Methemoglobinemia: a Puzzling Case Study

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Case Study

- 71 y/o male patient
- Admitted 3/7/14 for AAA repair
- Had surgery on 3/7/14 to repair 75 mm Abdominal Aortic Aneurysm
- Patient also worked up for CVA while hospitalized on 3/13/14
  - CT and MRI of brain showed hemorrhage
  - TEE ordered to rule out cardiac cause of stroke

Transesophageal Echocardiogram

COMPLICATIONS:
None.

INDICATION:
The patient is a 71-year-old male. He had a recent acute stroke. Transesophageal echocardiogram was requested to rule out cardiac source of embolism.

DESCRIPTION OF PROCEDURE:
The patient was in a nonsedated, fasting state. Informed consent was obtained. He was placed in the usual left lateral position. Hurricaine spray was administered to the posterior pharynx for topical anesthetic. A total of 2 mg IV Versed was given for IV sedation. After esophageal intubation with transesophageal echocardiogram probe, visual transgastric and transesophageal views were obtained.

- After the TEE our patient took a turn for the worse

Post TEE

- Patient became cyanotic, dyspneic
- Breathing became labored
- Tachycardic
- Transferred to the ICU
- S_pO_2 was very low - 40 to 80%
- Placed on oxygen via non-rebreathing mask
- ABGs were ordered

ABG Results

- High P_aO_2 of 393 mm Hg
- Hyperventilation with high pH and low P_aCO_2
  - Why was patient cyanotic with a P_aO_2 of 393?

	03/13 0621	03/13 1605	03/13 1817	03/13 1840
Blood Gas				
ABG pH (7.35 - 7.45)			7.52H	7.48H
ABG pCO2 at Pt Temp (34 - 45 mm Hg)			31L	35
ABG pO2 at Pt Temp (75 - 100 mm Hg)			393H	216H
ABG HCO3 (23.0 - 28.0 meq/L)			24.8	25.2
ABG O2 Saturation (93 - 100 %)			97	98
ABG Base Excess (-3.0 - 3.0 meq/L)			2.3	1.9

Patient Transferred to ICU

- Physician's note shows:

Reason for consult:
Hypoxia
Chief complaint:
SoA
HPI:
71yo gentleman who is s/p AAA with repair, IPH, who was undergoing TEE today. Procedure was completed and pt oxygen saturations noted to be very low into the 40-50% range by RN. Pt noted to be cyanotic and with somewhat labored breathing. oxygen flow increased, but pt remained hypoxic on this, therefore pt transferred to ICU.

General appearance: awake, face symmetrical
Head/Eyes: PERRLA, abnl conjuctiva/sclera (mild icterus)
ENT: moist mucosal membranes
Cardiovascular: normal heart sounds, tachycardia
Respiratory: clear to auscultation, no distress
Abdomen: soft, non-tender
Extremities: no edema
Skin: dry, intact, abnormal color (cyanotic)

Intensivist Figured it Out

- Even without co-oximeter reading the physician determined the patient had methemoglobinemia
- The physician ordered methylene blue IV at 1 mg/kg and ordered a methemoglobin test by co-oximeter after methylene blue was given.

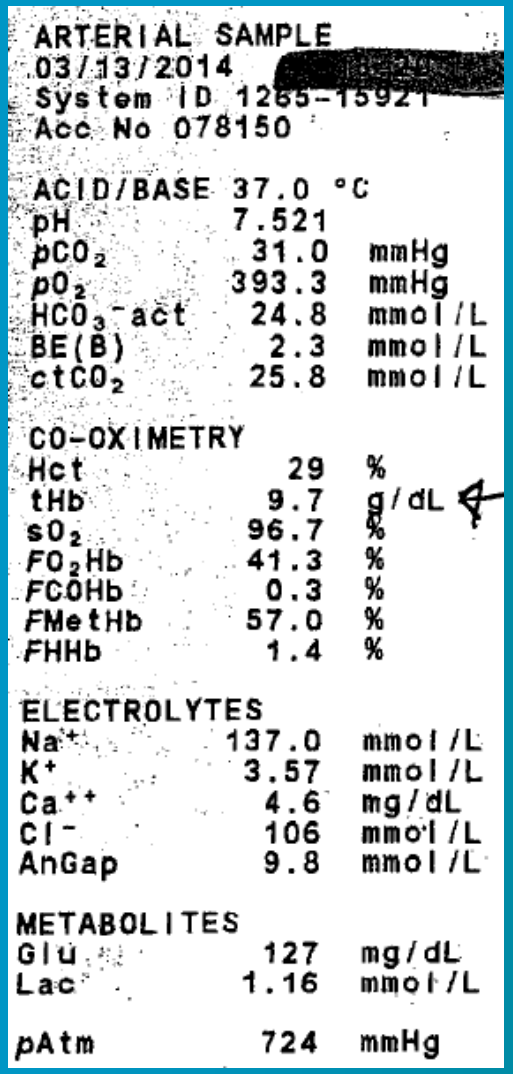
What Happened Next

- Methemoglobin level 40 minutes after methylene blue administered was 4%
- Patient was doing much better and no longer cyanotic
- Patient recovered and was dismissed to rehab hospital on 3/17/14
  - Lab went back and looked at full results panel from blood gas machine and saw the Met-Hb was 57%
    - So why didn't they report it?

What's Missing from this Picture

- All blood gases at WMC are processed through a blood gas machine that has electrolyte and metabolite electrodes as well as a co-oximeter
- However, physician orders were just for ABG not any co-oximeter results
  - The blood gas machine reported only ABG data for the test ordered:
    - The co-ox showed a critically high Met-Hb of 57%
    - New policy in place to report to technician any critical co-ox data regardless of blood panel ordered

Printer slip from ABG, Co-oximeter, Electrolyte machine



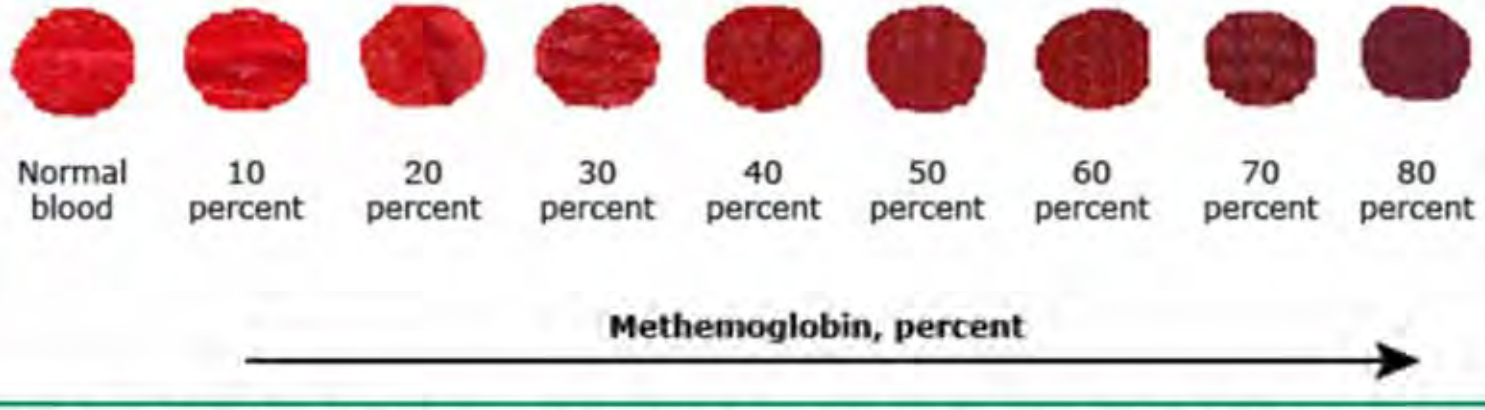
ARTERIAL SAMPLE
03/13/2014 [redacted]
System ID 1265-15921
Acc No 078150

ACID/BASE 37.0 °C		
pH	7.521	
pCO_2	31.0	mmHg
pO_2	393.3	mmHg
HCO_3^-act	24.8	mmol/L
BE(B)	2.3	mmol/L
$ctCO_2$	25.8	mmol/L
CO-OXIMETRY		
Hct	29	%
tHb	9.7	g/dL
sO_2	96.7	%
FO_2Hb	41.3	%
FCOHb	0.3	%
FMetHb	57.0	%
FHHb	1.4	%
ELECTROLYTES		
Na^+	137.0	mmol/L
K^+	3.57	mmol/L
Ca^{++}	4.6	mg/dL
Cl^-	106	mmol/L
AnGap	9.8	mmol/L
METABOLITES		
Glu	127	mg/dL
Lac	1.16	mmol/L
pAtm	724	mmHg

What Clues Helped Physician with Diagnosis

- High P_aO_2 and S_aO_2 on the blood gas
  - However patient is cyanotic with low S_pO_2
- Color of blood
  - Chocolate Brown
- Patient had benzocaine topical anesthetic during TEE
  - Benzocaine is an oxidizing agent

Blood Color as a Percent of Methemoglobin



Samples of blood with varying methemoglobin levels displayed on white absorbent material.

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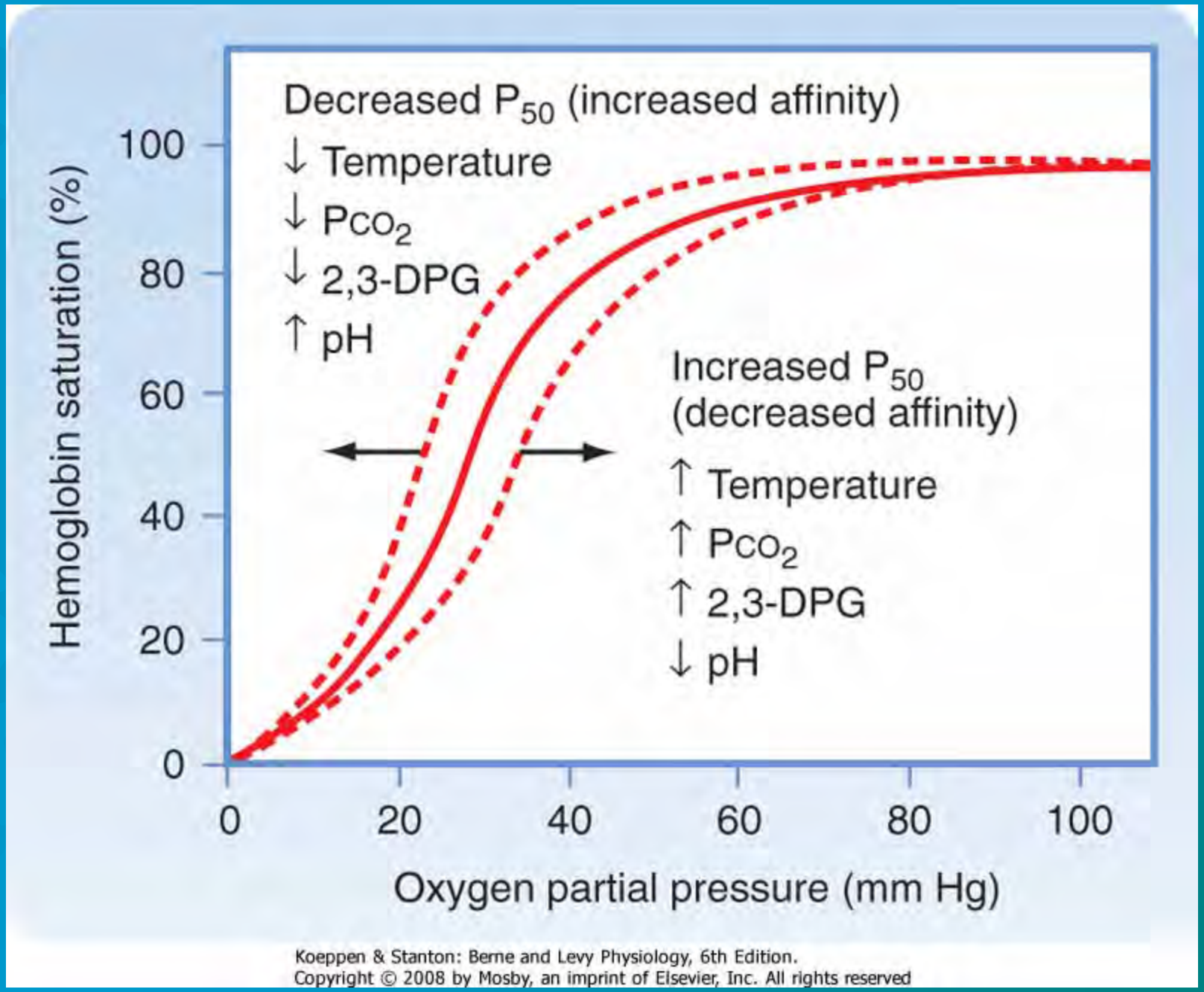
What is Methemoglobin?

- **Oxidized form of normal hemoglobin**, in which the iron atom in hemoglobin loses 1 electron to an oxidant, and the ferrous (Fe^{2+}) state of iron is transformed into the ferric (Fe^{3+}) state.
- Ferric hemes of methemoglobin are unable to bind with oxygen.
- Methemoglobin not only decreases the available oxygen-carrying capacity, but also increases the affinity of the unaltered hemoglobin for oxygen.
- This shifts the oxygen hemoglobin dissociation curve to the left, which further impairs oxygen delivery , leading to tissue hypoxia.



Methemoglobinemia Defined

- >1% of total hemoglobin is in the oxidized form.
- Due to imbalance due to either increased methemoglobin production or decreased methemoglobin reduction.
- High levels can lead to severe and irreversible tissue hypoxia and cell death.

What's Wrong with Being Blue?

Causes of Methemoglobinemia

- Hereditary
  - Cytochrome b5 reductase deficiency (Met H gene)
  - Hemoglobin M disease
  - Pyruvate kinase deficiency
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency

Blue Fugates of Troublesome Creek, Kentucky

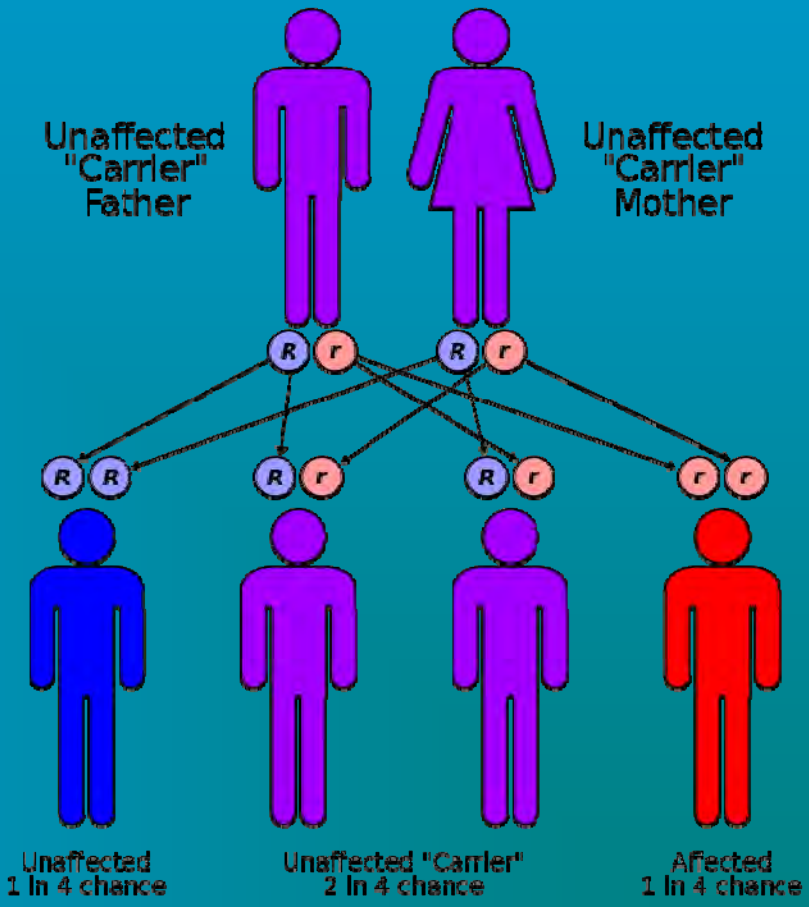
- The Fugates, commonly known as the "**Blue Fugates**" a family who lived in the hills of Kentucky, are notable for having blue-tinged skin, caused by methemoglobinemia
- Martin Fugate settled near Hazard, Kentucky in the early 1820's and his skin had a blue tint
  - His wife, Elizabeth Smith, was a member of a family clan who possessed the recessive Met-H gene
    - Intermarriage between families in around Hazard, Kentucky led to multiple blue skinned Fugates

Blue Fugates of Troublesome Creek, Kentucky

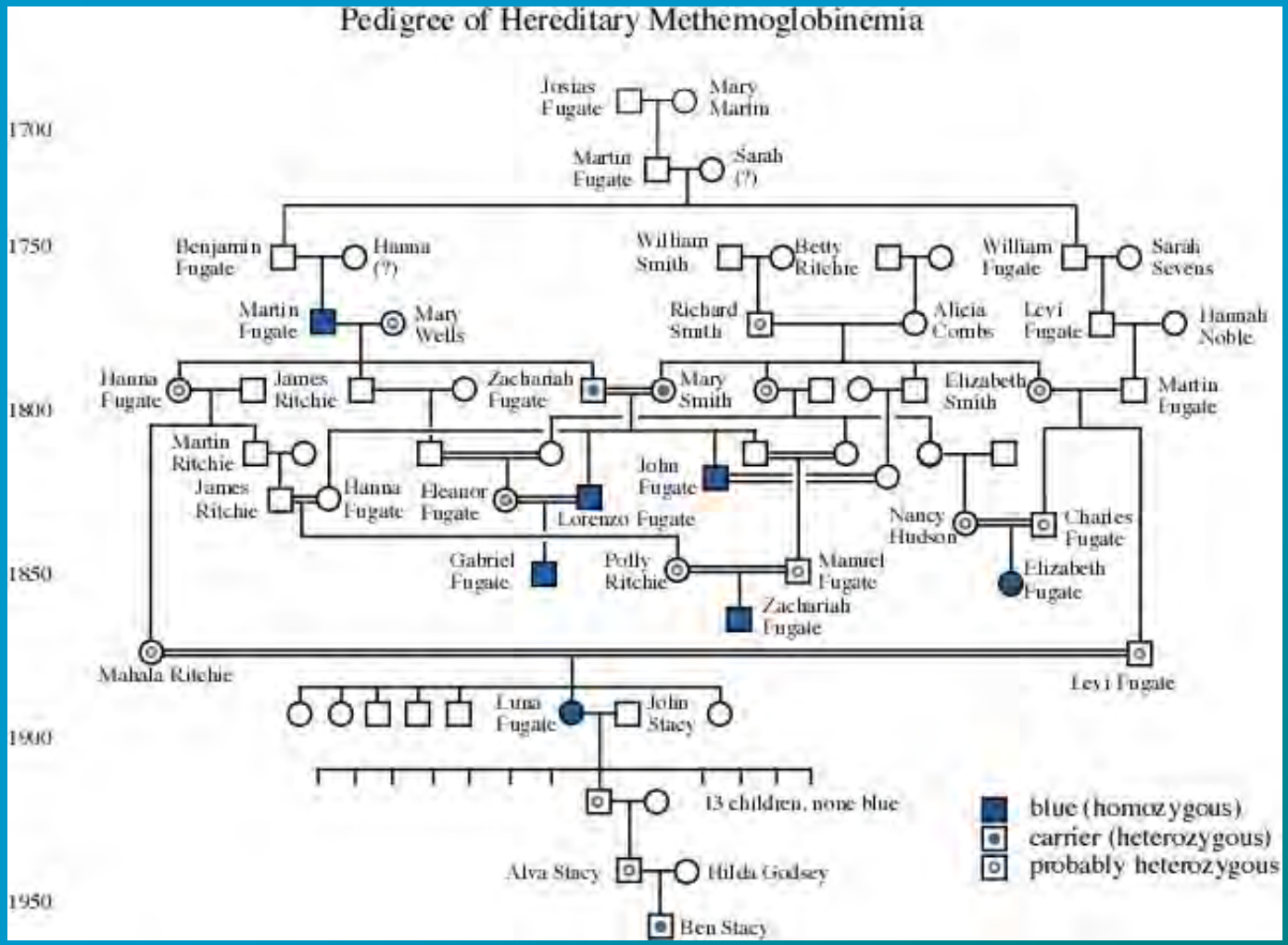
- Descendants with the disease gene continued to live in the area into the 20th century
- Hematologist Madison Cawein, III studied the family and published his findings in 1964
- Benjamin Stacy, born in 1975 is the last known descendent of the Fugates to have blue colored skin, but the blue faded as he grew older

Blue Fugates of Troublesome Creek, Kentucky

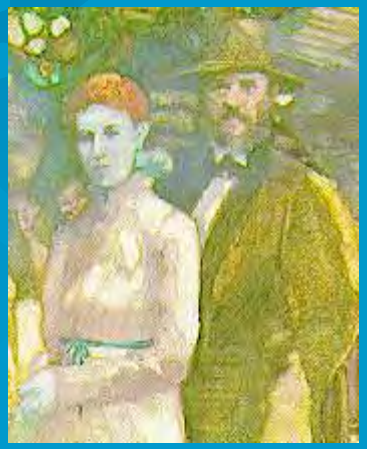
- The congenital form of methemoglobinemia has an autosomal recessive pattern of inheritance



Fugate Family Tree



Luna Fugate
& John Stacy



Causes of Methemoglobinemia

- Acquired
  - Drug classifications that can oxidize the iron ion in the hemoglobin are:
    - Antibiotics
      - Trimethoprim, sulfonamides and dapsone
    - Local anesthetics
      - Especially ’caines - articaine, benzocaine, and prilocaine
    - Other meds
      - Aniline dyes, metoclopramide, chlorates and bromates
    - Ingestion of compounds containing nitrates
      - Fertilizer leaked into ground water
    - RT medication
      - Nitric Oxide Therapy > 20 PPM

Blood in Methemoglobinemia

- Dark-red, chocolate, or brownish to blue in color
- Does not change in color with addition of oxygen, unlike deoxyhemoglobin

Clinical Features of Methemoglobinemia

- Cyanosis – detected when methemoglobin concentration exceeds 1.5 g/dL, or 8-12% of total hemoglobin.
- Early symptoms – headache, fatigue, dyspnea, lethargy
- At higher methemoglobin levels – respiratory depression, seizures, altered consciousness, shock, death
- Erythrocytosis – rare

Clinical Features of Methemoglobinemia

Methemoglobin Concentration	% Total Hemoglobin*	Symptoms^
< 1.5 g/dl	10%	None
1.5-3.0 g/dl	10-20%	Cyanotic skin discoloration
3.0-4.5 g/dl	20-30%	Anxiety, lightheadedness, headache, tachycardia
4.5-7.5 g/dl	30-50%	Fatigue, confusion, dizziness, tachypnea, tachycardia
7.5-10.5 g/dl	50-70%	Coma, seizures, arrhythmias, acidosis
> 10.5 g/dl	>70%	Death

*Assumes hemoglobin = 15 g/dl. Patients with lower hemoglobin concentrations may experience more severe symptoms for a given percentage of methemoglobin level.

^Patients with underlying cardiac, pulmonary, or hematologic disease may experience more severe symptoms for a given methemoglobin concentration.

Diagnosis

- Standard – Co-oximeter
  - Interprets all readings in 630 nm range as methemoglobin (peak absorbance at 631 nm)
  - False positives if sulfhemoglobin and methylene blue present
- Confirmatory – Evelyn-Malloy method
  - Adds cyanide and ferricyanide to measure total Hb and Met-Hb levels

Treatment of Methemoglobinemia

- Acquired Methemoglobinemia
  - Discontinue offending agents – especially if dapsone or xylocaine-related med
  - Transfusion of pRBCs if anemic
  - Activated charcoal if overdose
  - Supplemental O2
  - Methylene Blue – if severe
    - Converts Iron back from Oxidized ferric state Fe^{3+} to reduced ferrous Fe^{2+} state

Methylene Blue

- Usually given only if methemoglobin level > 40-50% of total hemoglobin.
- Dose of 1 to 2 mg/kg IV over 5 minutes
- Dose may be repeated in 1 hr.
- Large (>7 mg/kg) cumulative doses can cause dyspnea, chest pain, and hemolysis
- Should not be used in a pt. with G6PD deficiency b/c it may further produce hemolysis
  - Methylene blue paradoxically causes methemoglobinemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Ascorbic acid should be given instead

Methylene Blue

- Methylene blue is an oxidant, its metabolite leukomethylene blue is the reducing agent
  - Therefore, large doses of methylene blue may result in higher levels of methylene blue rather than the leukomethylene blue, which will result in hemolysis

Treatment of Methemoglobinemia

- Hereditary Methemoglobinemia
  - Cytochrome b5r deficiency
    - Methylene blue or ascorbic acid and dextrose
  - Methemoglobinemia due to hemoglobin M does not respond to ascorbic acid or methylene blue
    - N-Acetylcysteine, cimetidine, and ketoconazole are experimental therapies in the treatment of methemoglobinemia that have shown some promising results
  - **Exchange transfusion** is reserved for patients in whom methylene blue therapy is ineffective
  - Hyperbaric Oxygen Therapy

Take-Home Points

- Methemoglobinemia is a condition in which >1% of total Hg is in oxidized form (Fe^{3+}).
- Clinical Triad: Breathlessness, Cyanosis, Chocolate-colored blood
- Usually, if methemoglobin <40% of total Hg, can treat with O2, possibly pRBCs, and discontinuation of any offending agents
- If methemoglobin >40% of total Hg, can give methylene blue (unless G6PD deficient)
- If you are running ABGs on a machine with co-oximeter ensure that any critical value is reported regardless of test panel ordered and reported

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