Mercury, Cadmium, Arsenic , Uranium, Platinum, and Gold and kidney

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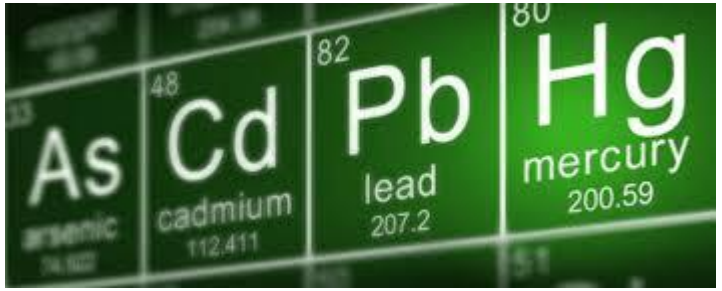


Kidney and heavy metals - The role of environmental exposure

- ✓Heavy metals are extensively used in agriculture and industrial applications such as production of pesticides, batteries, alloys, and textile dyes.
- ✓Kidney is a target organ in heavy metal toxicity for its capacity to filter, reabsorb and concentrate divalent ions.
- ✓The extent and the expression of renal damage depends on the species of metals, the dose, and the time of exposure.

Kidney and heavy metals…

- ✓Heavy metals in plasma exist in an ionized form, that is toxic and leads to acute toxicity and a bound, inert form when metal is conjugated with metallothionein and are then delivered to the liver and possible causing the kidney chronic damage.

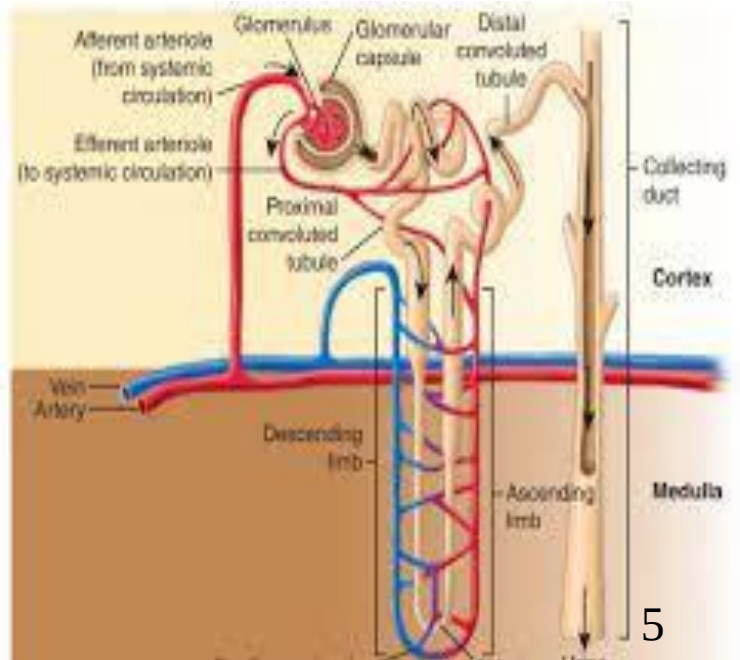
Introduction

- ✓The most common metals implicated in kidney toxicity are arsenic, barium, cadmium, cobalt, copper, lead, lithium, mercury and platinum.

- ✓Small amounts of these trace elements are necessary for good health because they are important factors and cofactors in many biochemical cellular pathways, including nucleic acids and proteins synthesis, and enzymatic reactions.

Mechanism of heavy metals toxicity

- ✓The luminal fluid in the early proximal tubule can contain both the bound form and the free form.
- ✓These compounds are subsequently reabsorbed through an endocytotic process in segment S1 of the proximal tubule and can lead to chronic inflammation, fibrosis and renal failure.



Symptoms of exposure and toxicity

- ✓Exposure to toxic heavy metals is generally classified as acute (1-14 days), intermediate (15-354 days) and chronic (≥365 days).

- ✓Symptoms of acute toxicity are severe, rapid in onset and associated with exposure or ingestion, headache, vomiting, dyspnoea , abdominal pain and sweating, whereas chronic intoxication is usually uneventful.

Mercury

Mercury

- ✓Mercury (Hg) is a silvery white liquid that is volatile at room temperature because of its high vapour pressure. Mercury exists in three forms: elemental, inorganic and organic.
- ✓***Source of exposure***. The general population is primarily exposed to the organic forms by fish (tuna, swordfish) and inorganic form by amalgam fillings. Occupational exposure occurs in alloys and thermometer factories, chloralkali industries and in dentistry

Clinical and laboratory features OF INTOXICATION WITH Mercury

✓

Acute exposure. acute dyspnoea, abdominal pain, altered mental status,, vomiting, tremors and hypotension , acute tubular necrosis appears, usually accompanied by oligo-anuria.

Clinical and laboratory features OF INTOXICATION WITH Mercury

- ✓ ***Chronic exposure***. Organic mercury gives skin manifestations and neurological disturbances such as hearing loss, paraesthesia and ataxia.

- Mercury-related kidney damage can due to tubular dysfunction with elevated urinary excretion of albumin, transferrin, retinol binding protein, and β-galactosidase and a nephrotic syndrome with membranous nephropathy pattern.

- ✓ ***Laboratory tests***. A mercury concentration >45 mg/dl in blood indicate acute poisoning.

Treatment of acute mercury exposure

- ✓ ***Chelating agents***. The antidotes currently available are BAL, DMPS, and dimercaptosuccinic acid (DMSA). Treatment with chelators should be established especially in patients with acute symptoms arising from the central nervous system.
- ✓

- ✓ ***Supportive measures***. A quick elimination of mercury is necessary and can be obtained by gastrointestinal decontamination and rapid administration of chelators, followed by intensive monitoring of hemodynamics and breathing.

- ✓ ***Extracorporeal therapies***. Plasma protein binding of mercury is 95%, and the toxin is distributed in a large apparent volume of distribution; for these reasons, HD, PD and HMP with charcoal are poorly efficient.

-TPE is the most efficient treatment to remove inorganic mercury and could be useful in association with chelation therapy

Cadmium

Cadmium

- ✓Cadmium (Cd) can induce critical toxicity in humans.
- ✓***Sources of exposure***.
- ✓Cadmium is present in major industrial and chemical applications, such as in the production of alloys and batteries.
- ✓Operation involving removal of cadmium paints by scraping or blasting may pose a significant hazard in ship yard employment, construction industry, and the agricultural industry.

Mechanism of kidney damage With cadmium intoxication

- ✓ ***Acute exposure***. The ionized free form induces cellular toxicity reducing phosphate and glucose transport and inhibiting mitochondrial respiration, with membrane rupture of the proximal tubular cells of the nephron.
- ✓ ***Chronic exposure***. After ingestion or inhalation, cadmium is transported to the liver and to the kidney by metallothionein, which binds cadmium.
- ✓ A typical, chronic tubular-interstitial nephropathy is produced by the accumulation of this metal in the medulla and S1 segment of the proximal tubule.

Cadmimum

- ✓ ***Clinical and laboratory features***

  Acute exposure. The toxic symptoms include mental status alteration, vomiting, nausea and dyspnoea, with hypotension, shock, and acute renal and liver failure.

- ✓ ***Chronic exposure.*** CKD, emphysema, cough and gastrointestinal bleeding results during chronic exposure.

-Cadmium-related renal impairment occurs with polyuria, loss of concentration capacity, tubular proteinuria, renal glycosuria, aminoaciduria, hyperphosphaturia and hypercalciuria

- ✓ ***Laboratory tests***. Exposure to cadmium is commonly determined by measuring the 24-h urinary cadmium excretion;

-an elevated urinary excretion of β2-microglobulin has proved to be useful in detecting the more subtle signs of cadmium nephrotoxicity

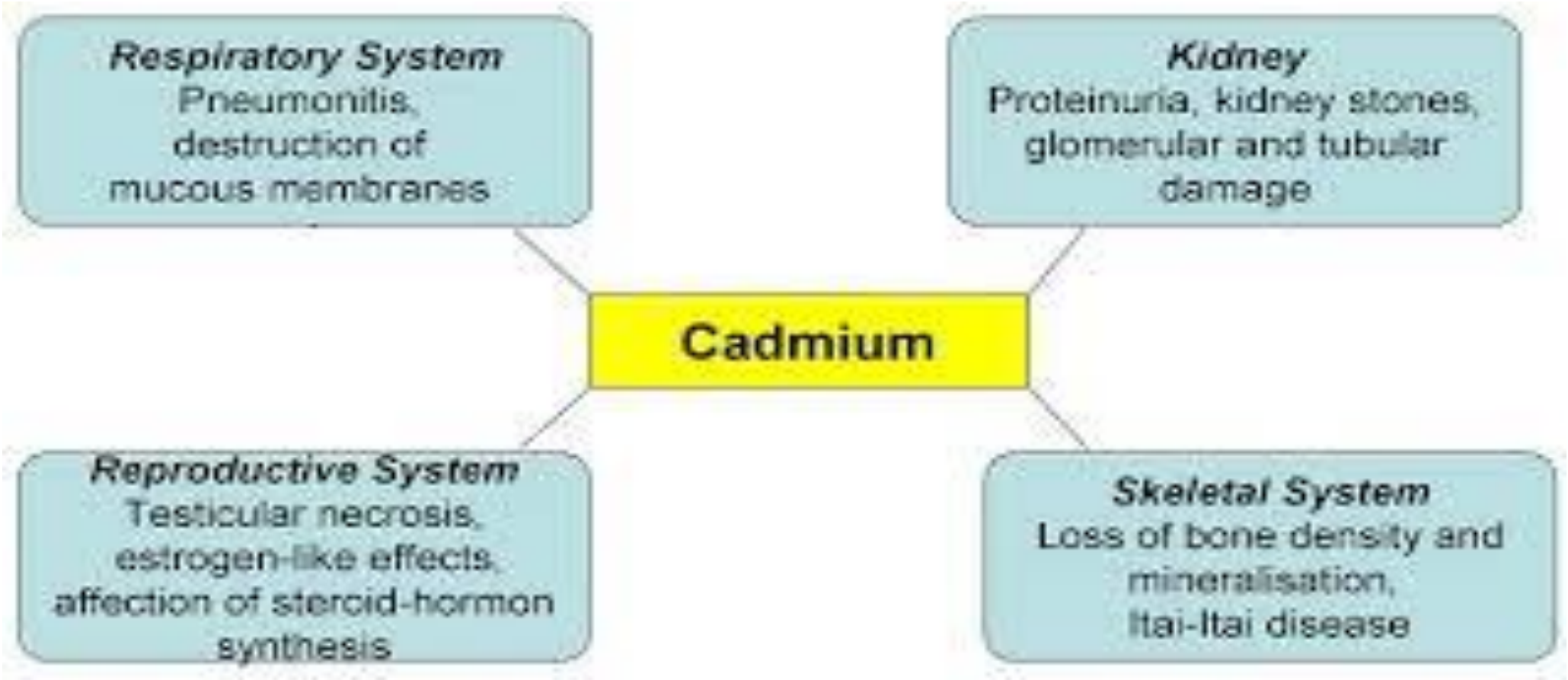
Treatment of acute cadmium exposure

- ✓ ***Chelating agents***. There are no antidotes for cadmium intoxication: almost immediately after absorption, cadmium is bound with metallothionein and stored in the erythrocytes.

In contrast to the other heavy metals, chelators seem to increase cadmium nephrotoxicity

- ✓ ***Supportive measures***. Gastrointestinal decontamination must be performed within few hours from ingestion with support for cardiac and pulmonary function; **forced diuresis is not indicated**.
- ✓ ***Extracorporeal therapies***. The extracorporeal measures of detoxification are ineffective, because cadmium is fixed to cells

✓


Respiratory System
Pneumonitis, destruction of mucous membranes
Kidney
Proteinuria, kidney stones, glomerular and tubular damage
Cadmium
Reproductive System
Testicular necrosis, estrogen-like effects, affection of stercid-hormon synthesis
Skeletal System
Loss of bone density and mineralisation, Itai-Itai disease

Arsenic

Arsenic

- ✓Acute high-dose intoxication may cause death and severe systemic toxicity.

- ✓***Source of exposure***. Common sources of exposure are herbicides, pesticides, contaminated water, food supplies and homeopathic remedies.
- ✓
- ✓***Mechanism of kidney damage***. Arsenic compounds are fully absorbed after ingestion or inhalation.
- ✓On entering the circulation, arsenic strictly binds haemoglobin.
- ✓ After 24 h, it is accumulated in soft tissue; after 2 weeks, arsenic is incorporated in hair and nails.

Clinical features of Arsenic intoxication

✓**Acute exposure**.

Acute toxicity symptoms include headache, vomiting, nausea, abdominal pain and diarrhoea, frequently followed by macula rash, diffuse itch, dehydration, respiratory failure and acute respiratory distress syndrome, hypotension and hemodynamic instability.

✓ AKI may result in acute tubular necrosis, haemoglobinuria due to haemolysis, haematuria, oliguria and proteinuria

✓**Chronic exposure**. In chronic poisoning, peripheral neuropathy and encephalopathy with cognitive impairment are the predominant manifestations.

Laboratory tests of arsenic intoxication

- ✓In acute exposure, urine arsenic levels are more relevant than hematic measurements because arsenic is rapidly cleared from the blood.
- ✓Excretion of more than 200 μg in a 24 h urine collection is suggestive of arsenic overload.
- ✓Chronic arsenic exposure can be confirmed by a 24 h urine collection and arsenic concentration determination.
- ✓***Hair and nails can confirm the diagnosis***


Whitish lines (mees lines)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Treatment of acute arsenic intoxication

- ✓ ***Chelating agents***. Chelating agents represent a **key treatment** in a severely ill patients with acute arsenic poisoning, BAL and dimercapo-1-propane sulfonate are the most frequently used agents.
- ✓ ***Supportive measures***. The first step is the elimination of further exposure. Gastrointestinal decontamination with charcoal and forced emesis is recommended. Furthermore, because arsenic is well eliminated by urine, it is useful to **force diuresis**.
- ✓ **Extracorporeal therapies**. HD can be used to remove chelators that are nephrotoxic but it has very limited efficiency in arsenic removal;
- ✓ CVVH-CVVHDF are preferred to carry on hemodynamic stability
- ✓ PD is inefficient and are not indicated.

Uranium

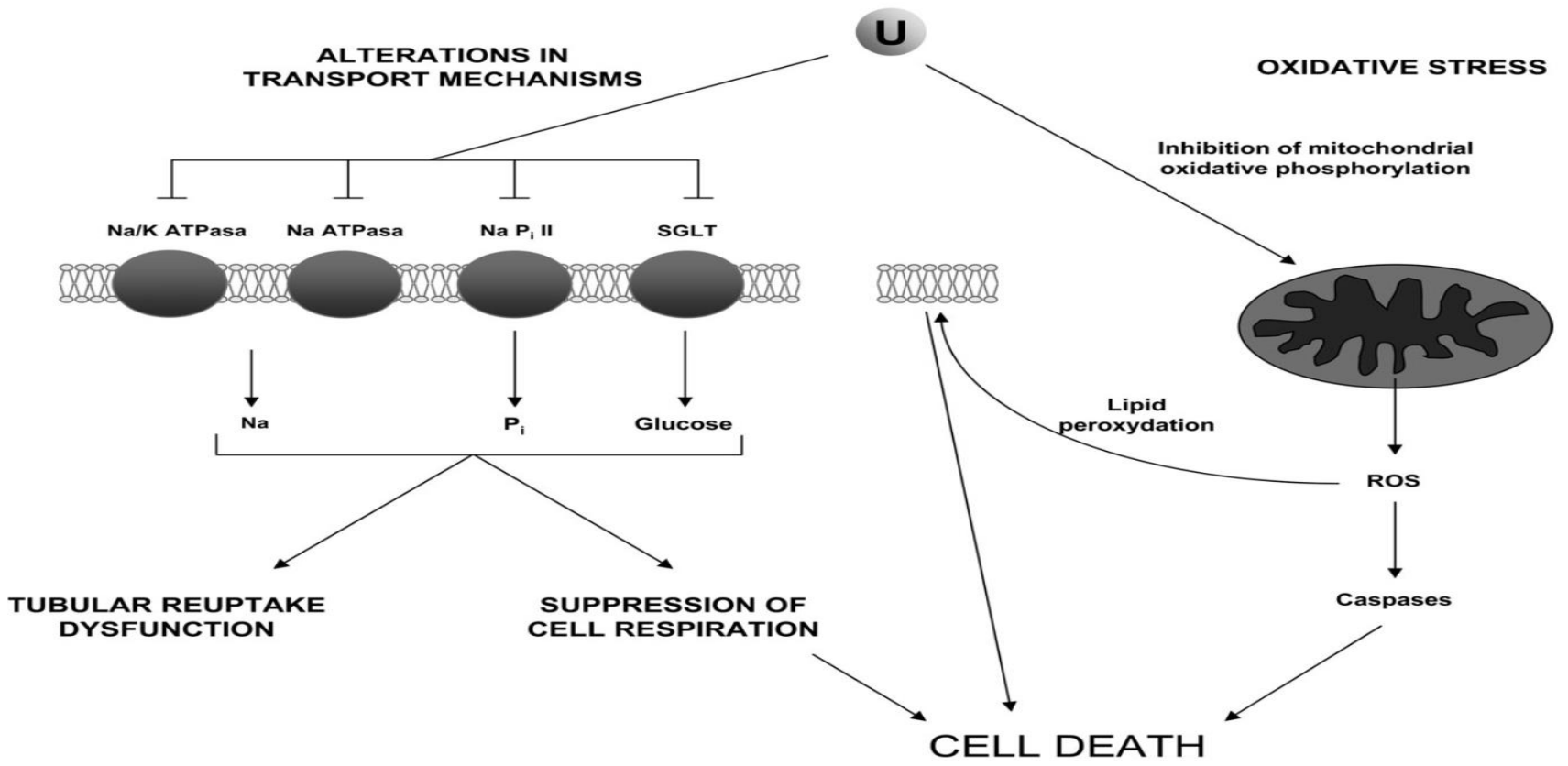


FIG. 1. Possible mechanisms involved in uranium nephrotoxicity. U, Uranium; Na/K ATPase, sodium-potassium pump; Na ATPase, sodium pump; Na, sodium; Pi, inorganic phosphate.

TABLE 2
Documented Cases of Acute Intoxication with Uranium in Humans

Study	Participants number	Exposure source	Uranium amount and type	Study moment	Observations
Bassett *et al.* (1948)	6 volunteers	iv	6.3–70.9 µg/kg UN (0.44–4.96 mg/kg)[a]	During exposure	> Urinary catalase > Prot. (for the highest dose used)
Butterworth (1955)	1 volunteers	Oral	1 g UN (14.3 mg/kg)[a]	During exposure	Vomiting, diarrhea > microalbuminury
Hursh and Spoor (1973)	4 patients	Oral	10.9 mg UN (0.16 mg/kg)[a]	During exposure	Without kidney damage
Pavlakis *et al.* (1996)	1 attempted suicide	Oral	15 g UN (214.3 mg/kg)[a]	After cessation	All renal parameters altered
Kathren and Moore (1986)	3 men	Inhalation	UF_6	Sortly after the accident	< Clcr
Fisher *et al.* (1990)	31 enrichment plant workers	Inhalation	0.47–24 mg/m^3 UF_6	After cessation	> U in urine
Lu and Zhao (1990)	1	Inhalation	NU	1 week after cessation	> Prot., NNP, aminoacidury > U in urine
Bijlsma *et al.* (2008)	2499 firefighters, police and airport workers	Inhalation	NU and DU	8.5 years after cessation	No > U in urine; No differences in the other renal parameters

Note. UN, uranyl nitrate; UF6, uranium hexafluoride; NU, natural uranium; DU, depleted uranium; Prot., proteinuria; Clcr, creatinine clearance; NNP, nonprotein nitrogen; U, uranium.

[a]Values between brackets represent the estimated dose (milligram per kilogram) for a 70-kg individual.

TABLE 4
Documented Cases of Chronic Intoxication with Uranium in Humans

Study	Participants number	Male	Female	Ages	Exposure source	Exposure time	Uranium amount and type	Study moment	Observations
Shiraishi *et al.* (1992)	—; general population	—	—	—	Oral (water)	10 years approximately	1.07–42.6 ng/dm^3 NU	During exposure	No clinical effects
Zamora *et al.* (1998)	30; 20	10; 7	20; 13	13–87; 16–68	Oral (water); oral (water)	3 years approximately	High dose (2–780 μg/l); Low dose (< 1 μg/l) NU	During exposure	> U in urine (exposed); > LDH, ALP and GGT (slightly); > Glc.; No changes in Prot. and NAG
Kurttio *et al.* (2002)	325; general population	—	—	15–82	Oral (water)	1–34 years	High dose (> 100 μg/l); low dose (10–100 μg/l)	During exposure	> U in urine; > Ca, Phosphate and glc in urine; No changes in Clcr. Albumin, BMG, Crs.
Pinney *et al.* (2003)	—; residents near uranium plant	—	—	—	Oral (water)	Years	—; NU	During exposure	> U in urine; > microalbuminury; > red cells and hematocit in blood
Orloff *et al.* (2004)	105; general population	50	55	15–79	Oral (water)	Months	High dose (620 μg/l) NU	6–10 months after cessation	> U in urine
Karpas *et al.* (2005)	205; general population	102	103	18–81	Oral (water)	Years	0.03–2.775 μg/day NU	During exposure	> U in urine
Wyatt *et al.* (2008)	156; general population	—	—	—	Oral (water)	Years	> 30 μg/l NU	1 year after cessation	> Crs and BUN; > U in urine
Kurttio *et al.* (2006)	193; general population	95	98	18–81	Oral (water)	16 years approximately	25 μg/l NU	During exposure	> Glc and ALP in urine; > U in urine; No changes in NAG, LDH, GGT, Ca, Prot, phosphates, Glc, Crs
Magdo *et al.* (2007)	2 adults + 5 children; general population	5	2	3–37	Oral (water)	5 years approximately	866 and 1.160 μg/l NU	3 months after cessation	> BMG; > U in urine
Oeh *et al.* (2007)	—; workers during Balcans War	—	—	—	Oral	Years	17.7 μg/l NU	2–6 years after cessation	No differences in uranium excretion
Selden *et al.* (2009)	453; general population	227	226	18–74	Oral (water)	Years	6.7–25.2 μg/l NU	During exposure	> U in urine; < NAG (exposed); > (tendency) BMG, kappa chains, HC protein; No changes in urinary Glc, phosphates, calcium, Prot., Cr.
Zamora *et al.* (2009)	54	39	15	12–73	Oral (water)	Years	0,4–845 μg/l NU	During exposure	> GGT, ALP, LDH, NAG and BMG in urine; No changes in Prot., and glc.
Anderson *et al.* (2007)	581; gas plant workers	—	—		Inhalation	Years	73 μg/m^3 NU and EU	During exposure	> U in urine
Boice *et al.* (2007)	2161; workers and residents near uranium factory	1368	796	> 18	Inhalation	> 1 year	—; NU	During exposure	> U in urine
Parrish *et al.*	—; residents near	—	—	—	Inhalation	Years	300 μg/ g U, DU	20 years after	> U in urine

Detection of Nephrotoxicity of uranium

- ✓A slight proteinuria and amino aciduria or decrease of GFR are indicative of this damage (Saccomanno et al., 1982; Thun et al., 2017), together with other markers of tubular damage, such as urinary glucose, ALP, and b-2-microglobulin (Zamora et al., 2012).

Detection of Nephrotoxicity of uraniu

- ✓In the case of acute renal impairment, some urinary markers that appear in the urine a few hours after the start of the damage have been identified.
- ✓Among them is neutrophil gelatinase–associated lipocalin (lipocalin 2), Kidney Injury Molecule 1 (KIM-1), interleukin 18, and cystatin C, to mention but a few, that are in an advanced stage of validation (reviewed in Vaidya et al., 2018).

Prevention of Action of uranium

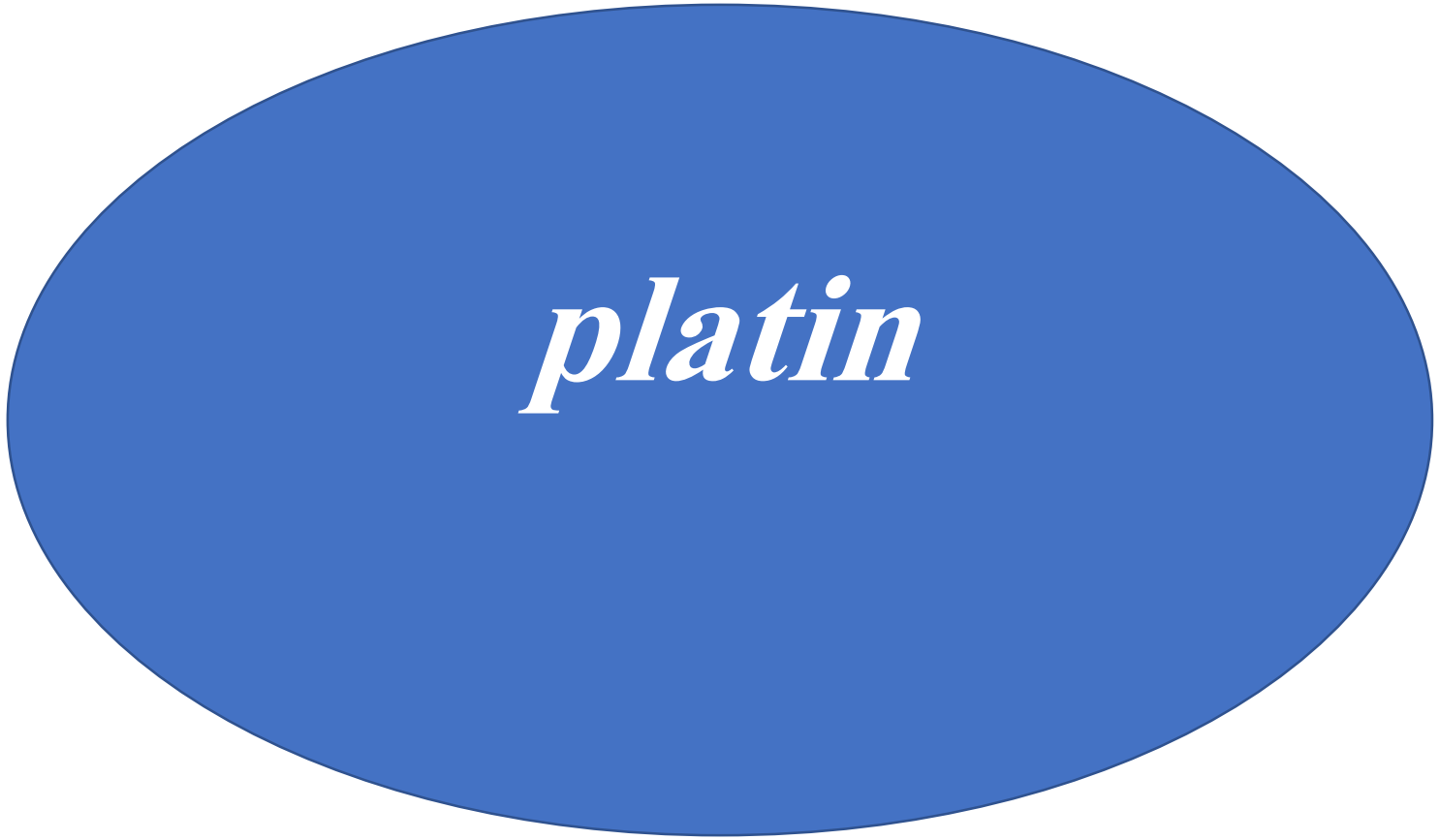
- ✓EDTA has been used both in human medicine and in experimentation with animals for the treatment of intoxications by inorganic substances.

- ✓DTPA is a chelating agent belonging to the polyaminocarboxylate series that forms highly stable water-soluble complexes that are excreted by the kidney.

Repair of Renal Damage of uranium

- ✓As mentioned above, another important therapeutic aspect is the repair of the damage produced, involving the regeneration of kidney tissues.

- ✓Investigators are developing treatment with growth factors that regulate the viability, proliferation, and migration of cells, among which hepatic growth factor (reviewed in Matsumoto et al., 2010, and Nigam and Lieberthal, 2017), but also insulin-like growth factor and epidermal growth factor (reviewed in Nigam and Lieberthal, 2015), are of interest.


platin

platin

✓Cisplatin is a common chemotherapic agent used against various types of solid and haematological malignancies; common side effects of cisplatin include myelotoxicity, neuro- toxicity, ototoxicity and nephrotoxicity.

✓***Mechanism of kidney damage***. Cisplatin toxicity is **dose-related.**

-It is a strong renal tubular toxin that can injure the **S3 segment cells** of the proximal tubule with a variable involvement of the distal nephron.

-The earliest change in proximal tubule function is the rapid production, via cytochrome P450 enzymes, of highly reactive hydroxyl radicals that produce injury by DNA binding that lead to decreased protein synthesis .

platin

- ✓ ***Clinical and laboratory features***. Accidental or suicidal attempt overdose of cisplatin may result in nausea, constipation, hearing loss, vomiting or gross haematuria, and reduce urine output.
- ✓ ***Laboratory tests***. Liver failure, expressed by elevated bilirubin values, alanine transferase (ALT) aspartate transferase (AST), γ-glutamyl transferase (GGT), and elevated markers of renal dysfunction are common findings during acute cisplatin intoxication.
- ✓ Cisplatin is commonly associated with anaemia for the erythropoietin deficiency induced by kidney injury.
- ✓ Macroscopic or microscopic haematuria with urine casts are common.
- ✓ Concentrating defect reflects platinum-induced damage of the loop of Henle.

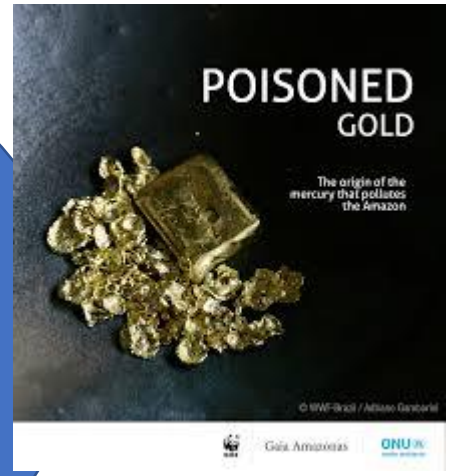
Treatment of acute cisplatin intoxication

- ✓ ***Chelating agents***. There is no specific chelation therapy for cisplatin intoxication. An organic thiophosphate, i.e., **amifostine**, may attenuate cisplatin-induced toxicity by donating a protective thiol group and reducing oxidative stress.

- ✓ ***Supportive measures***. Hydration with electrolyte solutions,
- ✓ myelosuppression frequently requires the administration of granulocyte colony-stimulating factors

- ✓ ***Extracorporeal therapies***. HD is able to reduce free cisplatin in plasma.
- ✓ However, after administration, the metal binds to plasma proteins very quickly and cannot be further eliminated by this procedure.
- ✓ **Therapeutic plasma exchange (TPE) appears able to remove both the protein-bound fraction and the cisplatin free form.**

Gold


POISONED
GOLD
The origin of the mercury that pollutes the Amazon

Gold nephropathyPMID: 7036839

- ✓The early use of gold in medicine and dentistry dates back to the ancient Chinese and Egyptians.
- ✓The discovery in 1890 that gold salts were toxic in vitro to tubercle bacilli led to the extensive treatment of tuberculosis with gold salts in the first three decades of this century.
- ✓ Eventually, gold therapy was extended to arthritis and lupus erythematosus, because of the belief that these diseases were forms of tuberculosis.
- ✓Toxicity of gold salts includes hypersensitivity reaction of skin and mucous membranes, bone marrow depression, and nephrotoxicity

Gold nephropathy

- ✓The nephrotoxic clinical manifestations are renal insufficiency, proteinuria and hematuria, and the nephrotic syndrome.
- ✓The pathologic changes are tubular degeneration, acute tubular necrosis or immune complex glomerulonephritis.
- ✓Aurosomes (gold inclusions in proximal tubular epithelial cells.)

can at times be visualized by light microscopy, are usually seen by electron microscopy.

Renal tubular dysfunction as a complication of gold therapy in patients with rheumatoid arthritis

- ✓Forty-five patients with uncomplicated rheumatoid arthritis and 45 control individuals were subjected to immunochemical investigation of the urinary excretion of renal tubular basement membrane antigen (TBM), renal tubular epithelial antigen (RTE), and beta-2-microglobulin.
- ✓ Tubular proteinuria occurred significantly more frequently in patients treated with gold salts than in those not treated (P less than 0.05).
- ✓Large amounts of RTE and TBM were detected only in the urine of patients who received gold salt therapy.
- ✓However, the amounts of these proteins in urine did no correlate with the total dose of gold.
- ✓These results indicate that renal tubular damage frequently occurs in patients with rheumatoid arthritis who are treated with gold salts

Chronic interstitial nephritis associated with gold therapy

- ✓Probable mechanisms of injury to renal tubular epithelial cells include uptake of gold by tubular epithelial cells and incorporation of gold into mitochondria, with subsequent cellular injury; interstitial deposits probably occur after necrosis of tubular epithelial cells, with release of gold into the interstitium and resultant inflammation.

- ✓Thus, chronic interstitial nephritis can be added to the patterns of renal injury seen after gold therapy for rheumatoid arthritis.

SUMMARY

- ✓The kidney is a target organ in heavy metal toxicity for its capability to reabsorb and concentrate divalent ions and metals.
- ✓The magnitude of kidney impairment depends on the nature, the dose, and the time of exposure.
- ✓Heavy metals in plasma exist in two different patterns: protein bound (non-diffusible) and complex/ionized (diffusible) forms.
- ✓ Metals are quickly cleared from the blood and are sequestered in many tissues.

SUMMARY

Laboratory testing

- ✓ The diagnosis of heavy metal toxicity requires observation of presenting symptoms, the history of potential exposure and the result of laboratory tests.
- ✓ Specific tests include blood count, liver and renal function, urinalysis, faecal tests, X-rays and fingernail analysis.
- ✓ Given the limitations of serum creatinine as a marker of renal function, different urinary and serum molecules have been investigated as possible markers of acute or chronic kidney diseases.
- ✓ One of the most promising novel biomarkers is neutrophil gelatinase-associated lipocalin (NGAL) .
- ✓ Urinary NGAL has also been shown to predict kidney injury and dialysis requirement in welding workers .
- ✓ Pennemans *et al* showed that urinary kidney injury molecule-1 levels are positively correlated with urinary cadmium concentration.
- ✓ Biomarkers and nephrotoxicity (e.g., renal tubular injury) will be an emerging concern in occupational health.

Table I. Therapeutic approaches in acute heavy metal toxicity [adapted from Lentini *et al* (11)].

Metal	HD	PD	CVVH	CVVHDF	TPE	HMP	Chelators
Arsenic	HD+DMSA or HD+BAL	PD+DMSA or PD+BAL	Unknown	Unknown	Unknown	Unknown	BAL, DMSA, D-penicillamine
Cadmium	No	No	No	No	No	No	Calcium-EDTA
Copper	HD+ D-penicillamine	Unknown	Unknown	CVVHDF+ D-penicillamine	No	Yes	D-penicillamine, BAL
Lead	No	No	No	No	Unknown	No	Calcium-sodium EDTA, BAL, DMSA
Lithium	Yes	Yes	Yes	Yes	No	No	No
Mercury	No	No	No	CVVHDF+DMPS	Unknown	No	BAL, DMSA, DMPS (inorganic only)
Platin	Yes	Yes	Unknown	Unknown	Yes	No	No

HD, hemodialysis; PD, peritoneal dialysis; CVVH, continuous venous-venous hemofiltration; CVVHDF, continuous venous-venous hemodiafiltration; TPE, therapeutic plasma exchange; HMP, hemoperfusion; DMSA, dimercaptosuccinic acid; BAL, dimercaprol; EDTA, ethylenediaminetetraacetic acid; DMPS, dimercapto-1-propane sulfonate.

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Kidney and heavy metals - The role of environmental exposure (Review)

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CLINICAL RESEARCH

Toxic Nephropathy Secondary to Chronic Mercury Poisoning: Clinical Characteristics and Outcomes

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Introduction: Kidney disease secondary to mercury poisoning has not been well documented and is often misdiagnosed and mistreated.

Methods: We performed a retrospective analysis of patients diagnosed with having mercury poisoning over a 6-year period between July 2013 and June 2019. Demographics, clinical measures, renal pathologic examinations, treatments, and outcomes were compared between patients with kidney disease and those without kidney disease.

Results: Of the 172 patients with mercury poisoning, 46 (26.74%) had renal damage. Among the 46 patients, 41 (89.13%) presented nephrotic syndrome, and 5 (10.87%) showed proteinuria alone. The pathologic abnormality associated with kidney disease caused by mercury poisoning was mainly membranous nephropathy (18 of 35 patients, 51.43%). Among 41 patients with nephrotic syndrome, 25 were treated with chelation therapy alone and 12 with mercury chelation therapy and glucocorticoids. The remaining 4 patients were treated with chelation therapy, glucocorticoids, and immunosuppressive therapies. The overall effective rate was 97.5% (40 patients). There was no significant difference in complete remission rate among the 3 treatment methods ($P < 0.05$).

Conclusion: The main clinical manifestation of kidney disease secondary to chronic mercury poisoning was nephrotic syndrome, which was reflected in pathologic examinations as membranous nephropathy.

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REVIEW

Nephrotoxicity of Uranium: Pathophysiological, Diagnostic and Therapeutic Perspectives

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As in the case of other heavy metals, a considerable body of evidence suggests that overexposure to uranium may cause pathological alterations to the kidneys in both humans and animals. In the present work, our aim was to analyze the available data from a critical perspective that should provide a view of the real danger of the nephrotoxicity of this metal for human beings. A further aim was to elaborate a comparative compilation of the renal pathophysiological data obtained in humans and experimental animals with a view to gaining more insight into our knowledge of the mechanisms of action and renal damage. Finally, we address the existing perspectives for the improvement of diagnostic methods and the treatment of intoxications by uranium, performing an integrated analysis of all these aspects.

Key Words: **uranium; nephrotoxicity; chronic; acute; diagnosis; treatment.**

1996), and it is eliminated with the urine, rapidly from the blood and slowly from organ depots (ICRP, 1996; La Touche *et al.*, 1987).

Human beings may be subjected to pathological overexposure to the metal, both acutely and chronically, as a consequence of (1) contamination of the usual sources of normal exposure with high amounts of uranium arising from the anisotropy of the distribution of the metal in the earth's crust, as in ground veins or water masses in contact with them, or from human dumping and (2) direct contact with new sources of exposure originated by human activity and enriched in the element, such as in materiel and aeronautics or in the fields of mining and industry. The main industrial use of uranium is for fuel in nuclear reactors, which produce 17% of the world's electricity (Uranium Institute, 1996). Many

Thanks for attention