# Metal toxicity

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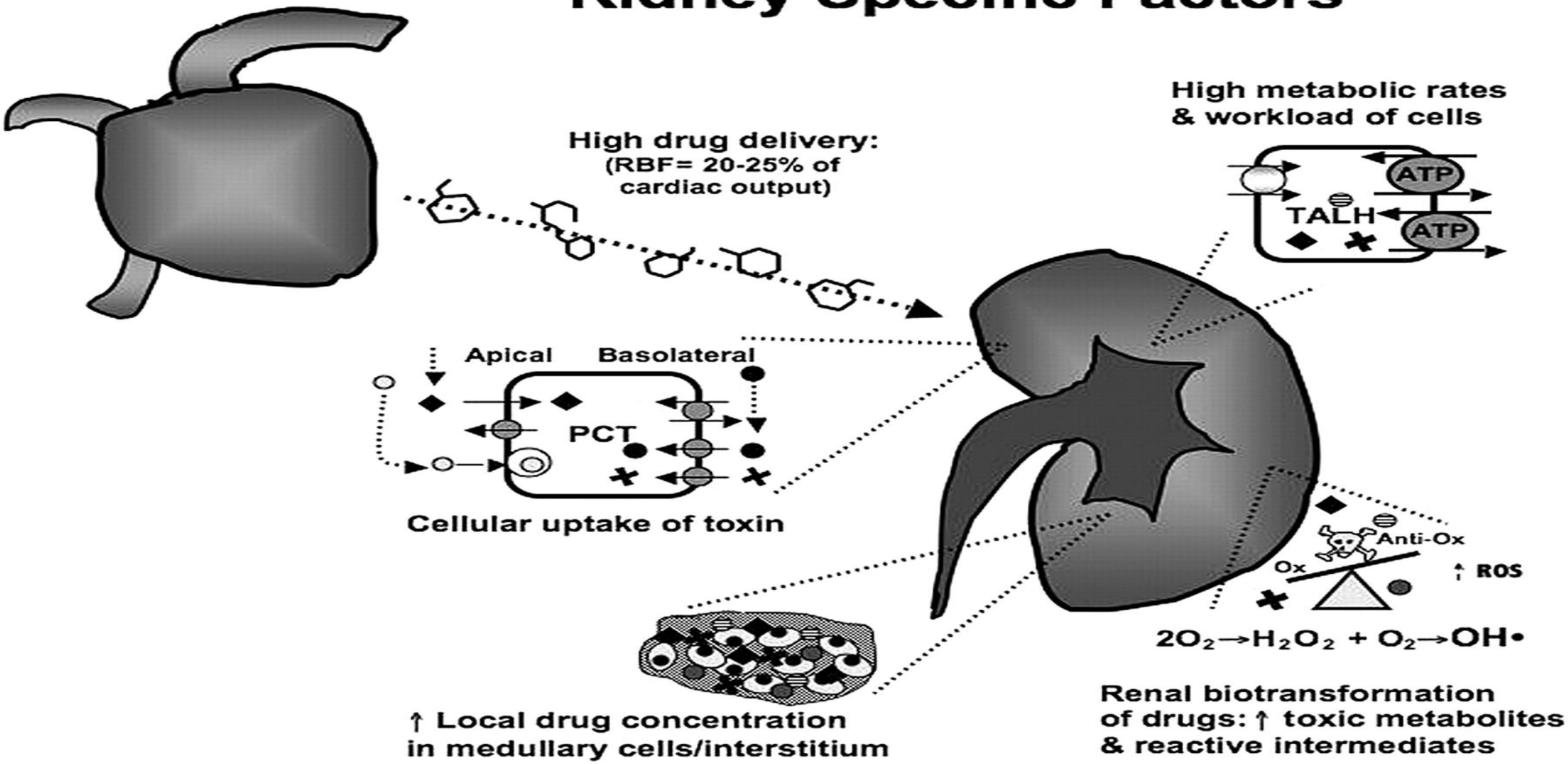
# Kidney Specific Factors




Renal Vulnerability to Drug Toxicity Mark A. Perazella CJASN July 2009, 4 (7)

| Clinical renal syndromes caused by nephrotoxins[a] |
| --- |
| Tubulopathies |
| Renal Tubular Acidosis/Fanconi Syndrome |
| Sodium Wasting |
| Potassium Wasting |
| Nephrogenic Diabetes Insipidus |
| Nephrotic Syndrome/Proteinuria |
| Glomerular Disease |
| Minimal Change Glomerulonephritis |
| Focal Segmental Glomerulosclerosis |
| Membranous Glomerulonephritis |
| Other |
| Thrombotic Microangiopathy |
| HUS/TTP |
| Acute Kidney Injury |
| Hemodynamic Disturbances |
| Parenchymal Kidney Disease |
| Collecting System Disease |
| Chronic Kidney Disease |
| Analgesic Nephropathy |
| Chronic Tubulointerstitial Nephritis |
| Secondary Progression of Toxin-induced Kidney Disease |

# Toxic nephropathy

proxiaml tubule injury

renal medullary injury

intratubular obstraction

distal  tubule dysfunction

oxygen  free radical production

# MECHANISM OF HEAVY METALS TOXICITY

## The kidney is a target organ in heavy metal toxicity because of its ability to reabsorb and concentrate divalent metal

The extent of renal damage depends on the nature, the dose, and the time of exposure.

In general, acute damage differs from chronic damage in its mechanism of toxicity.

Heavy metals in plasma exist in nondiffusible (protein-bound) and diffusible (complexed and ionized) forms. The luminal fluid in the early proximal tubule can contain the bound form and the free form.

The ionized form is toxic and produces direct cellular toxicity; the mechanism consists of membrane rupture and uncoupling of mitochondrial respiration, with the release of numerous death signals such as reactive oxygen species and cytokines

# THERAPEUTIC APPROACH

chelation therapy, decontamination procedures (e.g., charcoal, cathartics,

emesis, gastric lavage), supportive care (e.g., intravenous fluids, cardiac stabilization, mechanicalventilation, exchange transfusion), and extracorporeal therapy.

The choice of treatment depends on clinical parameters such as age; preexisting pathologies of the liver and kidney (affecting endogenous clearance); cardiovascular disease;toxicologic parameters such as total body, liver, and renal clearances; elimination half-life; molecular weight; toxic dose; protein binding;  apparent distribution volume

# LEAD

## Source of Exposure

Lead exists in three different forms: metallic lead, inorganic lead (water-soluble lead salts), and organic lead such as tetramethyl lead, which is more toxic than the inorganic form.

## Acute Exposure

rare and occurs after accidental or intentional ingestion of water-soluble inorganic lead salts or inhalation of tetramethyl lead.

## Chronic Exposure

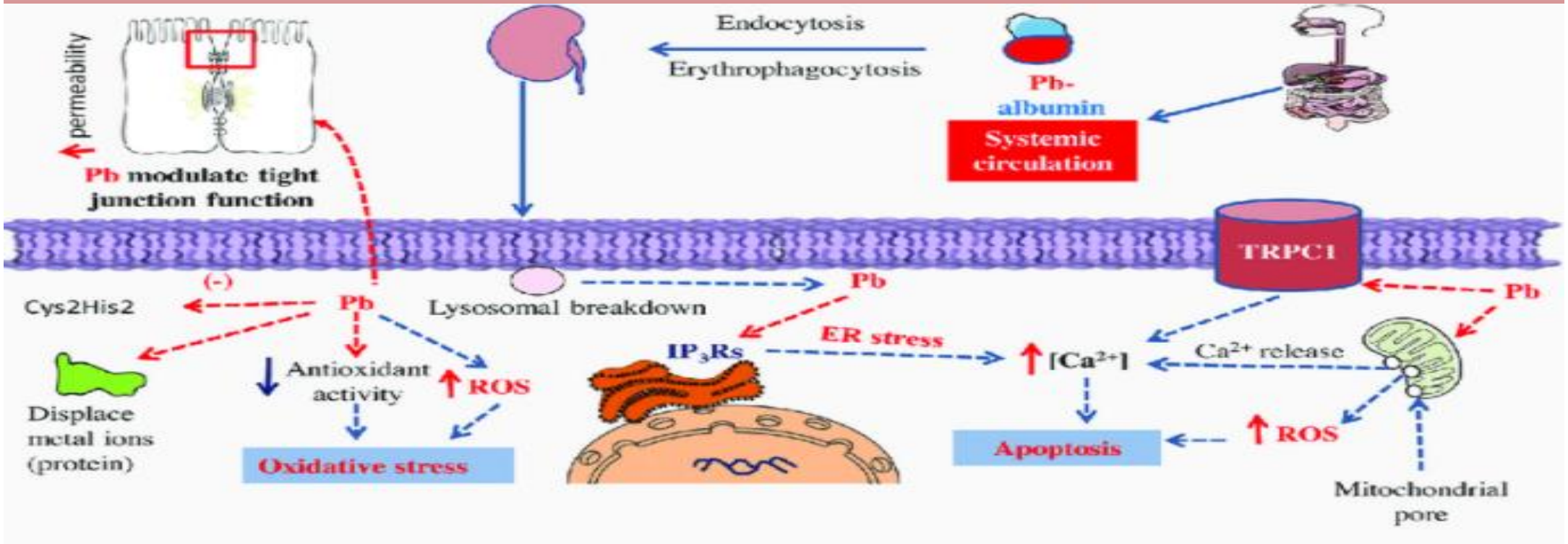
Lead paint, drinking water, lead-glazed ceramics, and herbal remedies from Asia

Workers in certain occupations including manufacture of ammunition, batteries, sheet lead, bronze plumbing, radiation shields

Lead also contaminates emissions from motor cars with antiknock additives (tetramethyl lead)

# Lead Poisoning Symptoms Include:

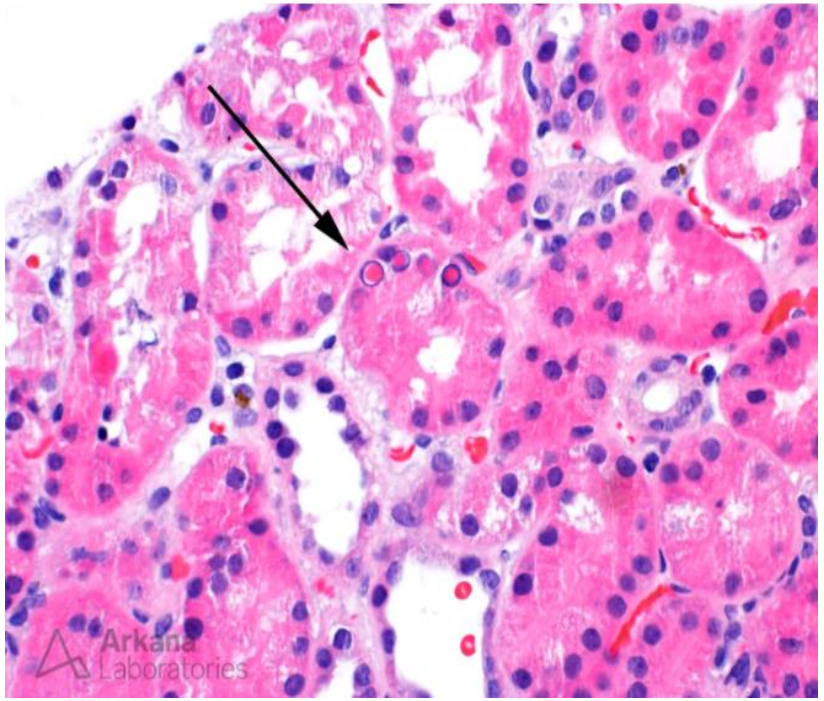
- abdominal pain
- abdominal cramps
- aggressive behavior
- constipation
- sleep problems
- headaches
- Irritability
- loss of developmental skills in children
- loss of appetite
- fatigue
- high blood pressure
- numbness or tingling in the extremities
- memory loss
- anemia
- kidney dysfunction



# Mechanism of Kidney Damage

## Acute Exposure

disrupts the proximal tubular architecture, histological changes such as eosinophilic intranuclear inclusions in tubular cells consisting of lead protein complexes as well as mitochondrial swelling

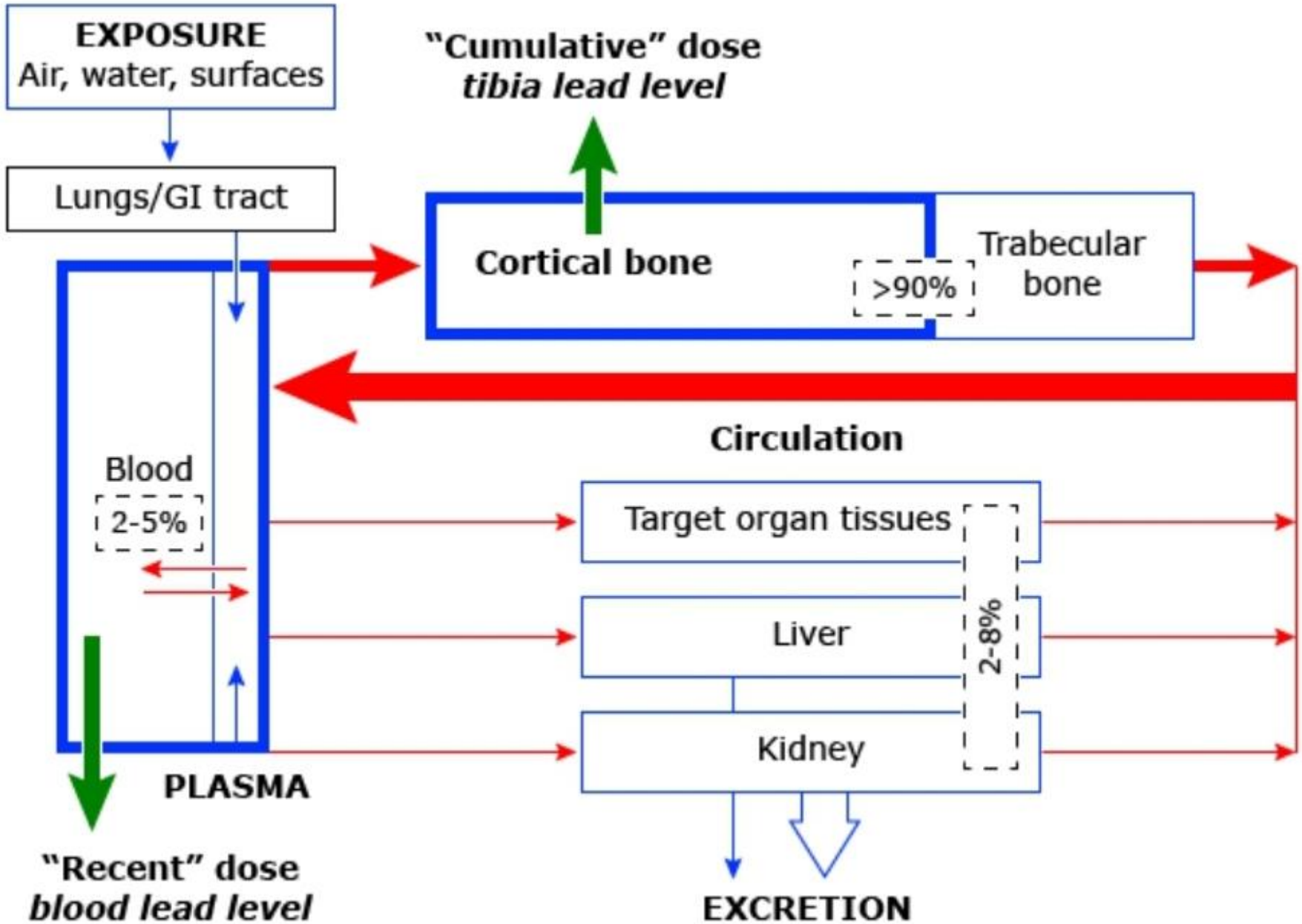



## Chronic Exposure

The damage extends to the proximal tubule and distal tubule with decrease urate secretion, vasoconstriction, glomerulosclerosis , hypertension and interstitial fibrosis.

Several studies have explored the relationship between environmental Pb exposure and nephrolithiasis

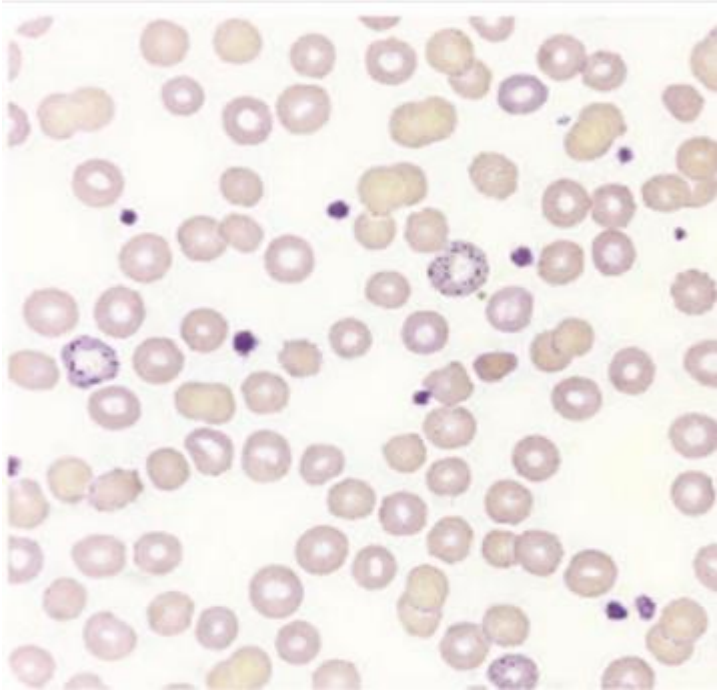
Hara A, Yang WY, Petit T. et al. Incidence of nephrolithiasis in relation to environmental exposure


EXPOSURE
Air, water, surfaces
Lungs/GI tract
"Cumulative" dose
tibia lead level
Cortical bone
>90%
Trabecular bone
Circulation
Blood
2-5%
Target organ tissues
Liver
Kidney
2-8%
PLASMA
"Recent" dose
blood lead level
EXCRETION

# Laboratory Tests

Normochromic or hypochromic anemia with basophilic stippling

elevated reticulocyte count; elevation BUN, creatinine, serum uric acid; with amino acids, glucose, and ALA in the urine (proximal tubule damage)



The lead level in the whole blood is an indicator of recent exposure;

the selected diagnosis to evaluate the lead level is the ethylenediamine tetra-acetic acid (EDTA) lead mobilization test

Portion of lead deposite in bone(half life 10-30 years)

## Treatment of Acute Lead Intoxication

Supportive Measures,Gastric lavage and decontamination with activated charcoal are indicated if lead salts have been ingested.

Fluid-electrolyte balance must be maintained.

## Chelating Agents

In an inorganic lead intoxication, there is an indication to use EDTA, dimercaprol (BAL), dimercaptosuccinic acid (DMSA), and D-penicillamine.

## Extracorporeal Therapies

Extracorporeal detoxification measures are ineffective because 95% of lead is stored in the erythrocytes; however, chelators, which are nephrotoxic, can be removed effectively by hemodialysis.(half life 9 vs 96h)

Peritoneal dialysis, hemoperfusion, CRRTs and therapeutic plasma exchange are generally ineffective

# MERCURY

## Source of Exposure

The general population from dental amalgam and the diet;

amalgam fillings are the most important source of inorganic mercury,  fish important source of the organic one.

Occupational exposure occurs in dentistry, in thermometer factories,in the alloys and chloralkali industries

### Mechanism of Kidney Damage

Mercury accumulates in the kidney and induces epithelial injury and necrosis in the pars recta of the proximal tubule.

After acute exposure to mercury, ATN appears, usually accompanied by oligoanuria

## Clinical and Laboratory Features

### Acute Exposure

Elemental mercury in vapors produces symptoms after a few hours such chills, vomiting, diarrhea, acute dyspnea

with the occasional fatal form of interstitial pneumonitis,and neurologic symptoms with hypotension and profuse salivation.

### Chronic Exposure

Organic mercury gives skin manifestations and neurologic disturbances such as ataxia, paresthesias, and deafness.

different types of kidney damage, such as nephrotic syndrome with membranous nephropathy pattern(secondary with PLA2r- and IgG1+) ,tubular dysfunction with elevated urinary excretion of albumin, transferrin, retinol binding protein, and β-galactosidase.

### Remission with withdramal

Supportive Measures Immediate elimination of the metal by gastrointestinal decontamination and rapid administration of chelators,followed by intensive monitoring of hemodynamics and breathing, is necessary.

## Extracorporeal Therapies

Plasma protein binding of mercury is 95%, the toxin is distributed in a large apparent volume of distribution hemodialysis, peritoneal dialysis, hemoperfusion with charcoal are poorly efficient.

hemodialysis is useful to eliminate chelators that are highly water soluble.

CVVH is more effective in removing the complex mercury-DMPS than is hemodialysis

plasma exchange appears to be the most efficient treatment to remove inorganic mercury and could be useful in association with chelation therapy

# CADMIUM

## Sources of Exposure

eating contaminated food, smoking cigarettes, and working in cadmium-contaminated work places. Major industrial applications are in the production of alloys and batteries.

Urinary level use as biomarker of ongoing and chronic exposure

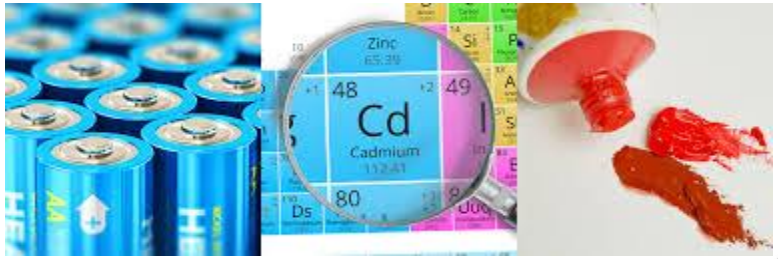
Mechanism of Kidney Damag

Acute Exposure

The ionized free form is primarily responsible for acute intoxication. It induces cellular toxicity by reduction of phosphate and glucose transport and by inhibition of mitochondrial respiration with membrane rupture of the proximal tubular cells

Chronic Exposure

A chronic tubular-interstitial nephropathy is produced by the accumulation of this metal in the S1 segment of the proximal tubule and in the medulla.



# Clinical and Laboratory Features

## Acute Exposure

The toxic symptoms include dyspnea, nausea, vertigo and vomiting, hypotension,shock, and acute renal and liver failure

## Chronic Exposure

Emphysema, cough, chronic kidney damage, and gastrointestinal ulcerations

Renal damage by cadmium may result in tubular proteinuria with renal glycosuria, aminoaciduria, hyperphosphaturia, hypercalciuria, and polyuria with loss of concentration capacity.Anemia , severe bone pain and osteomalasia(itai itai disease)

## Laboratory Tests

measuring 24-hour urinary cadmium excretion; an elevated urinary excretion of β2-microglobulin has proved to be useful in detecting subtler signs of cadmium nephrotoxicity

## Treatment of Acute Cadmium Exposure

Supportive Measures Within 3 hours from the ingestion, it is recommended that gastrointestinal decontamination be performed, with support for cardiac and pulmonary

Forced diuresis is notindicated, because cadmium is highly nephrotoxic

### Chelating Agents

Very soon after absorption, cadmium is stored in the erythrocytes and bound with metallothionein. There are no antidotes for cadmium intoxication. In contrast to the other heavy metals, chelators actually may increase cadmium nephrotoxicity.

### Extracorporeal Therapies

The extracorporeal measures of detoxification are ineffective, because cadmium is fixed to cells; peritoneal dialysis,hemodialysis, and CRRT are used to remove chelators in acute renal failure caused by cadmium

| Metal | Source of exposure | Kidney injury | Mechanisms |
|---|---|---|---|
| Cadmium | Contaminated food (rice); cigarette smoke; industrial waste; occupational exposure (mining, production of batteries, plating of steel and plastic manufacturing) | Proximal tubular dysfunction (glucosuria, aminoaciduria and low-molecular-weight proteinuria)[83,84,131]; reduced GFR | Oxidative stress[85]; impaired DNA repair[86]; reduced antioxidant ability; cellular apoptosis[87] |
| Lead | Contaminated food; petroleum; contaminated air, water and soil polluted with industrial waste; cigarette smoke; occupational exposure (mining, production of batteries, welding and lead soldering) | Proximal tubular dysfunction[110–113]; interstitial fibrosis[132]; tubular atrophy[133]; reduced GFR | Oxidative stress[134]; increased TGFβ expression and lipid oxidation[115,116]; mitochondrial dysfunction[114]; DNA fragmentation[135] |
| Mercury | Contaminated water; fish from polluted waters; fuel combustion; skin-whitening creams; mining | Secondary membranous nephropathy[136]; interstitial nephritis; acute tubular necrosis[137]; reduced GFR | DNA damage[90,91]; mitochondrial dysfunction[138]; reduced enzymatic activity[139] |
| Arsenic | Occupational exposure (mining, wood preservatives, smelting metal ores and pesticides); contaminated seafood and water; specific medication | Tubular interstitial nephritis; acute tubular necrosis[140]; reduced GFR | Oxidative stress; reduced expression of RKIP[141]; DNA methylation and histone acetylation[142]; DNA oxidation; reduced antioxidant defences[143] |

# lithium

1-acute

2-acute-on-chronic

3-chronic when a patient on a stable lithium regimen suffers a reduction in renal

secondary to dehydration, change in renal perfusion (CHF) or a new medication

Medication that cause dehydration and renal impairment :NSAID ,ACE inh,diuretic

Anticipated toxic effects of any lithium exposure dose will depend on renal function, hydration status, and whether the patient takes lithium chronically

# Clinical Features

The patient with acute lithium intoxication has stupor, tremor, confusion, hemodynamic instability, vomiting, diarrhea, hyperreflexia, and acute renal failure, sometimes with polyuria and casts in the sediment.

Chronic lithium ingestion is a common cause of nephrogenic diabetes insipidus, renal tubular acidosis, nephrotic syndrome (minimal change or FSGS), and chronic interstitial nephropathy

Acid base disorders do **not** typically occur as a result of lithium toxicity and if present should raise suspicion for other ingestions, such aspirin or toxic alcohols

# Serum lithium concentration

**When to obtain measurements** — Serum lithium concentrations are one tool in the assessment of the severity of an overdose and help to determine the need for hemodialysis.

A concentration should be obtained in any patient with suspected toxicity.

Early levels  helpful to confirm exposure but may not represent peak serum concentrations in a patient who has ingested sustained release tablets.

repeated every two to four hours initially to determine the adequacy of therapy (IV hydration or hemodialysis) and to confirm a trend of improvement.

# Correlation with clinical toxicity

Serum lithium concentrations often do not correlate with clinical signs of toxicity.

Patients with acute ingestions may be relatively asymptomatic despite serum concentrations above 4 mEq/L (4 mmol/L) due to slow absorption into the CNS.

In addition, reports exist of severe clinical toxicity despite therapeutic lithium concentrations

treatment should be based upon clinical manifestations and not solely upon drug levels.

## Treatment of Acute Lithium Intoxication

-ABC and Supportive Measures

-Gastric lavage and emetics should be carried out within 8 hours after acute overdose

-Patients with normal renal function treated with a rapid infusion of saline to increase the urinary lithium output.

-Oral activated charcoal does **not** prevent the absorption ofcharged particles

-There is no chelating agent specific for acute lithium toxicity

severe intoxication with coma, convulsions, and acute renal failure, the only treatment should be the application of renal replacement therapy.

Cardiac monitoring and mechanical ventilation are recommended during acute intoxication

# Hemodialysis

- Serum lithium concentration is greater than 5 mEq/L (5 mmol/L).

- Serum lithium concentration is greater than 4 mEq/L (4 mmol/L) in patients with renal impairment (creatine >2.0 mg/dL, or 150 mcmol/L)

- In the presence of decreased level of consciousness, seizure, or life-threatening complications

- Serum lithium concentration is greater than 2.5 mEq/L (2.5 mmol/L) and the patient manifests signs of significant lithium toxicity (eg, seizures, depressed mental status), has renal insufficiency or conditions that limit lithium excretion, or suffers from an illness that would be exacerbated by aggressive IV fluid hydration :DHF

## Extracorporeal Therapie

HEMODIALYSIS. a small, non–protein-bound molecule, lithium is removed rapidly by HD

Mixed diffusive-convective therapies such as hemodiafiltration and dialysis with high-flux membranes (e.g., polysulfone, polyamide, polymethylmethacrylate [PMMA]), seem to be even more efficient, and they represent the first-choice therapy for severe acute lithium intoxication.

The efficiency of extracorporeal removal is limited by a high postdialysis rebound of lithium levels resulting from compartmentalization of the molecule

PD. its clearance is much lower than in HD. alternative when hemodialysis is not available.

Hemoperfusion. the adsorption of lithium with activated charcoal or resins is very limited, the technique of hemoperfusion is poorly efficient.

CRRT : removing also intracellular lithium by preventing postdialysis rebound. However, CRRT in cases of acute intoxication does not reduce the lithium levelas rapidly as HD

Best treatment : combination of hemodialysis for rapid removal

followed by continuous hemodiafiltration to prevent postdialysis rebound

# NEPHROTIC SYNDROME

Lithium has infrequently been associated with the nephrotic syndrome. Most cases are due to MCD, but FSGS has also been described due to direct toxicity of podocyte

The mechanism by which lithium leads to glomerular injury is not completely understood

Proteinuria begins within 1.5 to 10 months after the onset of therapy and, in MCD, completely or partially resolves in most patients one to four weeks after lithium is discontinued .

In several patients, reinstitution of lithium led to recurrent nephrosis .

Corticosteroids have occasionally been required to induce remission; it is possible that the minimal change disease in such cases was unrelated to lithium .

# CHRONIC INTERSTITIAL NEPHRITIS AND KIDNEY FUNCTION IMPAIRMENT

Long-term lithium use is associated with CKD that occasionally progresses ESKD .

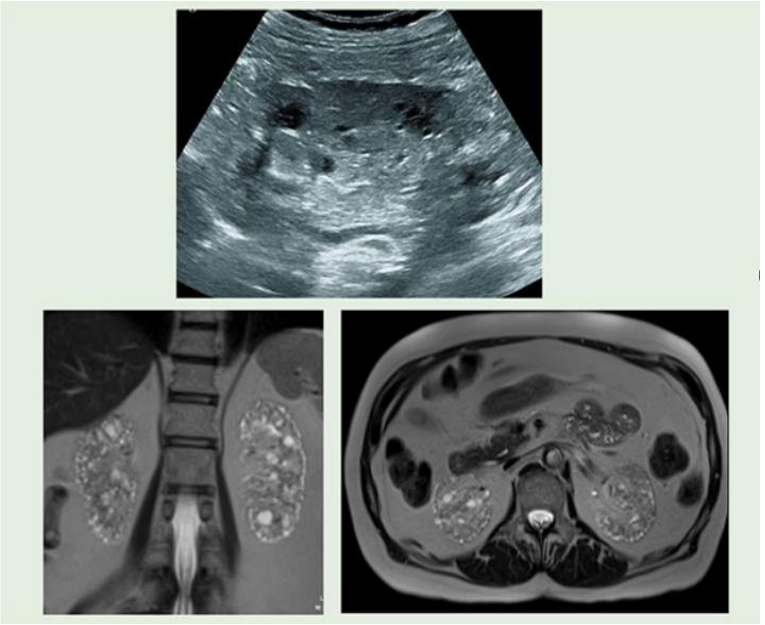
Major risk factors for nephrotoxicity  duration of lithium exposure and the cumulative dose

Other RF include episodes of acute intoxication, increased age , comorbid illnesses (eg, hypertension, diabetes mellitus, hyperparathyroidism, and hyperuricemia), and concomitant use of other antipsychotic medications.

The degree of interstitial fibrosis on kidney biopsy may be directly related to the duration and cumulative dose of lithium .

Additional histologic lesions may be suggestive of chronic interstitial nephritis due to lithium:

In humans, the presence of tubular cysts, which have been demonstrated to be of distal and collecting tubular origin, probably correspond to these tubular lesions .



# HYPERPARATHYROIDISM AND HYPERCALCEMIA

## Hypo and hyperthyroidy

complication of long-term therapy with lithium carbonate is hyperparathyroidism, with associated hypercalcemia and hypocalciuria .

several mechanisms by which lithium may increase serum calcium levels:

- Increasing the threshold for the calcium-sensing mechanism within the parathyroid gland.
- Inducing PTH overproduction via inhibiting the action of glycogen synthase kinase 3b (GSK-3b).
- Inhibiting calcium transport (influx) across cell membranes.

# The question of lithium's propensity to cause ESKD is also difficult to answer

The different results over time might indicate that the modern guidelines for lithium treatment minimize the risk of lithium induced ESRD,

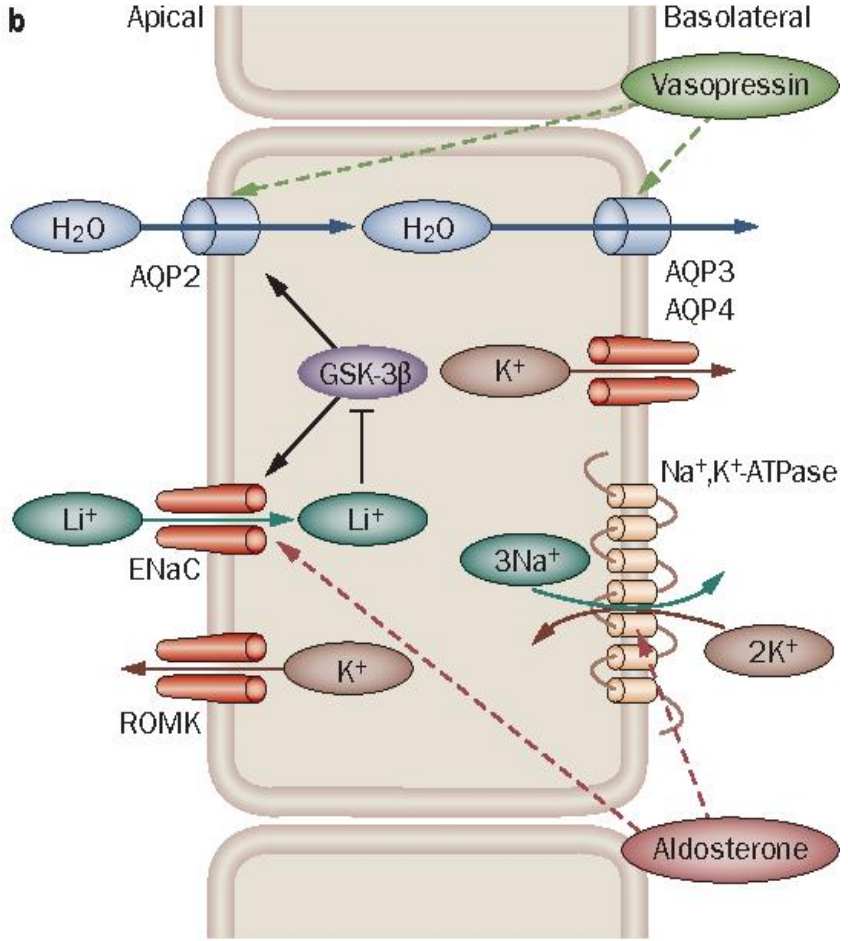
patients exposed to serum lithium levels above 0.8 mmol/L had an increased risk of decreasing estimated glomerular filtration rate as compared to those exposed to lower levels.

Lithium and renal impairment: a review on a still hot topic '2018

# LITHIUM INDUCED NEPHROPATHY/NEPHROGENIC DIABETUS INSIPIDUS: PATHOPHYSIOLOGY

than 80% is then reabsorbed within the proximal tubules by the NHE3.

Within the collecting ducts, lithium is taken up by principal cells through the ENaC which have a much greater affinity for lithium when compared to that of sodium. Lithium then accumulates within principal cells due to the much lower affinity for the basolateral sodium efflux pump (the Na/K ATPase for lithium when compared to sodium.




Asian pacific society if nephrology 2018

# NDI MECHANISM

Lithium may increase expression of cox-2 and therefore increase urinary PG E2 excretion by medullary interstitial cells .

These prostaglandins then act on principal cells to induce lysosomal degradation of AQP2 water channels and a decline in urine concentrating ability

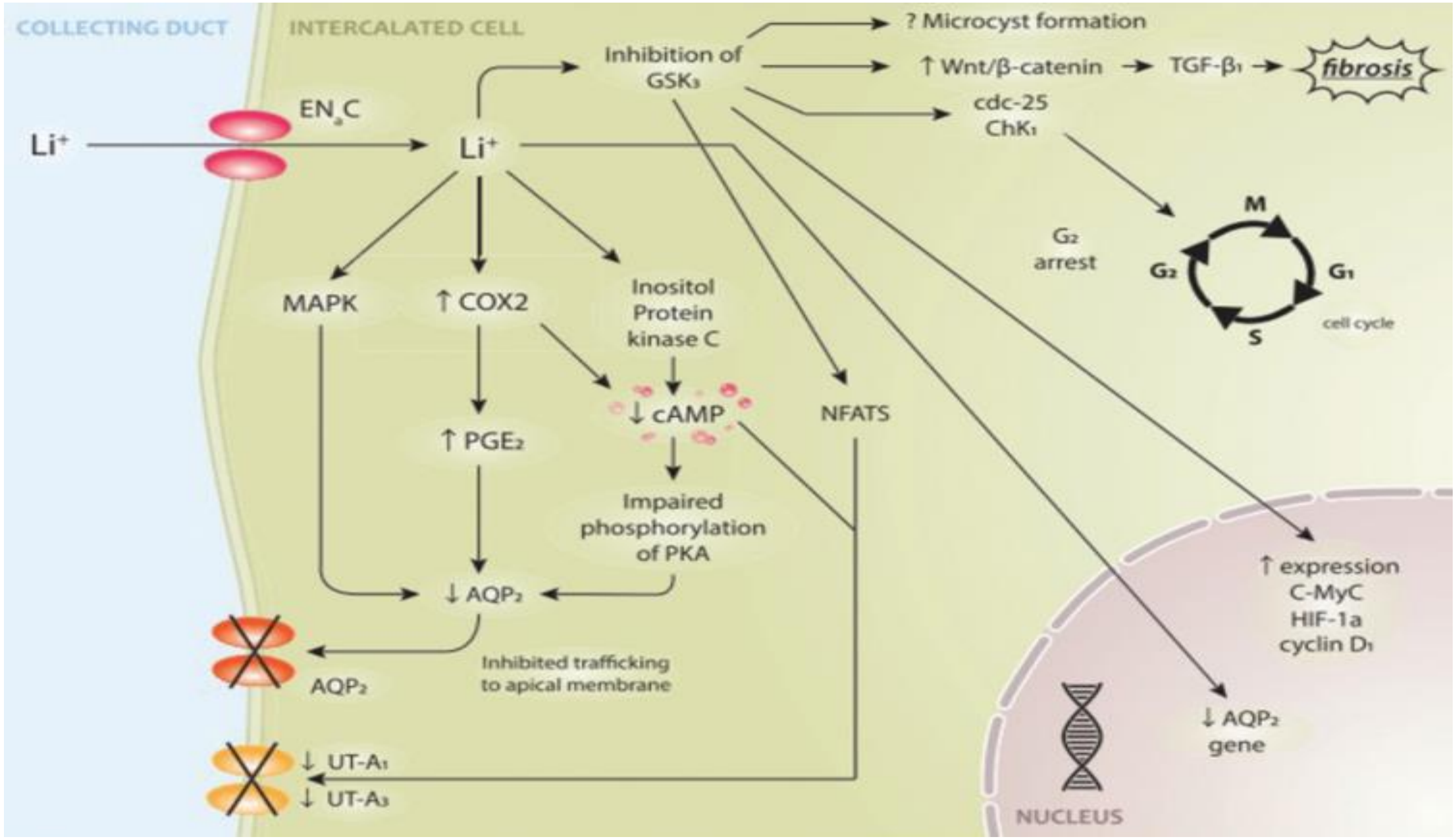
Acute onset nocturia is an important clue to the presense of NDI

Polyuria due to impaired urinary concentrating ability occurs in up to 20 percent of patients treated with chronic lithium therapy; an additional 30 percent have a subclinical impairment in concentrating ability

- Lithium may reduce *AQP2* gene transcription, an effect that is prostaglandin independent, leading to a further decrease in concentrating ability
- Lithium induces collecting duct remodeling characterized by a decreased population of principal cells relative to the number of intercalated cells, a phenomenon that was previously presumed to be due to apoptosis .However, lithium may actually lead to proliferation of principal cells, which then undergo cell cycle arrest .

This may also be responsible for the development of interstitial nephritis and renal fibrosis.

Lithium also appears to reduce levels of medullary organic osmolytes including inositol , taurine, betaine and sorbitol, which may reduce the medullary osmotic gradient


COLLECTING DUCT
INTERCALATED CELL
? Microcyst formation
Inhibition of GSK3
↑ Wnt/β-catenin
TGF-β1
fibrosis
ENaC
Li+
Li+
cdc-25
ChK1
M
G2
arrest
G2
G1
S
cell cycle
MAPK
↑ COX2
Inositol Protein kinase C
↓ cAMP
NFATS
↑ PGE2
Impaired phosphorylation of PKA
↓ AQP2
↑ expression C-MyC HIF-1a cyclin D1
AQP2
Inhibited trafficking to apical membrane
↓ AQP2 gene
↓ UT-A1
↓ UT-A3
NUCLEUS