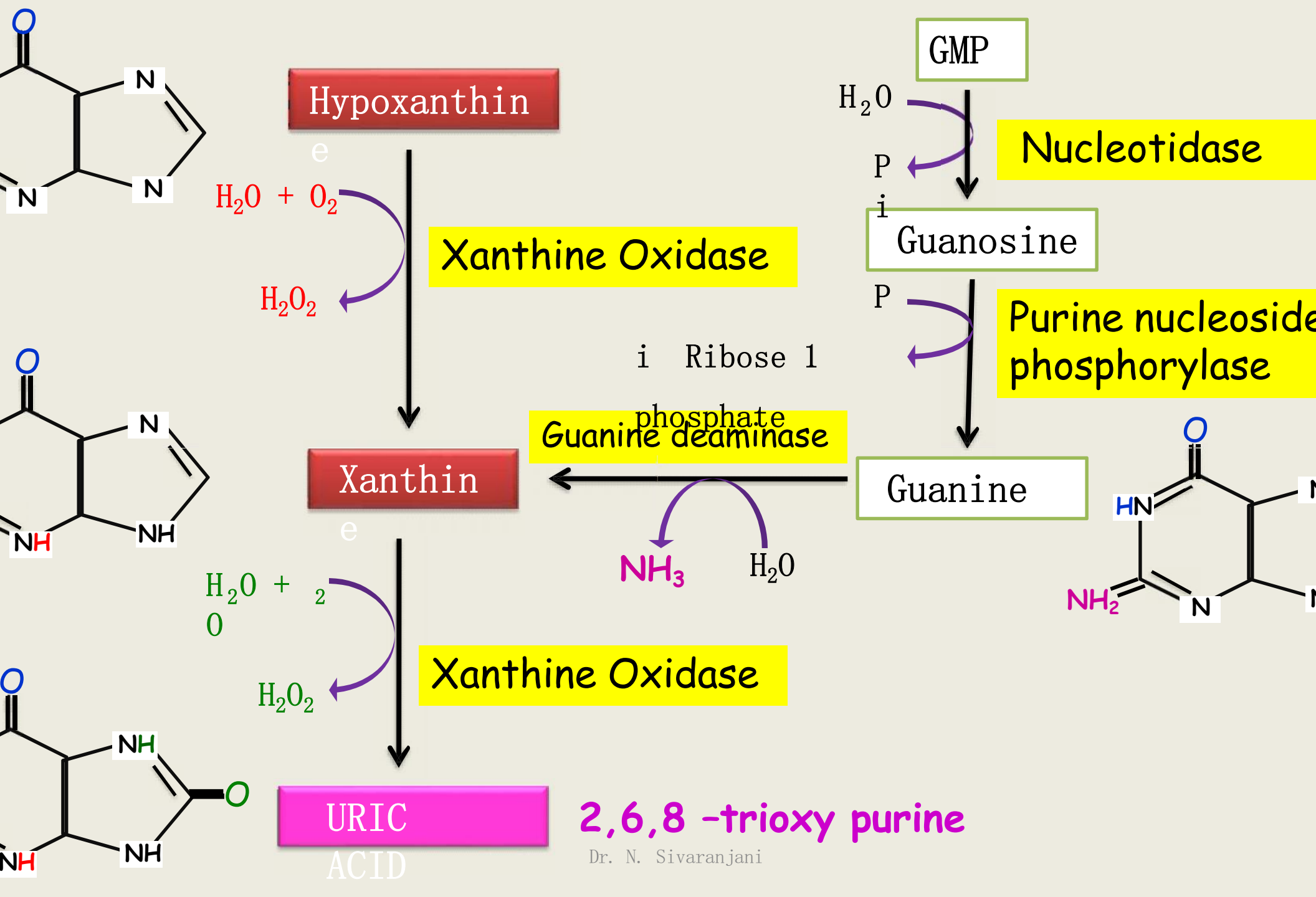
me of bases are reused to form nucleotides by Salvage pathw

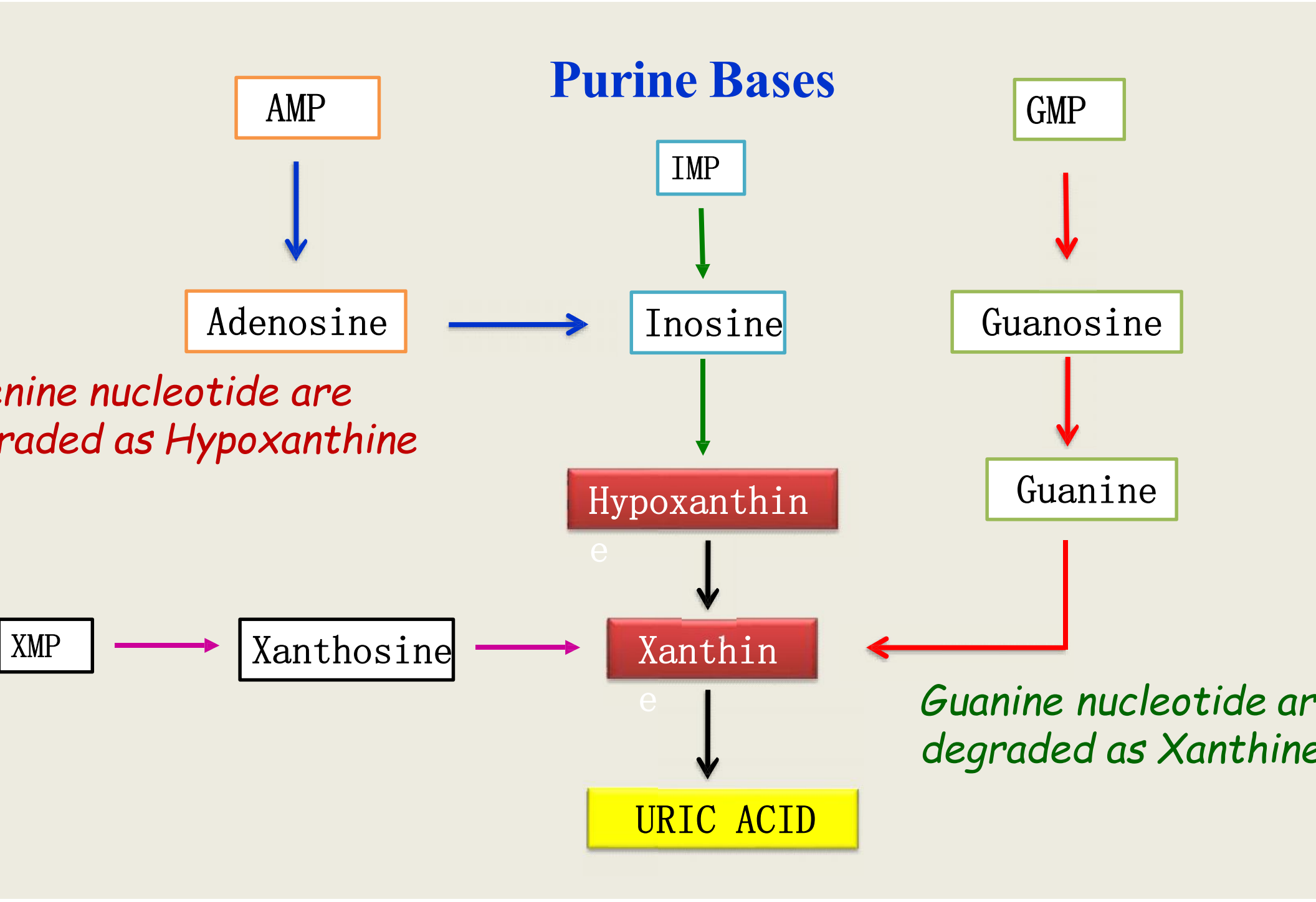
hers are degraded to products that are excreted.

ic acid is end product of purine catabolism



osine is not
aded by PNP, but
rted to inosine &
er metabolized


GMP
H_2O
P
i
Nucleotidase
Guanosine
P
Purine nucleoside phosphorylase
i Ribose 1 phosphate
Guanine
Guanine deaminase
NH_3
H_2O
Hypoxanthin
e
$H_2O + O_2$
H_2O_2
Xanthine Oxidase
Xanthin
e
$H_2O + O_2$
H_2O_2
Xanthine Oxidase
URIC ACID
2,6,8 -trioxy purine
Dr. N. Sivaranjani

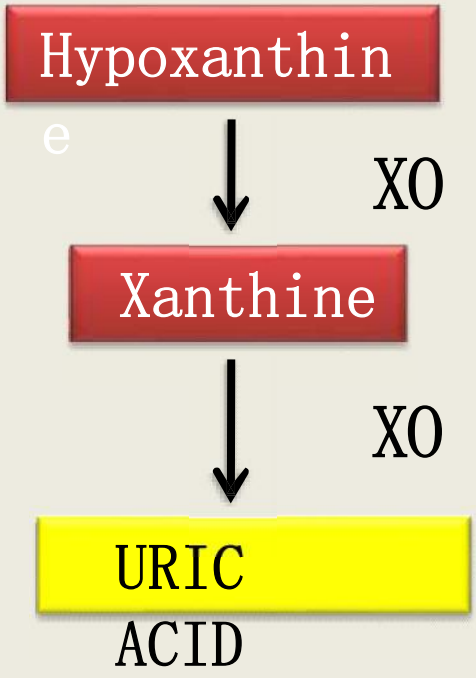

Purine Bases
AMP
GMP
IMP
Adenosine
Inosine
Guanosine
nine nucleotide are
raded as Hypoxanthine
Hypoxanthin
e
Guanine
XMP
Xanthosine
Xanthin
e
Guanine nucleotide ar
degraded as Xanthine
URIC ACID

thine oxidase

ound in LIVER & Small intestine

Metallo flavoprotein

ontains FAD, Molybdenum and Iron



his reaction produces H_2O_2 (reactive oxygen species)

$$H_2O_2 \xrightarrow{\text{Catalase}} H_2O + O_2$$

e end product of purine catabolism is **uric acid** in humans.

excreted as uric acid is very little in humans, as humans are
otelic (nitrogen is excreted as urea).

birds, amphibians and reptiles are **uricotelic** - they excrete u
d as major end product of purine and amino acid catabolism.

wer primates and some mammals have the enzyme **uricase** whi
nverts uric acid to **allantoin** (which is more soluble).

kdown of Endogenous purine

Diet - 300 mg

De novo synthesis -

Purine nucleotides

Cataboliz ed

uric acid pool in Men 1200 mg,
ale – 600 mg

URIC ACID

Renal Excretion

Uricolysis

$CO_2 + NH_3$

Sources and excretion of Uric acid

nal serum **Uric acid** concentration :

- **7 mg /dl** in males , **2 - 5 mg/dl** in females

ic acid pool –It is on average of **1200 mg**

etion - **500 to 700 mg** /day excreted

ic acid is **cleared** by both **glomerular filtration** and **tubular cretion.**

ic acid acts as Natural ANTIOXIDANT

uricemia and gout:

eruricemia –

eased serum uric acid levels above 7 mg/dl in
n & above 6 mg/dl in women.

uses – Excessive Alcohol consumption, CRF,
erited metabolic disorders, Malignancies, Pre-eclampsia.

t is a metabolic disorder of **purine catabolism**, resulting in
rproduction of uric acid.

physiological pH , uric acid is found in a minimal soluble form
no sodium urates – easily ppt at lower temperature.

es of gout :

rimary gout :

herited - 90% ,due to an Inborn error of metabolism caused b
ective enzymes of Purine synthesis.

opathic - 10 % cases

riant form of **PRPP synthetase-** not subject to allosteric cor

riant of **PRPP glutamyl amidotransferase** - not sensitive to
edback control.

ucose 6 phosphatase deficiency - Von Gierke's disease
-P enters HMP shunt produces excess R-5-P & PRPP – purine overprodu
ic acidosis in Von Gierke's disease – impairs UA excretion.

ficiency of enzymes of salvage pathway –**HGPRT** deficiency
ding to **Lesch-Nyhan syndrome**.

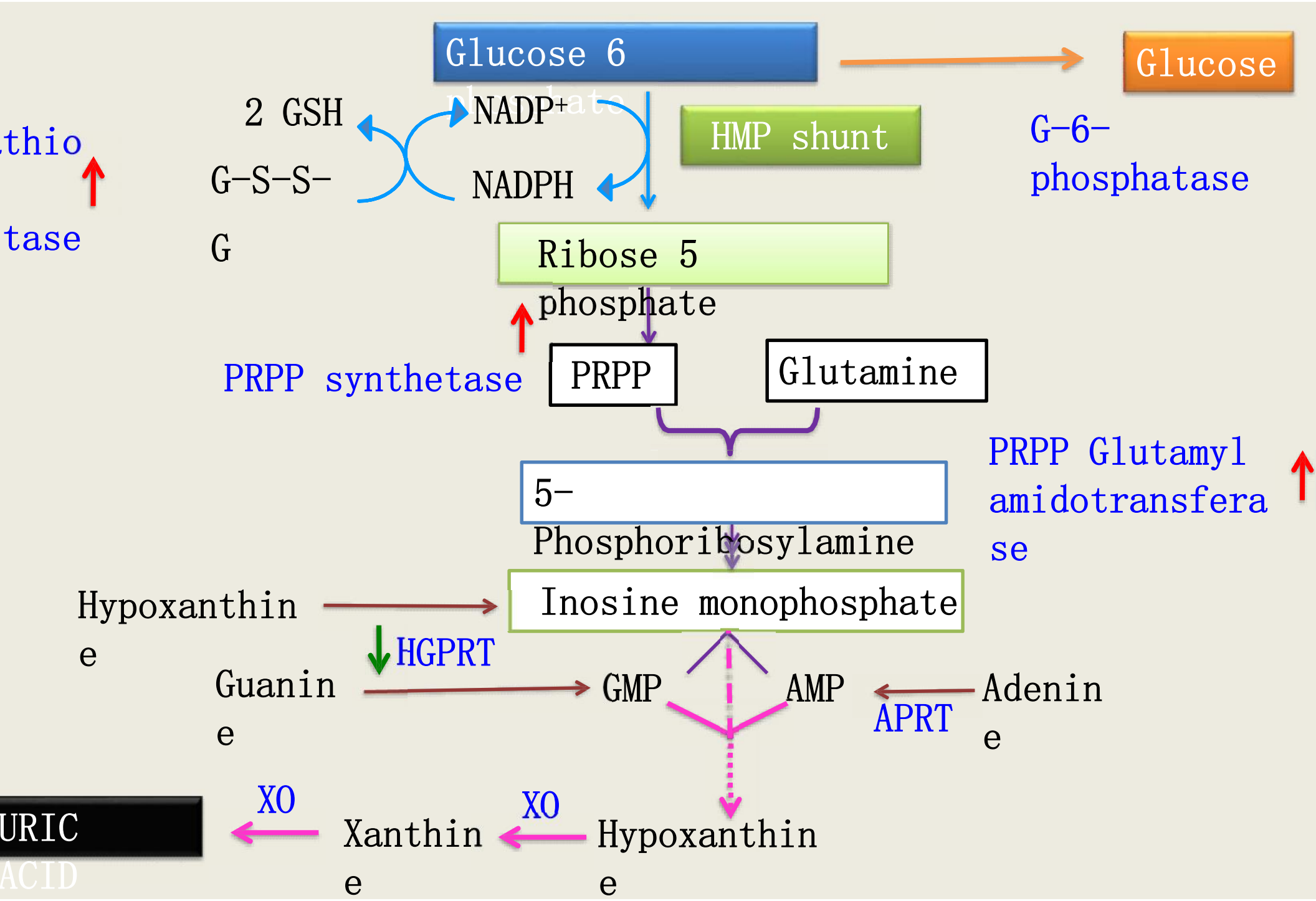
utilization of purines by salvage pathway – diverts PRPP to purine synth

salvage pathway – dec. IMP & GMP – impairs feedback reg. of denovo
hesis of purine – leads to overproduction of purines.

vation of **Glutathione reductase**

overts oxidized Glutathione to reduced form by utilizing NADPH from H
t.

ormal activity of GR - Inc. NADP+ - Inc. HMP shunt – which rises R-5-P
synthesis – overproduction of purines.


Glucose 6
Glucose
2 GSH
NADP+
HMP shunt
G-6-
phosphatase
thio
tase
G-S-S-
G
NADPH
Ribose 5
phosphate
PRPP synthetase
PRPP
Glutamine
PRPP Glutamyl
amidotransfera
se
5-
Phosphoribosylamine
Hypoxanthin
e
Inosine monophosphate
HGPRT
Guanin
e
GMP
AMP
Adenin
e
APRT
XO
XO
URIC
ACID
Xanthin
e
Hypoxanthin
e

condary gout:

to various disease causing increased synthesis or decreased excretion

rproduction of uric acid – due to enhanced turn over rate
eic acids

creased tissue turn over due to psoriasis.

idly growing malignant tissues - CANCER - Leukemias,

ythemia, lymphomas.

reased tissue break down – after treatment for large tumo

s –radiotherapy & chemotherapy, trauma and starvation.

duced excretion of uric acid

onic Renal failure due to reduced GFR.

creased alcohol consumption leads to lactic acidosis - Lactic a
reases tubular excretion of uric acid.

toacidosis – decreases the tubular excretion of uric acid

iazide diuretics inhibits tubular secretion of uric acid.

Clinical features:

to the **low solubility of uric acid.**

e common in Males, post menopausal women.
ical gouty arthritis **affects first metatarso angeal joint (GREAT TOE)** – Classical site

Gout , serum urate levels exceed solubility limit, leading to nation of **MSU crystals** and get **deposited in joints.**
deposits are called **Tophi.**
nflammation of joints
ainful acute gouty arthritis → chronic gouty arthritis.
er complications like **urolithiasis** and renal damage.

increased serum uric acid

↓

Mono-sodium urate crystals

" redness, swelling, and
-hallmarks of a gout a

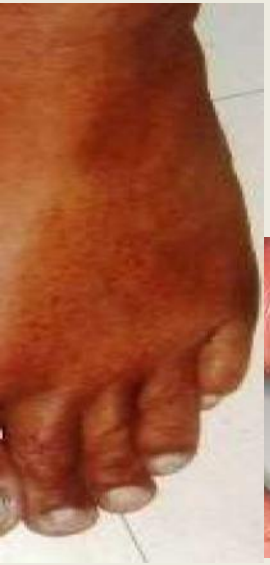
form – body uric acid
ach 20,000 -30,000 mg

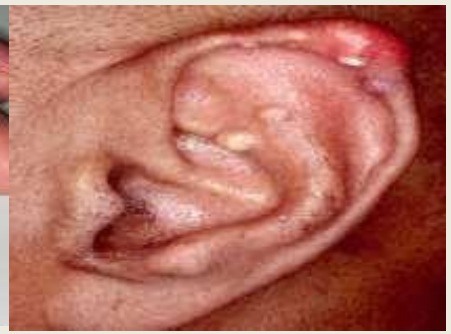
↓

Deposited in areas where body temperature is lower – Tophi

↓

Gouty arthritis



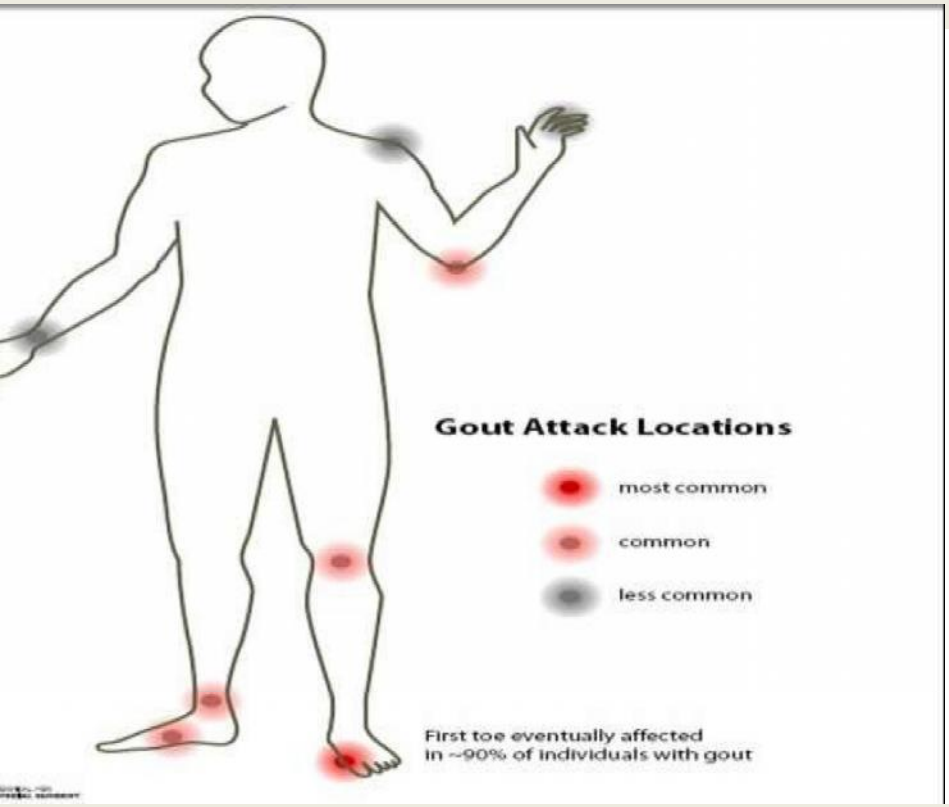


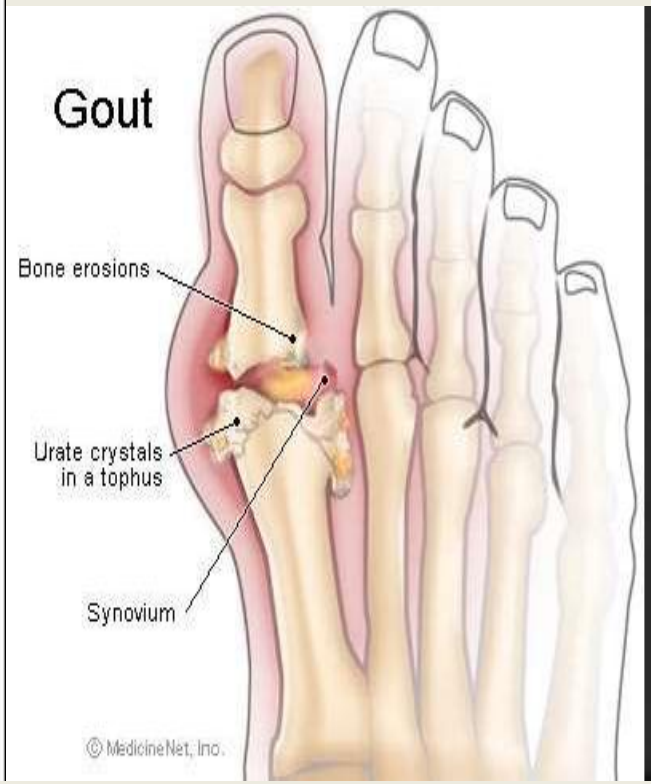
→

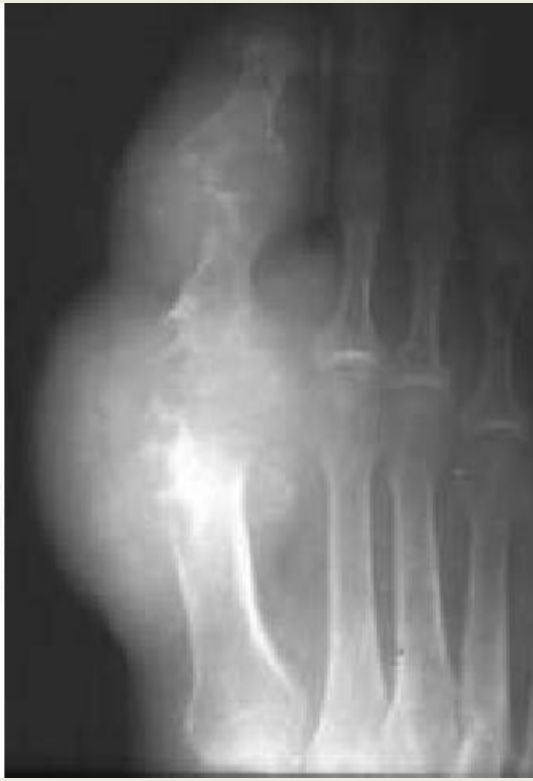
Deposited in Kidney

↓

Renal calculi /stone
Renal damage







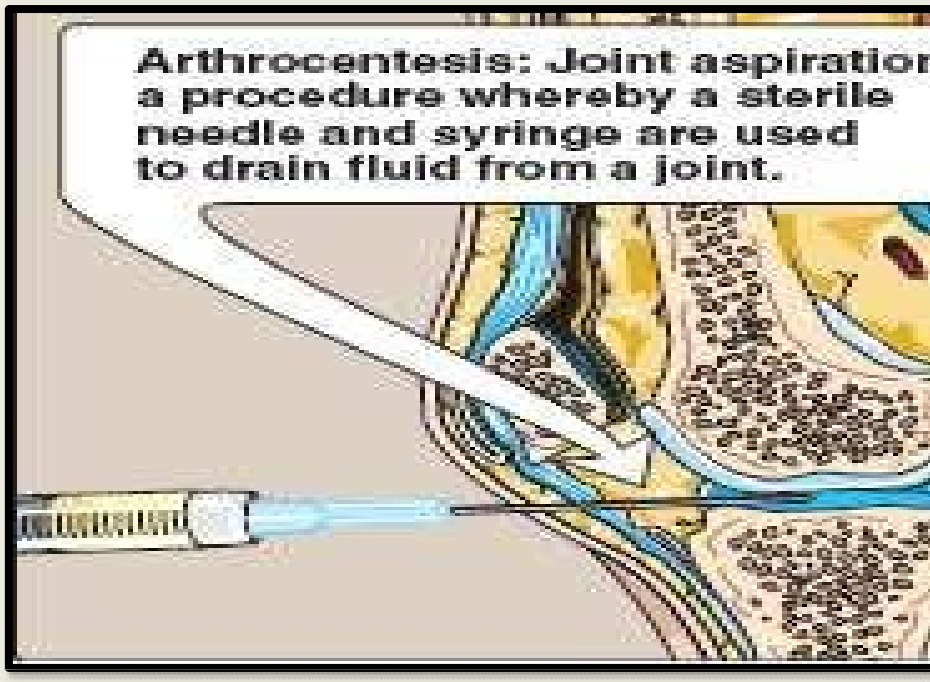
HISTORY is - patient have few drinks at night , go to sleep symptoml
are awakened during early hrs by severe joint pains.

eruricemia doesn't always cause gout. Over the course of yrs, sharp ura
tals build up in the synovial fluid of the joints.

tating event - infection, surgery, stress or often heavy ALCOHOL drin

estigations :

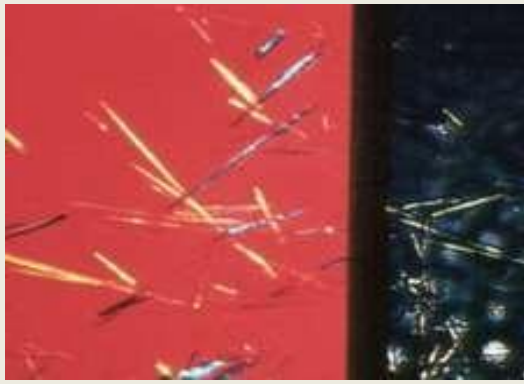
um uric acid level -increased



roscopic Examination of Synovial

reveals uric acid crystals - **rod / needle –shaped crystals.**

efringent crystals under polar microscope is
gnostic.



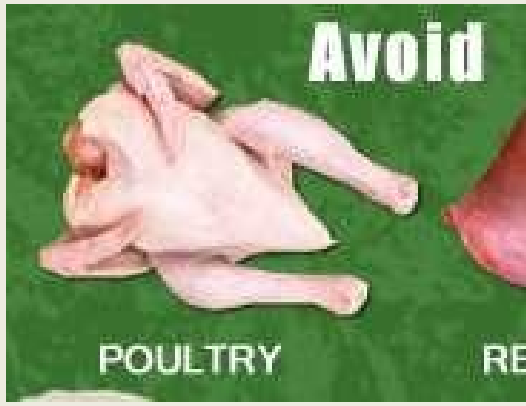
atment of gout :

intake of Purine diet- like **red meat, acidy fruits and etables, lentils**

trict Alcohol

ume plenty of Water

:



ti-inflammatory drugs - Colchicine is used for treatment of g hritis. NSAID - indomethacin , ibuprofen. Corticosteroids als ful for acute attacks.

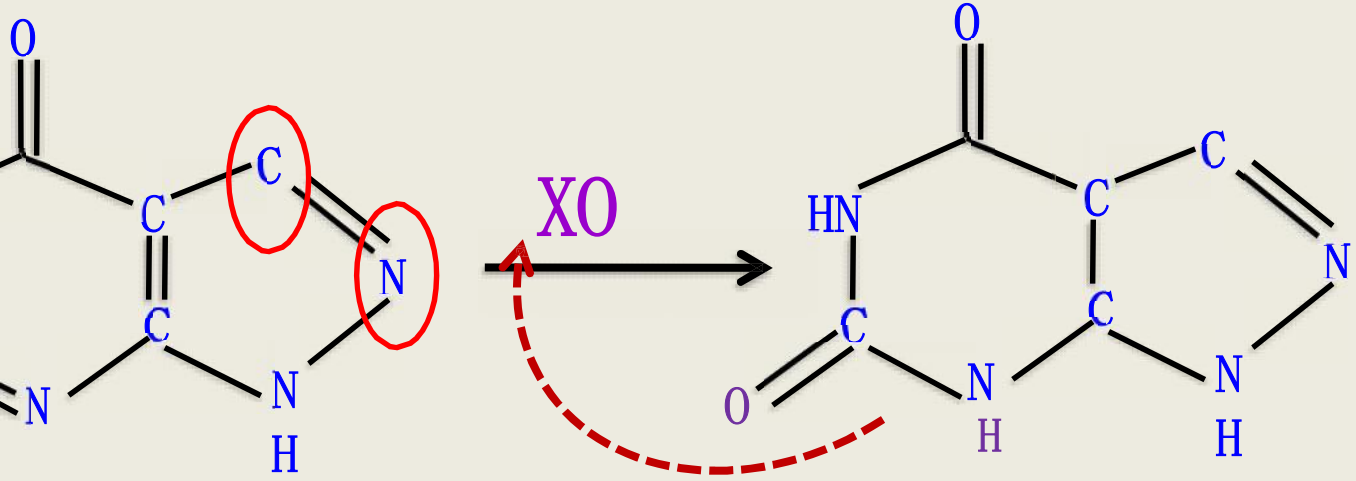
cosuric drugs – Probenecid.

nthine oxidase inhibitors - **ALLOPURINOL**

of choice for treatment of Gout.

structural analog of hypoxanthine.

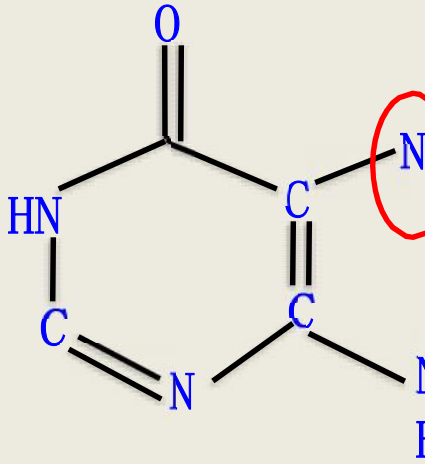
etitively inhibits XO enzyme.



opurinol

Alloxanthine

Suicide inhibition



Hypoxant

Hypoxanthine , Xar
are more soluble ar
excreted in urine.

ogout :

rum uric acid level **normal.**

mptoms as seen in gout.

r it is characterized by deposition of **calcium – pyrophosphat**
stals in joints.

h-Nyhan syndrome:

crited **X-linked recessive disorder, affects only males**

yme defect – **hypoxanthine guanine phoshoribosyl transferase (HGPRT**

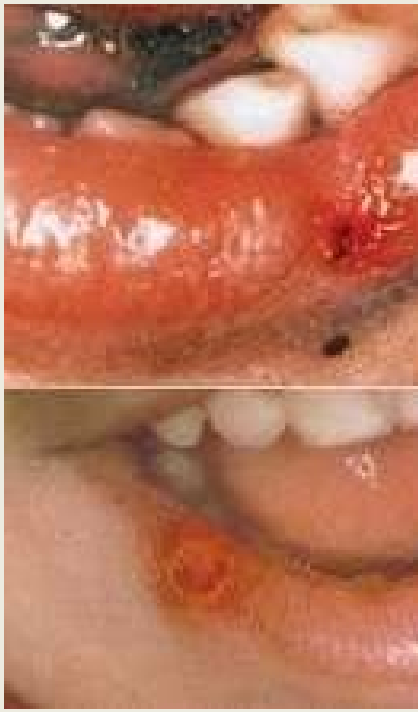
racterized by excess production of uric acid leads to GOUT.

f mutilation – bite their fingers and lips

urological abnormalities like mental - ardation, aggressive behavior , learning bilities occur.

urological symptoms may be due to **dependence** **rain** on the salvage pathway.

hrolithiasis – leads to renal failure.



pouricemia

creased in uric acid level

nthinuria

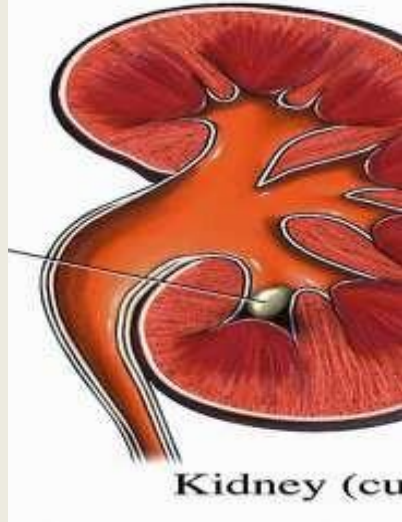
thine oxidase deficiency, due to either genetic defect or due to severe
ER damage.

Hypoxanthine $\xrightarrow{XO}$ Xanthine $\xrightarrow{XO}$ URIC ACID

excretion of xanthine & hypoxanthine

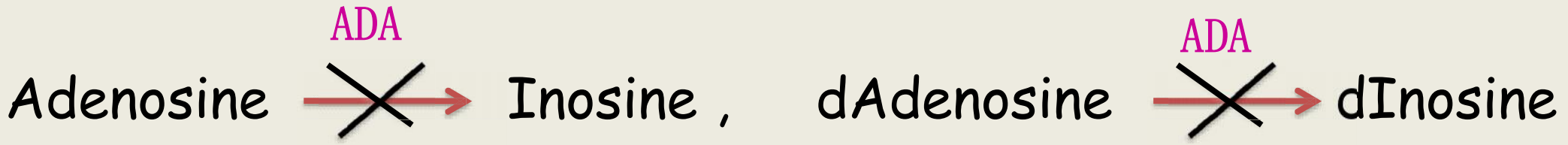
ecreased uric acid

thine lithiasis occur in severe XO def.



Adenosine deaminase deficiency

ds to Both T and B cells are dysfunctional – Severe Combined
nunodeficiency (SCID)



nune dysfunction is due to high levels of deoxy Adenosine
xyadenosine is converted to dAMP, dADP, dATP.
TP allosterically inhibits Ribonucleotide reductase - decrease
A synthesis.

Purine-nucleoside phosphorylase deficeincy

deficiency

acid formation is decreased.

aired T-cells function with normal B cells function.

e dGTP accumulates which inhibits Ribonucleotide reductase.

DA and PNP deficiency

th are inherited as autosomal recessive

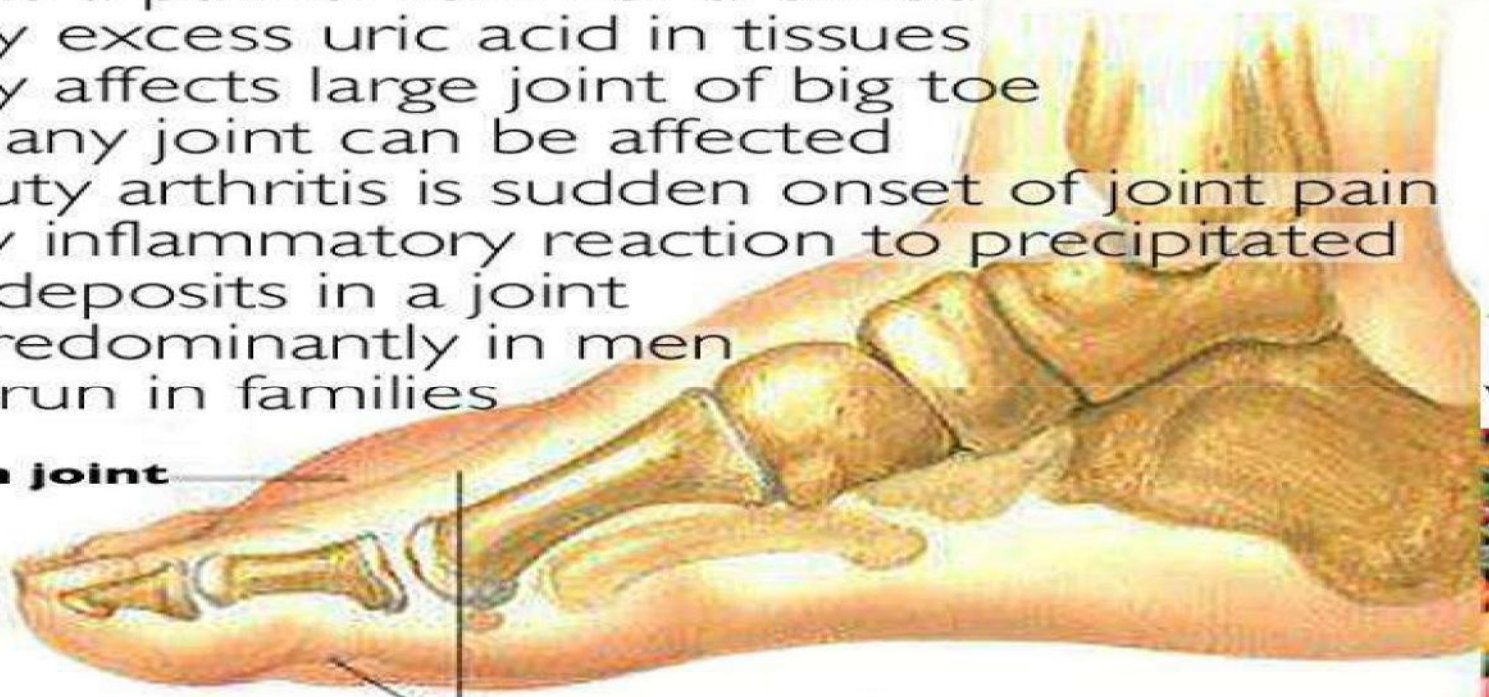
ypouricemia seen

th associated with symptoms of recurrent and chronic infec

OODS THAT PREVENT GO

OUT

resents as a painful form of arthritis
aused by excess uric acid in tissues
equently affects large joint of big toe
though any joint can be affected
cute gouty arthritis is sudden onset of joint pain
aused by inflammatory reaction to precipitated
ric acid deposits in a joint
ccurs predominantly in men
ends to run in families



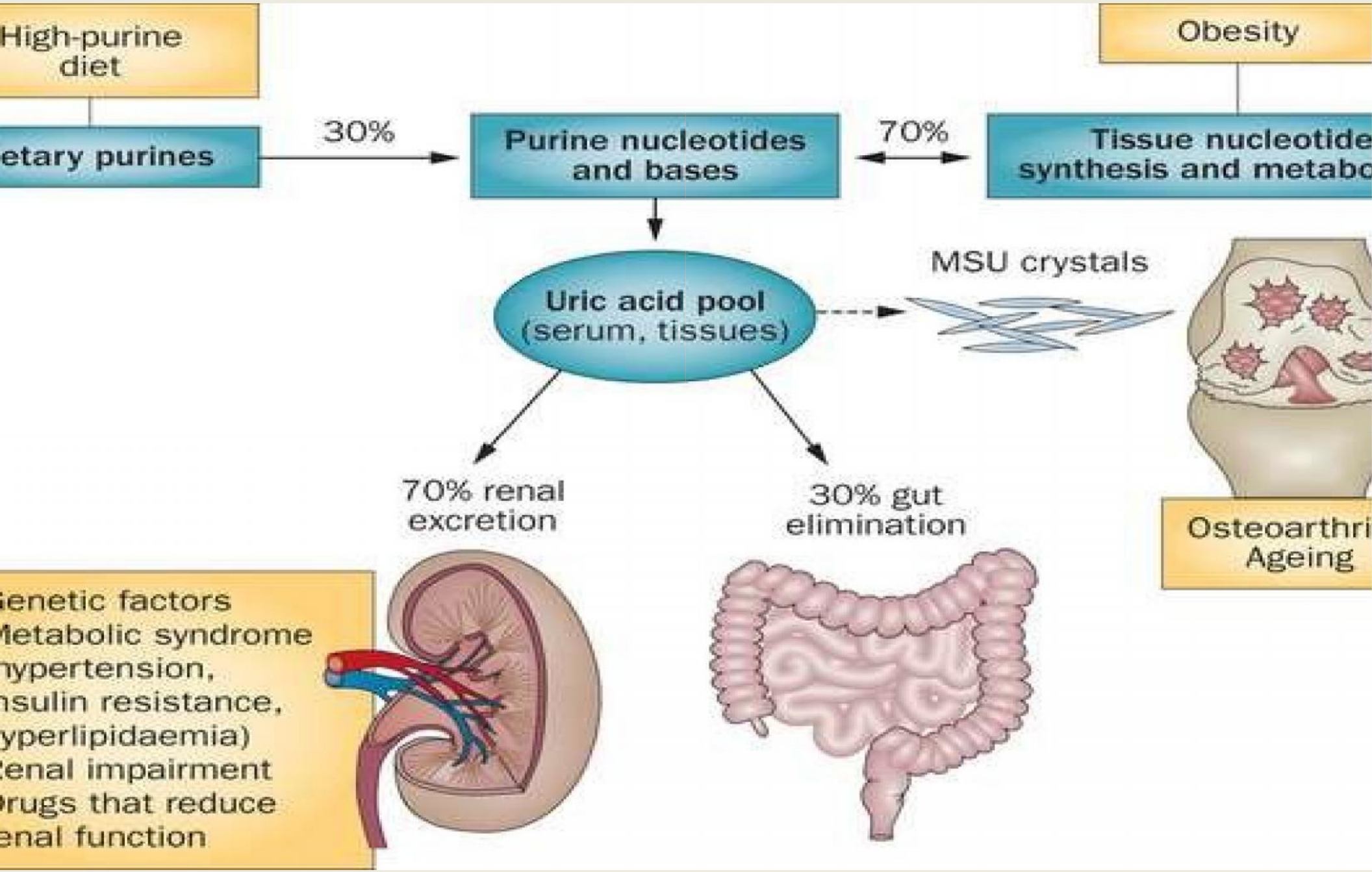
ineapple

ginger

turmeric

cherr

/dave.sommers1


High-purine diet
etary purines
30%
Purine nucleotides and bases
70%
Obesity
Tissue nucleotide synthesis and metabo
Uric acid pool (serum, tissues)
MSU crystals
70% renal excretion
30% gut elimination
Osteoarthri
Ageing
enetic factors
Metabolic syndrome
ypertension,
nsulin resistance,
yperlipidaemia)
enal impairment
rugs that reduce
enal function