

## Appearances can be Deceiving

### Clinical Synopsis:

Carrie Smith was a 35-year-old investment banker from Detroit. Up until a few weeks ago she had a happy life. It was just 9 months ago that her great aunt Martha died and left her with an inheritance of approximately 5 million dollars, and she just recently, a month ago, celebrated her 10<sup>th</sup> wedding anniversary with her husband John. They had two wonderful kids, and appeared to have the perfect family. Then, 3 weeks ago, her life seemed to collapse. Carrie discovered that her husband was having an affair with his 23-year-old secretary, and that it had been going on for over a year. Then, a couple of weeks ago she started to see a dark pigmentation on her hands and began to feel tired all of the time, even when she got plenty of sleep. Her husband told her that it was probably all due to the stress of finding out about his affair, which he insisted was over. He also told her how sorry he was, and that he loved her and didn't want a divorce. As she got sicker he began to take care of her, but things got worse. Against John's advice she decided to go to a doctor while he was at work. When the doctor examined her, he saw that melanosis (dark pigmentation) was present on her palms. He also noticed spotted pigmentation or spotted melanosis on her chest, back, and limbs. Melanosis was also present on her tongue (Figure 1), and she appeared to be jaundice. He then decided to do some blood tests. Carrie turned out to be anemic, and had an elevated level of hepatic

enzymes. It was discovered that in the proximal tubular cells of the kidney there was mitochondrial damage present, and also swollen mitochondria (Figure 2). Finally, after talking to many of his fellow doctors he came up with a possible diagnosis. He wanted to make sure, so he ordered a urine sample, and atomic mass spectroscopy, which is used to screen for heavy metals such as mercury (absorbs at 254nm) and lead (absorbs at 283nm).

- 1) What is your diagnosis for Carrie?
- 2) Why was atomic mass spectroscopy performed?
- 3) What further tests can be done to confirm the diagnosis?
- 4) What biochemical pathways/enzymes are involved?
- 5) What are some treatments for this condition?

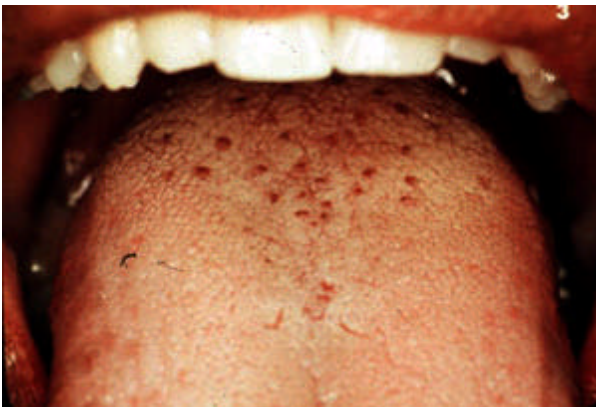


Figure 1  
Melanosis of the Tongue

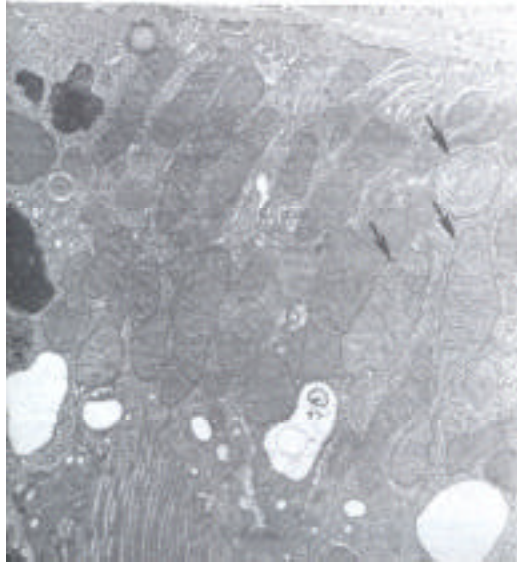


Figure 2

An electron micrograph of a proximal tubule cell after exposure to arsenic. Arrows show swollen mitochondria.

#### Case Summary:

1.) Carrie has been exposed to arsenic poisoning. She has some of the major symptoms of chronic arsenic poisoning, which include: melanosis, spotted melanosis, leucomelanosis, dorsal keratosis, mucus membrane melanosis, Blackfoot disease, anemia, jaundice, an enlarged liver, and damage to the kidneys.

2.) The doctor was trying to see if she had been poisoned by arsenic, which is a heavy metal, and could be confirmed by mass spectroscopy.

3.) Samples of Carrie's hair and nails could have been taken. Arsenic kills by attaching to sulfhydryl groups. Hair and nails are rich in these groups and grow at a known rate, so the doctor could also confirm when she began to be poisoned. If he did this he would have seen that it was 9 months earlier, the exact time that she inherited the money and her husband's affair was in full swing!

4.) The pyruvate oxidase complex is needed to produce acetyl coenzyme A and carbon dioxide before entry into the tricarboxylic acid cycle. This enzyme system is made up of several cofactors and enzymes. One protein molecule of enzyme has one lipoic acid. In one lipoic acid, there are two sulfhydryl (-SH) groups that are present. They are essential for proper functions of this complex. When arsenite is present, it replaces the two hydrogens of the thiol group and also attaches with a sulfur molecule. This forms a dihydrolipoylarsenite chelate complex, which blocks the reoxidation of the dihydrolipoyl group and, therefore, enzyme activity is blocked. As a result, energy production is reduced.

Arsenate also blocks the enzymatic activity of the mitochondria. Because arsenic can replace phosphorus, it combines with ADP to replace phosphate. This creates an unstable arsenate ester bond that is rapidly hydrolysed. Oxidation still occurs, but production of ATP through phosphorylation reduced.

Carrie is anemic due to a direct hemolytic or cytotoxic effect on the blood cells, and also a suppression of erythropoiesis. The mechanism of hemolysis involves the depletion of GSH. This results in oxidation of sulfhydryl groups in the hemoglobin from a ferrous to ferric state.

She is jaundice and has increased levels of hepatic enzymes because the liver tends to accumulate arsenic. Arsenic has been observed to produce mitochondrial damage, and might be expected to interfere with porphyrin metabolism. The kidneys also tend to accumulate arsenic. They are the major route of arsenic excretion. Sites often damaged in the kidney are the capillaries, tubules, and glomeruli.

It is unclear why Carrie has melanosis, but it could be due to induction of p53RE

and GADD153. In a recent study, they were induced when there was exposure to arsenate. This indicates a cellular response to DNA damage done by the arsenate. The arsenate puts the cells under toxic stress and evokes many responses that act through signal transduction pathways. Involvement of these additional signal transduction pathways may, in the future, explain melanosis.

5.) Some treatments for chronic arsenic poisoning are BAL, Penicillamine, and BMSA/DMPS. They are chelating agents, and are used for clearing melanosis. Methionine is used for treatment of liver damage. Parenteral dimercaprol, a chelating agent, is administered intramuscularly at an initial dose of 3 to 5 mg/Kg of body weight every 4 hours. The administration is continued until the urinary arsenic excretion is less than 50Kg per 24 hours.

### Bibliography

- 1.) Focal Melanosis and other Pigmented Conditions.  
[http://www.usc.edu/hsc/dental/opfs/QL/c\\_ql\\_03.html](http://www.usc.edu/hsc/dental/opfs/QL/c_ql_03.html)
- 2.) Saha, J.C., et al. A Review of Arsenic Poisoning and its Effects on Human Health. *Critical Reviews in Environmental Science and Technology* 29(3): 281-313, 1999.
- 3.) Tully, D.B., et al. Effects of arsenic, cadmium, chromium, and lead on gene expression regulated by a battery of 13 different promoters in recombinant HepG2 cells. *Toxicol Appl Pharmacol* 168(2): 79-90, 2000.
- 4.) Weaver, Daniel C. The poultice of time. *Discover* 16: 40+, 1995.
- 5.) U.S. Department of Health, Education, and Welfare. *Health Effects of Occupational Lead and Arsenic Exposure: A Symposium*, Ed. Carnow, Bertram W., Chicago, 1976.

