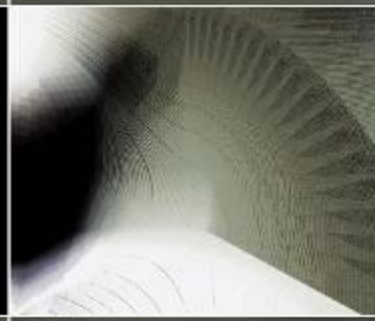
Biochemistry of Arsenic Poisoning



Taylor J. Stone, MSIV

Decedent History

- **11/15: To ER with nausea, vomiting, diarrhea, 2 hours after bowling with "friends"**
  - **Drank one beer in bowling alley that "tasted funny" and ate a hot dog**
  - **Admitted to OSH → became hypotensive → sent to ICU for pressors**
  - **Several labs & studies obtained during hospitalization:**
    - **Elevated cardiac enzymes; ESR >80; pancytopenia**
    - **Colonoscopy – pseudomembranous colitis; EF = 40%**

- **11/21: Transferred to UNC**
  - **Repeat echo shows left ventricular hypokinesis – presumed myocarditis**
- **11/24: Discharged from UNC**

- **12/1: Returns to OSH with nausea, vomiting, diarrhea, SOB, cough, sweats**
  - **Also complained of sleep disturbance and tingling in his feet**
  - **Admitted and started on succimer several hours into stay after previously ordered "heavy metals screen" returns**
  - **Cardiac arrest < 24 hours after admission and resuscitation efforts failed**
- **12/2: Autopsy performed at OCME**

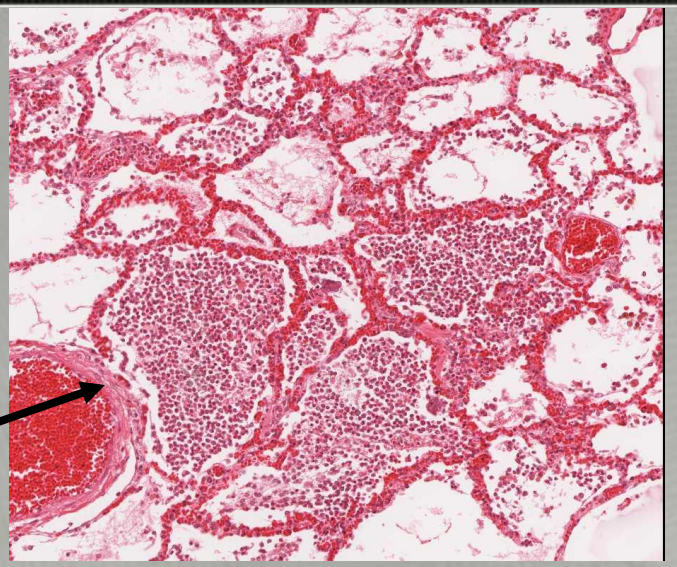
Autopsy Findings

Internal Examination

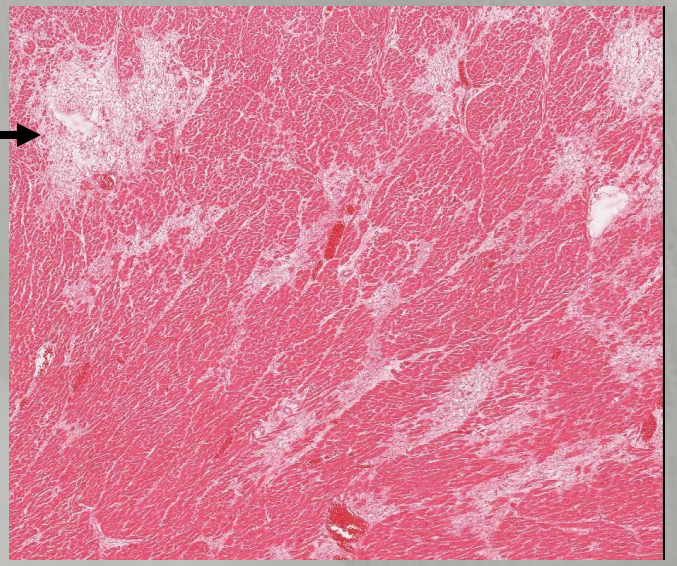
- **No gross abnormalities**

Microscopic Examination

- **Pulmonary**
  - **Evidence of aspiration**
  - **Early bronchopneumonia**

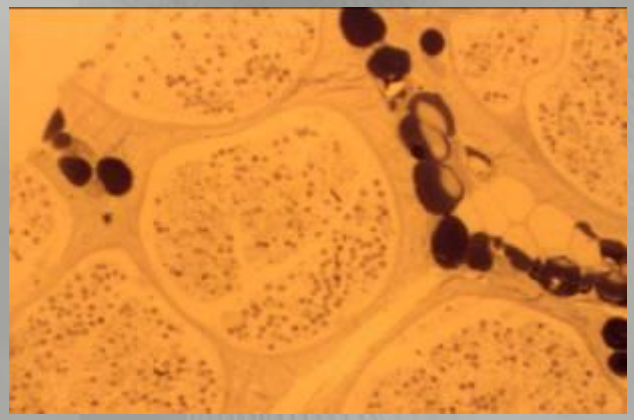


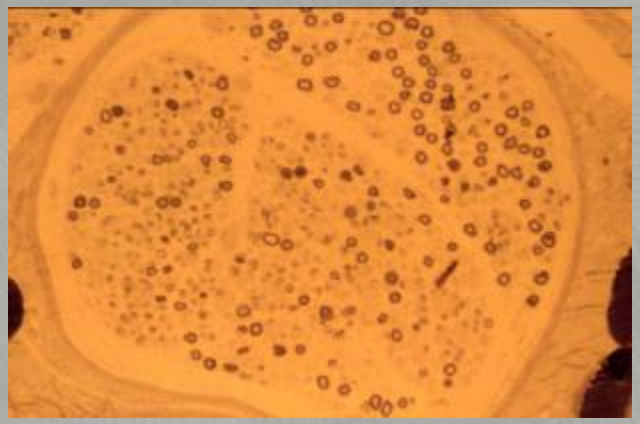
- **Cardiovascular**
  - **Multiple foci of resolving infarction**

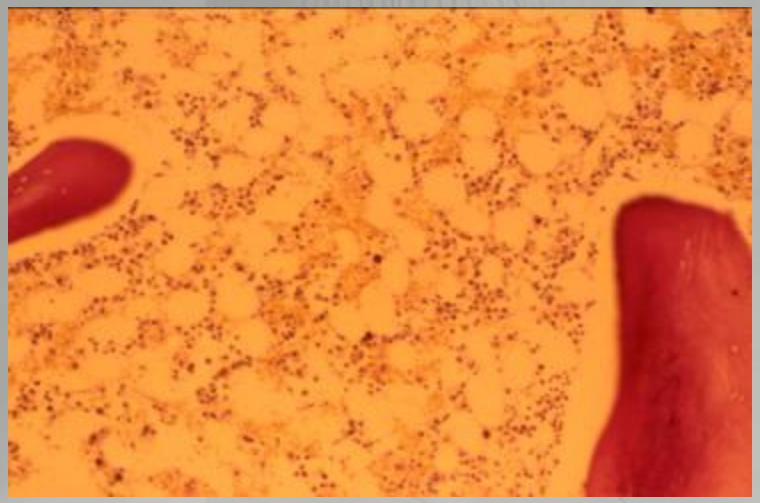


Other Histological Findings

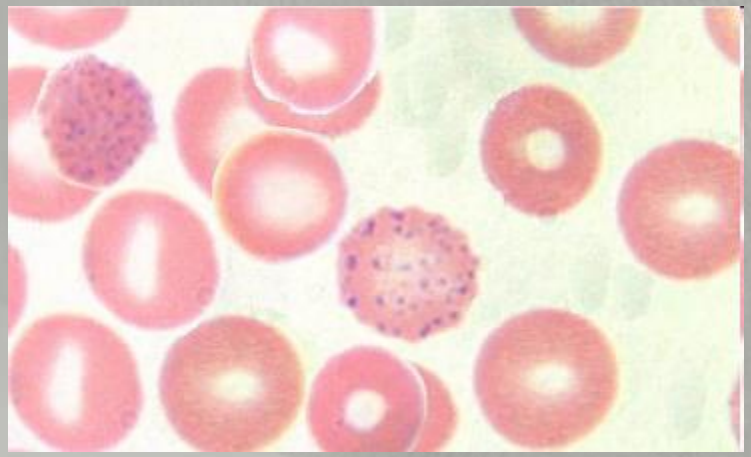
Peripheral Nerve







Bone Marrow



Peripheral Smear

Toxicology Findings

Serum

- Abnormal serum arsenic levels are detected for only a few hours (<4 hours) after ingestion.

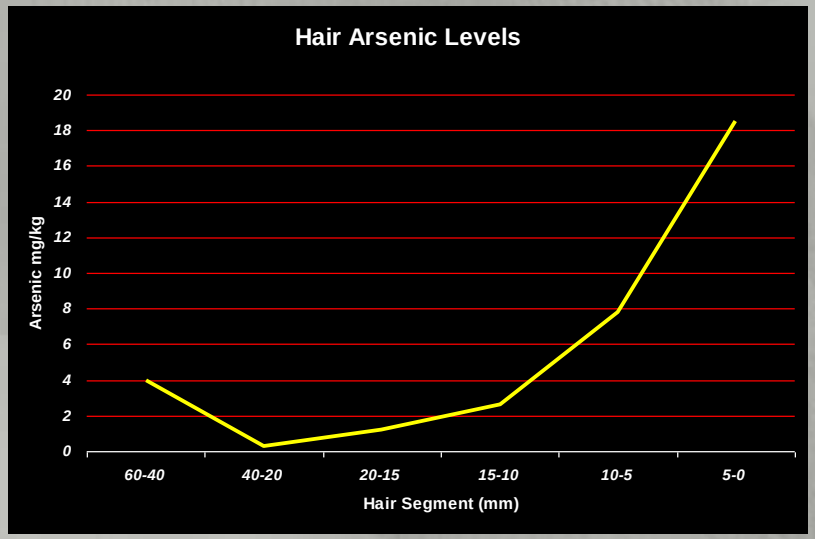
Urine

- 24-hour urine collection is method of choice for diagnosis!
- Levels > 50 µg/L (0.05 mg/L) strongly suggest arsenic poisoning.
- Elevated arsenic levels may be seen with diets high in seafood, but they are comprised of primarily organic arsenic.

Date	Blood	Urine
11/20	0.93 mg/L	--
11/22	0.46 mg/L	--
11/24	--	16.250 mg/L
11/30	0.07 mg/L	--
12/1	0.08 mg/L	--
12/2	0.07 mg/L	0.795 mg/L

Hair

- Concentrations of arsenic within hair can demonstrate longer exposure.
- Hair grows 0.4 mm per day.



Interpretation

- Received arsenic at least once prior to first hospitalization.
- At least one large dose given during first hospitalization.
- Possible that another dose was given in the interim, leading to final hospitalization.

Arsenic

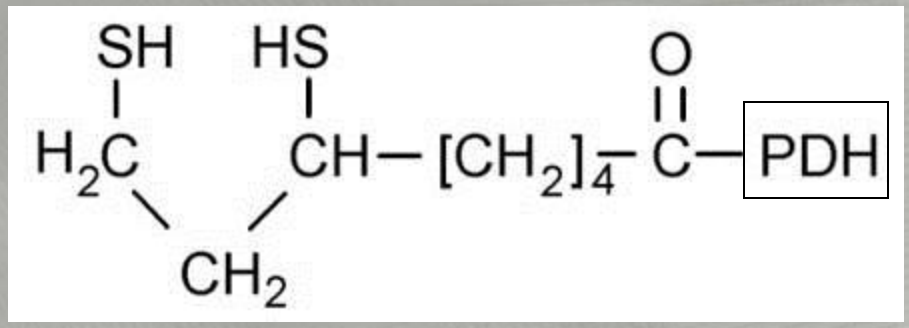
- **Metalloid – chemically similar to phosphorous.**
- **Found in water, soil, and air, from natural and anthropogenic sources.**
- **Exists in inorganic and organic forms.**
  - **Inorganic forms are generally more toxic**
  - **May be ingested, inhaled, or absorbed through skin/mucous membranes**
- **Human exposure is possible in many ways:**
  - **<u>Lumber "pressure" treated pre-2004 with CCA (Tanalith)</u>**
  - **Insecticides, ant poisons, weed killers**
  - **Kelp supplements**
  - **Animal feed**
  - **Semiconductors**
  - **Wallpaper, paint, glass, ceramics**
  - **Metal smelting**
  - **Component of British Lewisite poison from WWI**
  - **Several medical uses**

Poison of Kings

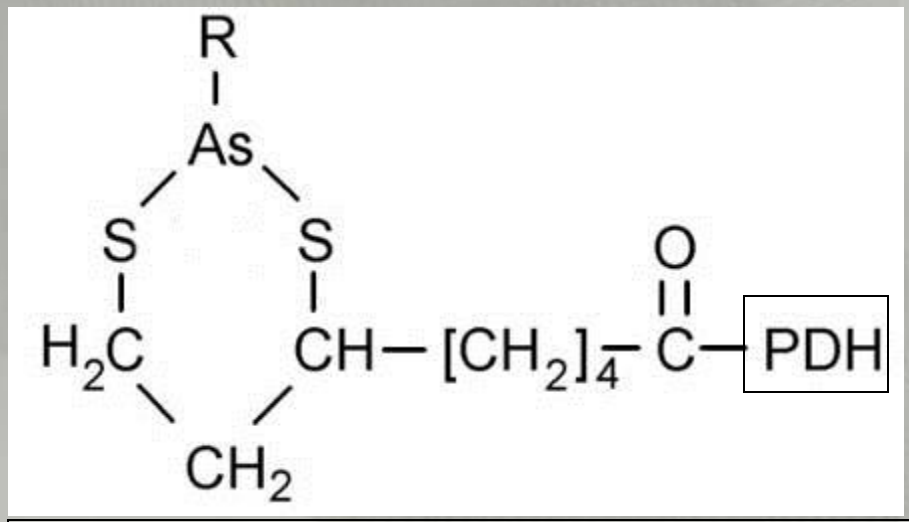
- **8th Century A.D. – arsenic trioxide first prepared**
  - **white tasteless, odorless powder.**
- **Middle Ages – "inheritance powder"**
- ***Modus operandi* of North Carolina serial killer Blanche Taylor Moore in the 1970s-80s.**
- **Emerald green, a pigment used by Vincent Van Gogh (and other impressionist painters) was arsenic-based, and some theorize that chronic exposure contributed to his mental episodes.**

Mechanism of Action

- Trivalent arsenic is the primary toxic moiety.
- Arsenic(III) binds avidly to enzymes and proteins with thiol (-SH) groups.
- Lipoic acid is an important enzyme cofactor that has two thiol groups.
- Multiple enzymes use lipoic acid as cofactors and are blocked as arsenic interferes with function:
  - pyruvate dehydrogenase
  - a-ketoglutarate dehydrogenase



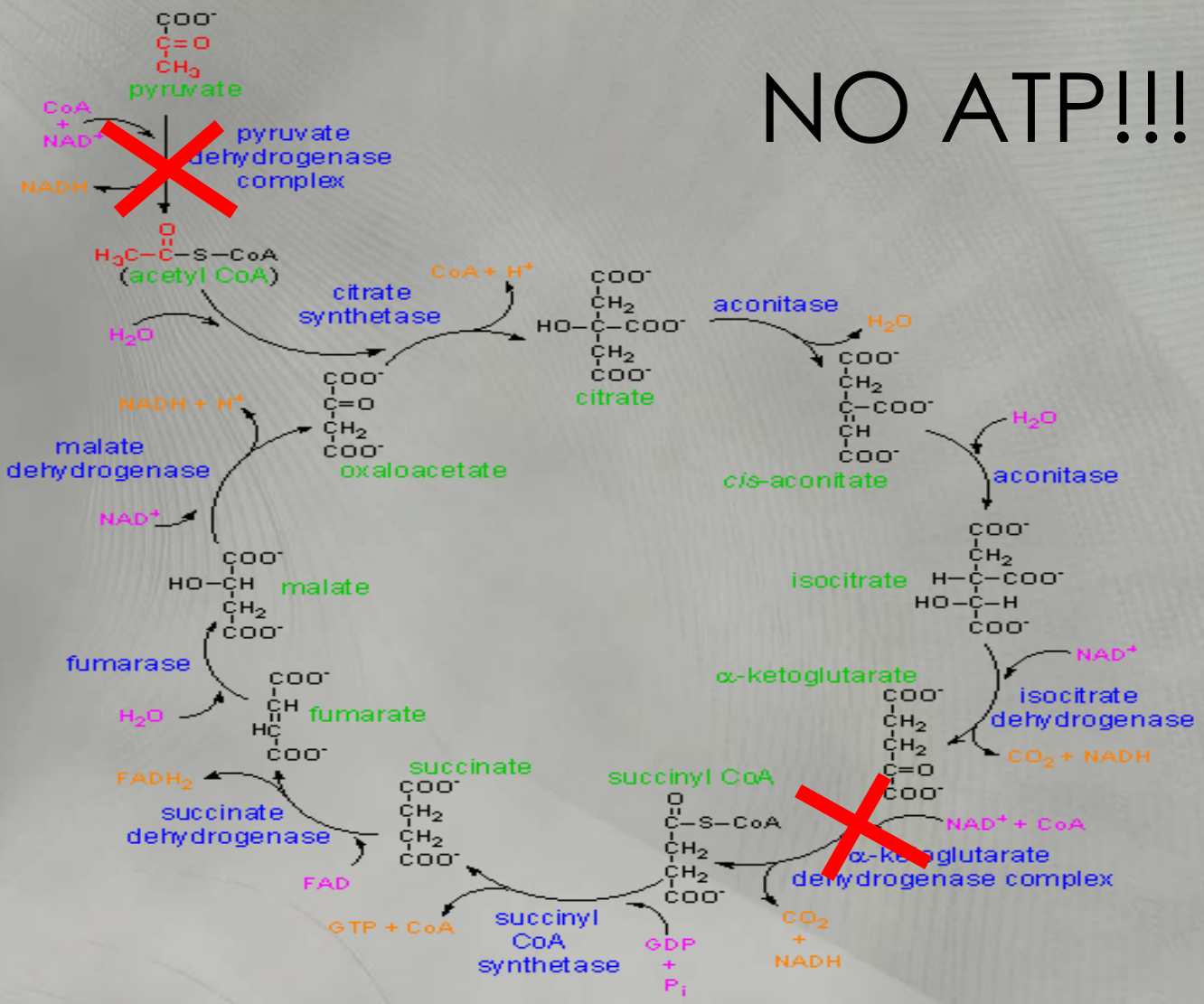
Lipoic acid with pyruvate dehydrogenase (PDH)



Arsenic bound to lipoic acid-PDH.

Mechanism of Action

NO ATP!!!



Other Mechanisms

- **Pentavalent arsenic is toxic as well because it resembles inorganic phosphate and substitutes for phosphate in metabolic pathways.**
  - **ATP → ADP-Arsenate**
  - **Bone phosphate → Bone arsenate**
  - **Glucose-6-phosphate → Glucose-6-arsenate**
- **Arsenic also alters confirmation of proteins and interferes with their function.**
- **Arsenic is classified as a known human carcinogen.**
  - **Inhalation predisposes primarily to lung cancer.**
  - **Oral exposure is associated with skin, bladder, liver, and kidney cancer.**
  - **Mechanism of carcinogenesis is unknown.**

Pharmacokinetics

- **Quickly and widely distributed -- peak serum levels occur 30-60 minutes after exposure.**
- **Excreted in urine as inorganic ion and methylated moieties.**
- **Blood clearance of arsenic occurs in three phases:**
  - **Phase 1 – a rapid decline occurs within 2-3 hours; up to 90% of arsenic cleared**
  - **Phase 2 – from 3 hours to 7 days, with estimated half-life of 30 hours**
  - **Phase 3 – a slower elimination phase, with estimated half-life of 200 hours**
- **Steps for elimination:**
  - **Pentavalent arsenic is reduced to trivalent arsenic**
  - **Followed by oxidative methylation to pentavalent organic arsenic**
  - **Stable intermediates excreted in the urine include monomethylarsonic acid (MMA^V) and dimethylarsinic acid (DMA^V)**

Clinical Symptoms & Signs

Initial Symptoms & Signs – 1h After Ingestion

- **Nausea / vomiting – severe gastroenteritis from diffuse capillary damage**
- **Burning esophageal pain & constriction**
- **Watery or bloody diarrhea**
- **"Garlicky" odor of breath and stools**

****Cardiovascular****

- **Diffuse capillary injury leading to shock**
- **Arrhythmias**

Genitourinary

- **Oliguria**
- **Hematuria, albuminuria, glycosuria**

Neurological

- **Vertigo**
- **Headache**
- **Delirium and/or mania**
- **Peripheral neuritis – symmetric, sensory**
- **Weakness**

Hematological

- **Pancytopenia**

Skin

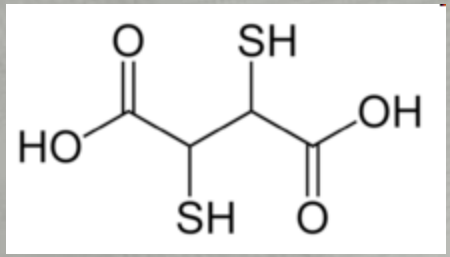
- **Numerous skin lesions**
- **Desquamation and hyperkeratosis**
- **Nail ridges (Mees' lines)**
- **Subcutaneous eyelid edema**

Treatment

- In addition to gastric lavage and fluid support, specific treatment is dimercaprol, a.k.a. BAL in oil (British Anti-Lewisite), which binds to arsenic via thiol groups and then is rapidly eliminated by the kidneys without damage to excretory organs.

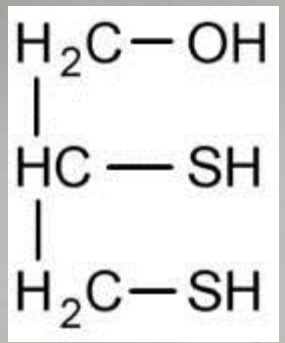
- Dose: ~3 mg/kg by deep IM injection
  - q4h for 2 days
  - q6h for 1 d
  - q12h for 10 days

- May alternatively use D-penicillamine or succimer.

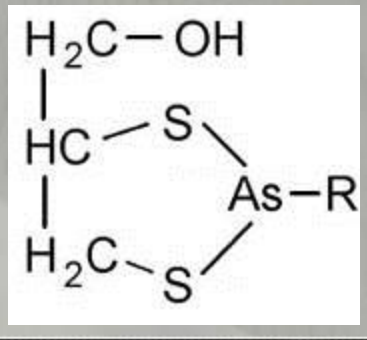


Succimer (DMSA)

Dimercaprol



Arsenic



References

- ATSDR. Toxicological Profile for Arsenic. Atlanta, GA.: U.S. Department of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, 2007. www.atsdr.cdc.gov/toxprofiles/tp2.html (Accessed on February 2, 2008).
- Bartolome B, Cordoba S, Nieto S, Fernandez-Herrera J, Garcia-Diez A: Acute arsenic poisoning: clinical and histopathological features. *Br J Dermatol* 1999, 141:1106-1109.
- Ford, MD. Arsenic. In: Goldfrank's Toxicological Emergenices, Goldfrank, L, Flomenbaum, N, Lewin, N, Howland, MA, Hoffman, R, Nelson, L (Eds), Mcgraw-Hill, New York 2002 p.1183.
- Hughes MF: Arsenic toxicity and potential mechanisms of action. *Toxicol Lett* 2002, 133:1-16.
- Jolliffe DM, Budd AJ, Gwilt DJ: Massive acute arsenic poisoning. *Anaesthesia* 1991, 46:288-290.
- Vahter M, Metabolism of arsenic. In Fowler BA (Editor) Biological and Environmental effects of arsenic. Elsevier, Amsterdam, pp. 171-198.
- Windebank, AJ. Arsenic. In: Experimental and Clinical Neurotoxicology, Spencer, PS, Schaumburg, HH, (Eds), Oxford University Press, New York 2000. p.203.

Questions?