PWHPTC 10th Anniversary Scientific Conference

雄黃
Realgar

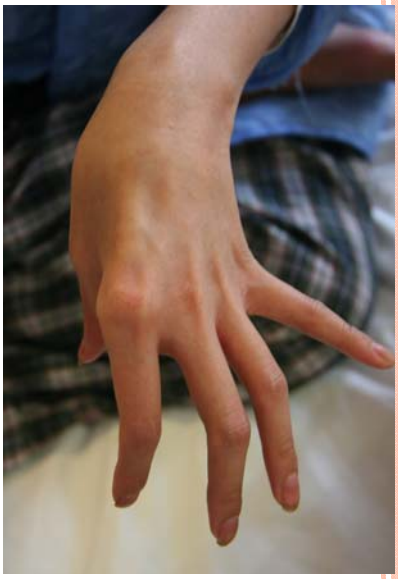
SEVERE INORGANIC ARSENIC POISONING CAUSED BY FOLK MEDICINES

Dr. Jones CM Chan
Associate Consultant
Prince of Wales Hospital Poison Treatment Centre

25 November 2015

A CASE OF PERIPHERAL NEUROPATHY

- 26/F, history of psoriasis
- 2 months history of progressive worsening of numbness and weakness over 4 limbs
- Affected walking and working



Clinical toxicities caused by folk medicine?

- Acute GI upset and profound weight loss of 30 pounds
- Generalized skin hyperpigmentation, increased hair growth over lower limbs
- Numbness, parasthesia, neuropathic pain, and weakness over palms and soles in early June 2015
- Progressive worsening of numbness and weakness till admission in August 2015

30 'herbal' pills/day for treatment of psoriasis between Feb to mid Jun 2015, prescribed by a herbalist from China

Diagnosis: Arsenic poisoning

Metal analysis

- Spot urine As/Cr = 87 nmol/mmol Cr (RF <68)
- Whole blood mercury = 9 nmol/l (RF <77)
- Whole blood lead = 0.11 µmol/l (RF < 0.24)

Toxicology analysis of the pill:

- As content = 42657 µg/g (ppm)
- Hg content = 6.59 µg/g (ppm)
- The pill weighted 0.22 g
- Each pill contains 9385 µg of As and 1.4 µg of Hg
- [HPLC-DAD, LC-IT-TOF/MS, ICP-MS]

Estimated daily As and Hg exposures were 281536 µg and 43.5 µg, respectively

Maximum permitted level (total intake) of Arsenic from Chinese Medicine < 1500 µg

A Psoriatic Patient's Experience on Alternative Medicine

我的個人經歷(陳 Chan)

我 Chan (陳) 要用最平宜方法/金錢去治療煩人牛皮癬(銀屑病)

「生命的意義不在於我們曾活着這麼簡單，而在於我們是否為其他人的生命帶來變化。」 我願望我的牛皮癬(銀屑病)心得幫到有需要的人出現曙光!

我在1988年不幸**患上牛皮癬**，牛皮癬(銀屑病)所帶來的煩惱及金錢，數之不盡！療程方法包括：西醫、中醫、自然療法、政府皮膚科光療、中醫(放血、推拿、定罐、刮痧、拍打、艾灸)、家用水療 SG-2000 Home Spa、氙氚治療、電解水、活流電治療法、**有改善牛皮癬(銀屑病)天然植物種籽果漿 Rain Soul** 等等。

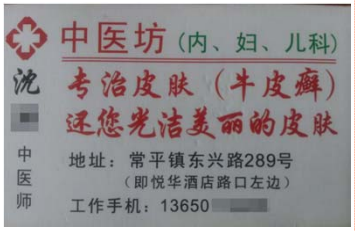
Chan 治療牛皮癬理論

1)戒口，每天都要食清淡，蔬菜，水果，小肉，戒吃所有奶類及奶類製成品。例如：奶茶、三白少吃（白糖、

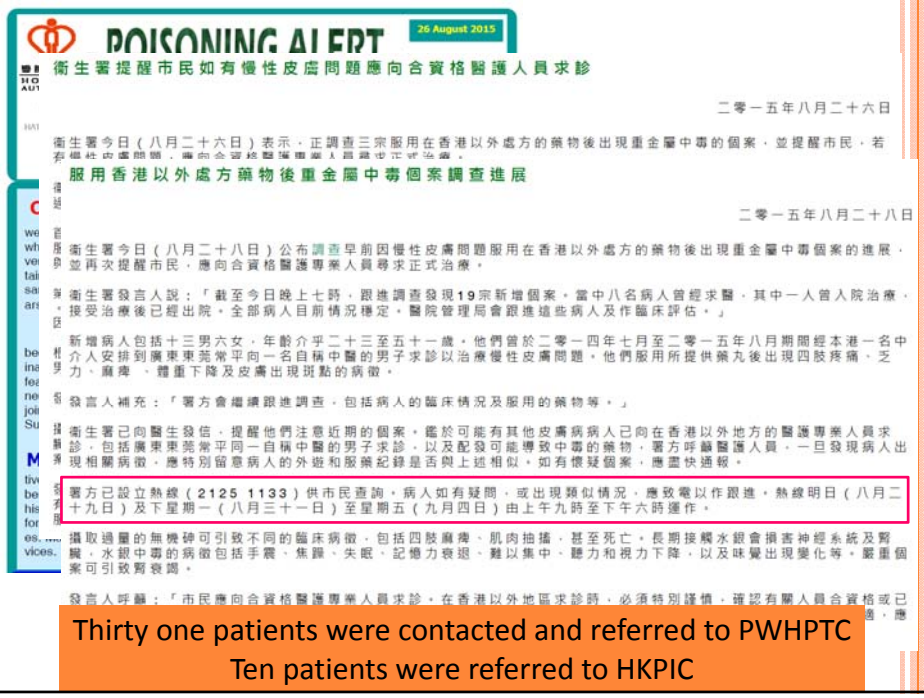
www.psoriasis-angus.com/index.htm (assessed 9/9/2015)

An Outbreak of Arsenic Poisoning Caused by Folk Medicine

- Up to 100 HK citizens had joined the “health tour” and ingested the pills



- Thirty patients were told about the diagnosis of arsenic poisoning and peripheral neuropathy via “Whatsapp”
- Some patients reported similar symptoms, some were as severe as the index case.



Thirty one patients were contacted and referred to PWHPTC
Ten patients were referred to HKPIC

APPLE DAILY 28-08-2015

■龔小姐手肘生蛇位置仍未徹底消退。

醫師認藥丸含朱砂

至於開出有問題藥丸的沈醫師，昨向本報記者承認，指在今年2月因有很多港人病者取藥，不夠時間將藥曬乾，製藥時改以烘乾方式。沈表示會繼續處方有關藥丸，但堅持不會向病人公開成份，但考慮改良配方，「（啲家）有好少份量朱砂，但唔關事」。據知，朱砂屬含毒中藥，主要成份[illegible]期服用可能令水

至於開出有問題藥丸的沈醫師，昨向本報記者承認，指在今年2月因有很多港人病者取藥，不夠時間將藥曬乾，製藥時改以烘乾方式。

《雄黃見火毒如砒》, some of the“ 雄黃” [As_4S_4] added to the pills could have been converted to the much more soluble and toxic “砒霜” [As_2O_3], and explained the severe manifestation

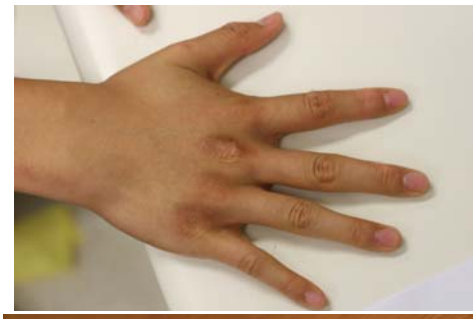
小時就要上番床」，主原任文職，現不能工作，要同住家人照顧。

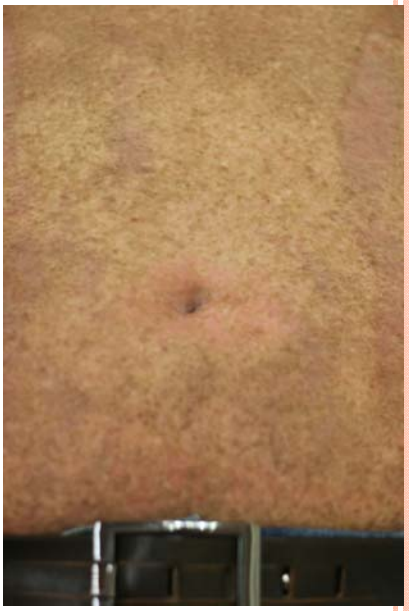
■記者周鴻熙、徐雲庭

INITIAL ASSESSMENT (N=31)

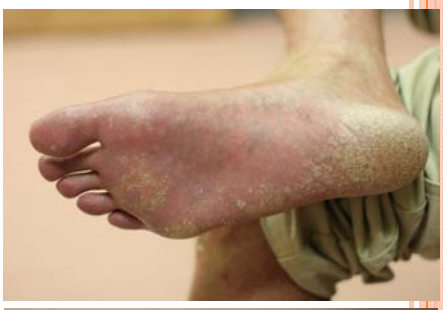
- 24 males and 7 females were assessed during early Sept 2015
- Mean age: 39.5 years old (23 – 64 years old)
- Estimated mean total inorganic As exposure per day: 259.8 mg/day (90.6 – 494.5 mg/day)
- Mean duration of exposure: 132.9 days (7 – 1098 days)

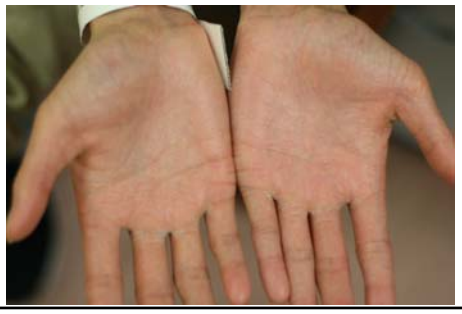
Hyperpigmentation / Hypopigmentation



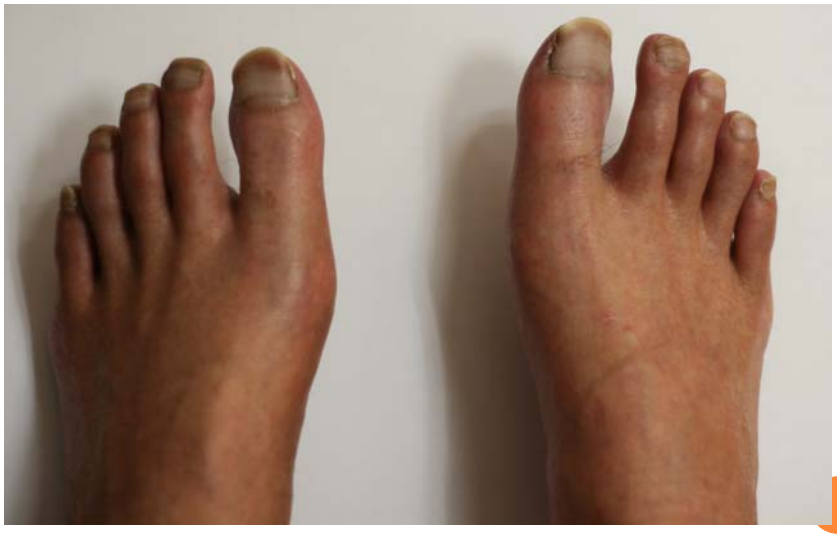


Palmar / Plantar Skin Keratosis





Nail changes – Mees' line



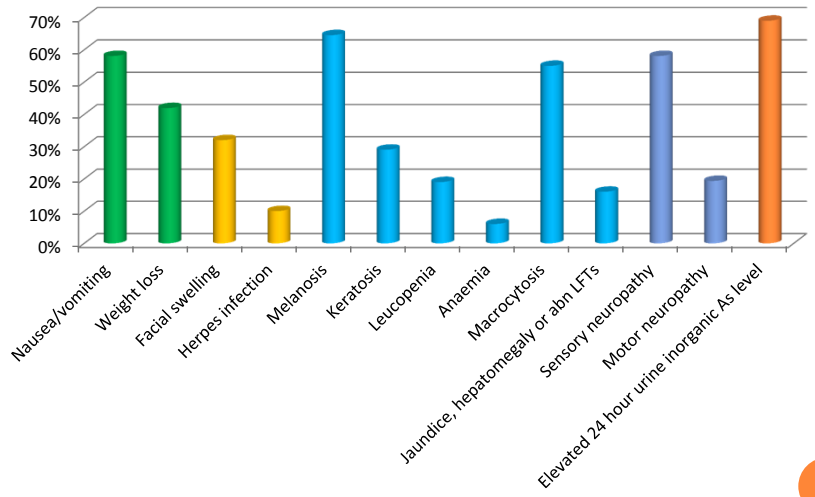
Other Severe Arsenic Toxicities Uncovered

- 27/M
- Good past health except psoriasis
- Admitted to hospital in March for vomiting after taking the folk medicine for 50 days
- Noted Hb 9.2 g/dL, Wcc 1.9, Plt 397
- BM aspirate: mild dysplastic haemopoiesis, need to exclude drug-induced causes
- BM Trephine biopsy: no significant pathology

Other Severe Arsenic Toxicities Uncovered

- 64/M
- Good past health except psoriasis
- Admitted to hospital in March for ankle edema and ascites after taking the folk medicine for 3 months
- LFT: albumin 34, globulin 26, Bili 20, ALP 154, ALT 22
- Platelet 160, Prothrombin time 13.5s
- US abd: hepatomegaly with fatty liver, splenomegaly, ascites, patent portal vein
- Ascites fluid – transudative
- Viral Hepatitis B or C infection, Autoimmuine hepatitis -ve
- CT liver: features of Budd Chiari syndrome, need to exclude drug-induced causes

Clinical Features of PWH Cohort (n = 31)



Mean spot urine inorganic As/Cr = 578.9 (68 – 4730 nmol/mmol Cr) (RF <68)

Mean 24h urine inorganic As = 4337.3 (959 – 15026 nmol/d) (RF <670)

SAHA'S GRADING OF ARSENOSIS AT DIAGNOSIS

Stages	Inference	Grades	N (%)
I. Preclinical	Pre-clinical	0-a, 0-b	5 (16.1)
II. Clinical	Melanosis	1-a, 1-b, 1-c	6 (19.4)
	Spotted keratosis on palms and soles	2-a, 2-b, 2-c	1 (3.2)
	Diffuse keratosis on palms and soles	3-a, 3-b, 3-c	1 (3.2)
	Dorsal keratosis	4-a, 4-b, 4-c	0 (0)
III. Complications	Hepatic disorder	5-a, 5-b, 5-c	0 (0)
	Sensory neuropathy	6S-a, 6S-b, 6S-c, 6S-d	12 (38.7)
	Motor neuropathy	6M-a, 6M-b, 6M-c, 6M-d	6 (19.4)
IV. Malignancy	Malignancy	6-a, 6-b, 6-c	0 (0)

Saha KC 2003

RESULTS OF URINE INORGANIC ARSENIC LEVELS (ICP-MS)

- 73% of patients have high spot urine As/Cr ratio (Reference range <68 nmol/mmol Cr)
- Mean spot urine As/Cr = 578.9 nmol/mmol Cr (68 – 4730 nmol/mmol Cr)
- 69% of patients have high 24h urine As (Reference range <670 nmol/d)
- Mean 24h urine As = 4337.3 nmol/d (959 – 15026 nmol/d)

Challenges in Management of Subacute Inorganic Arsenic Poisoning

- Who needs treatment?
  - With neuropathy?
  - With skin lesions?
  - With high urine Arsenic levels?
- How to monitor the treatment response?
  - Symptoms and signs?
  - Spot urine As?
  - 24 h urine As?
  - Monitoring frequency?

Natural progression of arsenic-induced skin lesions and peripheral neuropathy

After 1 year of stopping the Arsenic-contaminated water

- The neuropathy showed:
- Improvement in 30% of patients
- No change in 60% of patients
- Deterioration in 10% of patients
- (similar changes as in skin lesions)

Rahman MM, et al. Clin Tox 2001

After 5 years of stopping the Arsenic-contaminated water

- Pigmentation and keratosis improved in 50% of patients
- New skin lesions developed in 10% of patients
- No new peripheral neuropathy developed

Guha Mazumder DN, et. 1999

SAHA'S GRADING OF ARSENOSIS

Stages	Inference	Grades
I. Preclinical	Pre-clinical	0-a, 0-b
II. Clinical	Melanosis	1-a, 1-b, 1-c
	Spotted keratosis on palms and soles	2-a, 2-b, 2-c
	Diffuse keratosis on palms and soles	3-a, 3-b, 3-c
	Dorsal keratosis	4-a, 4-b, 4-c
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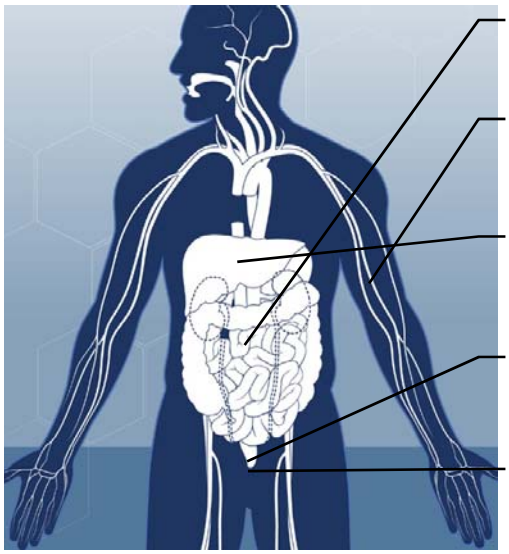
	Sensory neuropathy	6S-a, 6S-b, 6S-c, 6S-d
	Motor neuropathy	6M-a, 6M-b, 6M-c, 6M-d
IV. Malignancy	Malignancy	6-a, 6-b, 6-c

- Grade 1 – reversible by withdrawal As-water
- Progression from Grade 1-b to more advanced grade is preventable
- Grades 2-6 are irreversible
- Chelation tx is useful to prevent disease progression in grades 2, 3, and 4
- Chelation agent cannot rule out further advances of disease to the stage of malignancy

Saha KC 2003

KINETICS OF INORGANIC ARSENIC



Well absorbed in GIT, bioavailability ~ 60%

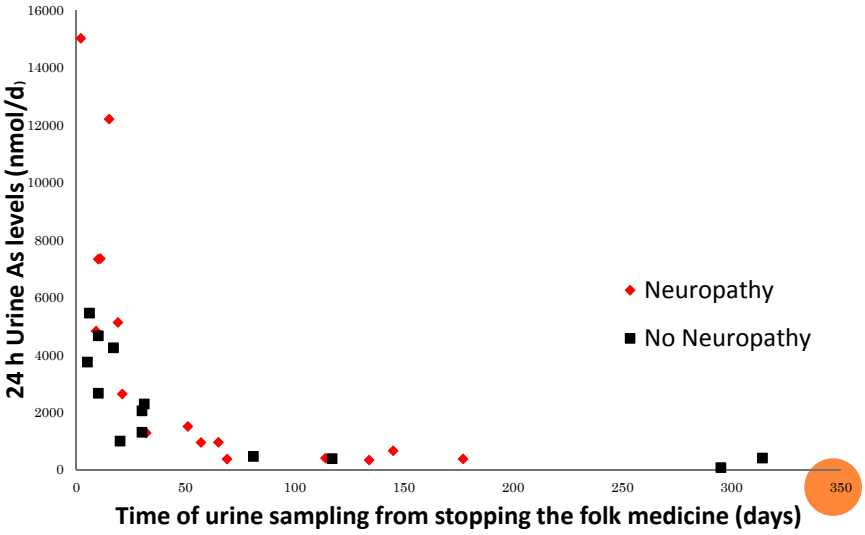
Widely distributed and bind to cellular proteins, mostly in keratinized tissues

Reduction of iAs (V) to iAs (III), and methylation to organic As take place in liver

Both iAs and organic As are excreted in urine and bile

75% of absorbed iAs is excreted in the urine within 1-3 days, T½ is ~40-60 h in human

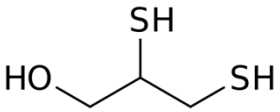
No Association between Neuropathy with Urine Inorganic Arsenic Levels



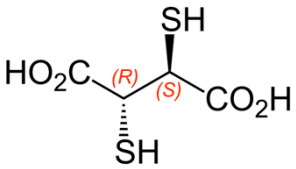
Challenges in Management of Subacute Arsenic Poisoning

- Which chelation therapy?
  - DMSA (Succimer) – only drug available, in limited quantity
  - DMPS – more effective? Oral form not immediately available
- Give DMSA (10 mg/kg tds po) for 5 days for those symptomatic, or with high urine As levels
- Monitor 24 h urinary arsenic levels on day 0 and day 1
- Drug holiday for 1-2 weeks
- DMPS therapy (100mg qid po for 7 days)
- Monitor 24 h urinary arsenic levels on day 0 and day 1

Chelation Therapy for Arsenic Poisoning

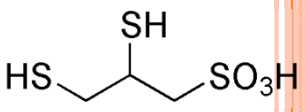


Dimercaprol
Or
British anti-Lewisite
(BAL)



Dimercaptosuccinic
acid
(DMSA)

Oral

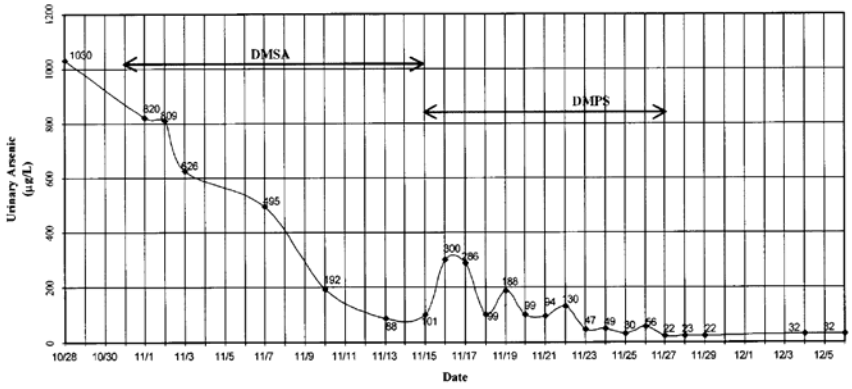


2,3-Dimercapto-1-
propanesulfonic acid
(DMPS)

Oral, IV

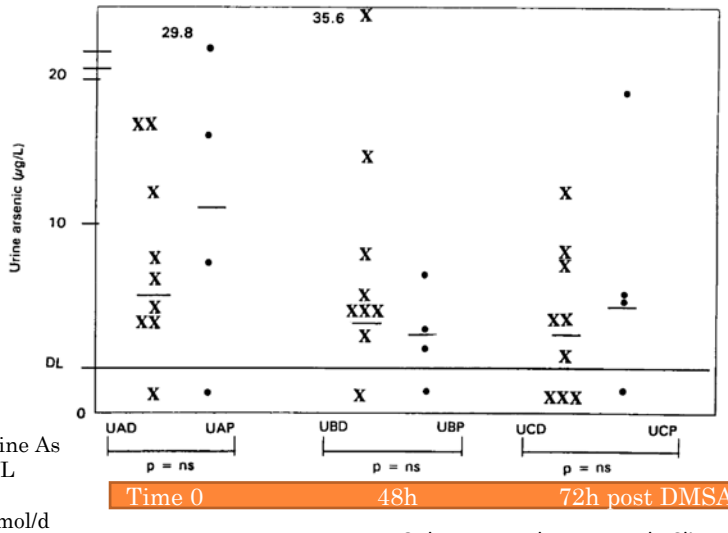
Difference between DMSA and DMPS is the later distributed both extracellularly and to a smaller extent, intracellularly

A Case of Acute Arsenic Poisoning Treated by DMSA Followed by DMPS



Wax PM Clin Tox 2000; 38(7): 777-80

Urine As Levels in DMSA- and Placebo-treated Patients



RF:
24 h urine As
<25 ug/L
Or
<670 nmol/d

Guha Mazumder DN, et al. Clin Tox 1998

Serial Urinary As excretion in 2 DMPS- and 1 Placebo-treated Patients during on and off treatment week

Pre-DMPS 24 h urine As = 44.05 ± 21.10 µg/L
Post-DMPS 24 h urine As = 110.32 ± 64.79µg/L

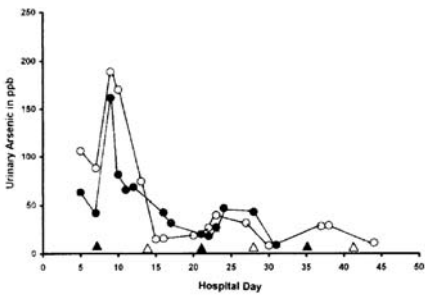


Figure 2. Serial concentrations of 24-hour urine As of 2 patients treated with DMPS showing increased As excretion following drug therapy. Patient 1 (●) and patient 2 (○). ▲ Drug and △ drug withdrawn.

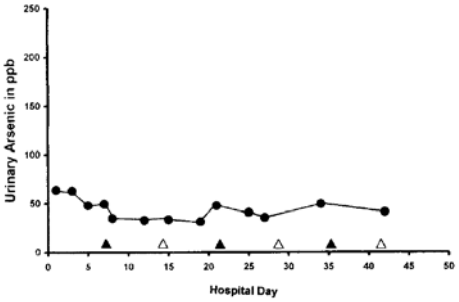


Figure 3. Serial concentrations of 24-hour urine As in a placebo-treated subject. ▲ Placebo and placebo △ withdrawn.

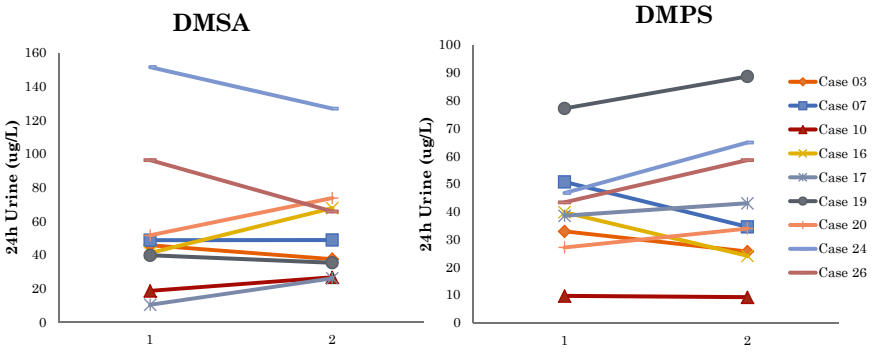
Guha Mazumder DN, et al. Clin Tox 2001

RESULTS

- 18 patients were treated with DMSA
- 1 patient was treated with IV DMPS
- 15 patients were treated with oral DMPS

	DMSA (µg/L) (n=16)
24h Urine As level (Pre-treatment)	87.07 ± 84.23
24h Urine As level (Post-treatment)	81.28 ± 66.93
Mean % change of 24 h Urine As level	9.3%
% of responder	50%

PRELIMINARY RESULT: CHANGE OF 24H URINE ARSENIC EXCRETION IN DMSA- AND DMPS-TREATED PATIENTS (N=9)



- Mean % change of 24 h urine As after DMSA = 24.90 ± 57.71 µg/L
- Mean % change of 24 h urine As after DMPS = 35.90 ± 26.97 µg/L
- No significant difference in U_{As} excretion before and after DMSA- and DMPS-treated patients (Wilcoxon signed-rank test)

Comparison of Hong Kong and West Bengal Cohorts

	West Bengal (n=11)	Hong Kong (n=9)
Duration of exposure (year)	15.25 ± 10.7	0.58 ± 0.92
Amount of As exposure	0.66 ± 0.39 (mg/L in drinking water)	59370.26 ± 102378.57 (mg/d in folk meds)
Duration of As-free before entry (months)	0.54 ± 1.37	2.36 ± 1.83
Urine As level before DMSA (μg/L)	7.89 ± 5.93	56.06 ± 43.12
Urine As level before DMPS (μg/L)	44.05 ± 21.10	40.65 ± 18.32

Safety of DMSA and DMPS

- Skin rashes and exanthems 1-10%
- Mucocutaneous eruptions
- Mild GI upset
- Mild rise in ALT
- Mild neutropenia
- Increase urinary excretion of Zinc and Copper
- Unlike BAL, DMPS was shown to produce no Arsenic redistribution to brain of rabbit
- 6 cases of Stevens Johnson Syndrome were found after use of DMPS

CONCLUSION

- Subacute inorganic As poisoning is very unique and rarely reported
- Significant acute and chronic toxicities observed
- Management of subacute inorganic As poisoning is not defined
- Peripheral neuropathy may not be recovered with chelation therapy. Role of chelation therapy for Arsenic-induced peripheral neuropathy is unclear
- Arsenic Chelation is similar with DMSA and DMPS in our study
- More patients responded to DMPS than to DMSA
- Safety of the chelation therapy
- Need to observe for malignancy potentials in long term
- Use of folk medicine may be dangerous

THE END

Thank you