IRON DEFICIENCY ANEMIA: How A Little Worm Had A Big Impact On The South

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OBJECTIVES

1. Discuss the historic impact of hookworm-related iron deficiency on people in the United States South.
2. Describe the physiologic roles and kinetics of iron in the body.
3. Relate the stages of iron deficiency to various clinical and laboratory features.

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POST-CIVIL WAR SOUTH

- Civil War – 1861-1865, fought primarily over slavery
- Won by Union/northern states
- Reconstruction era – 1865-1877
- South was very slow to recover economically

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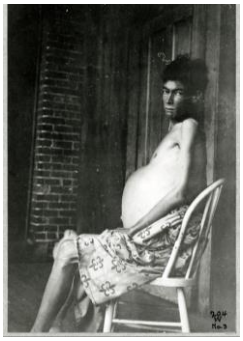

HOOKWORM DISCOVERED IN THE U.S. SOUTH

- 1902 – Charles Stiles
- *Necator americanus* – American murderer
- Intestinal, blood-feeding parasitic roundworms (helminths)
- Hookworm widespread in American South
  - Illness more prevalent in areas with certain types of soil
  - Farms and places with sandy soil
- Journalist coins nickname: "germ of laziness"
  - Southerners targeted by jokes
  - Hookworm blamed for separateness of South from rest of the nation, rather than more controversial issues like racism or education
  - Silver lining: hookworm became a more familiar concept

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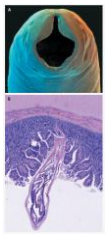
NECATOR AMERICANUS

- **Panel A:** Scanning electron micrograph of Necator americanus. The buccal capsule is characterized by cutting plates, which allow the adult parasite to feed on intestinal mucosa, submucosa, and blood. Each hookworm ranges in length from 5 to 13 mm and causes up to 0.3 ml of blood loss per day.
- **Panel B:** Adult hookworm feeding on intestinal mucosa and submucosa (hematoxylin and eosin stain).



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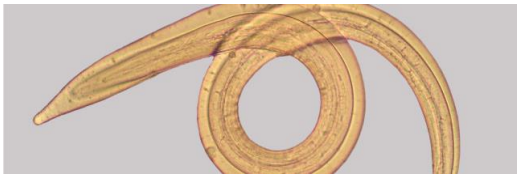

A LITTLE BIT ABOUT HOOKWORMS…

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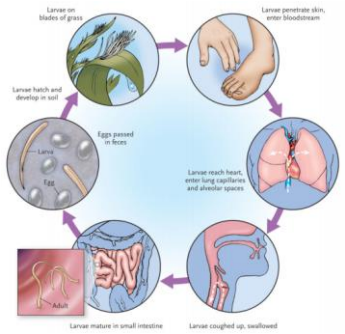
LIFE CYCLE OF HOOKWORM



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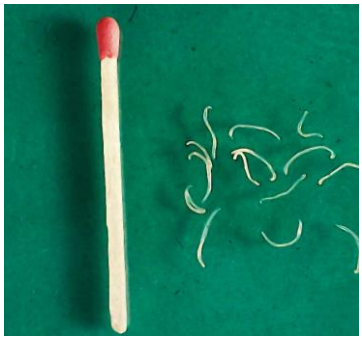
ADULT HOOKWORMS



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SYMPTOMS OF HOOKWORM INFECTION

- Symptoms depend on worm burden
- Intense itching and localized rash at site of larval penetration of skin, possible exposure to secondary infections
- Development of vesicles – "ground itch"
- Abdominal pain
- Diarrhea with black or red stools
- Loss of appetite and weight loss
- Fatigue, weakness, and pallor
- Microcytic, hypochromic anemia
- Impairment in physical and cognitive growth of infants and children

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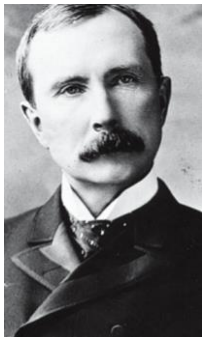
ROCKEFELLER SANITARY COMMISSION FOR THE ERADICATION OF HOOKWORM DISEASE (RSC)

- Formed in 1909 with a donation from John D. Rockefeller of $1 million over five years
- Objective: "… to bring about a co-operative movement of the medical profession, public health officials, boards of trade, churches, schools, the press and other agencies for the cure and prevention of hookworm disease."



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RSC STRATEGY

- Sought to convince southern states of the vital importance of public health
- Used health surveys to track disease
- Traveling dispensaries
  - Administered treatment
  - Gave lectures and demonstrations on disease prevention and sanitation
- Worked in conjunction with state health departments
- Conducted studies to show waste must be buried well past 4 feet deep to prevent worm migration

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POST-RSC

- RSC disbanded in 1914
- Over 1 million people examined by medical staff and nearly 500 million treated
- Despite the RSC efforts, very few behaviors were adopted
- Hookworm still existed in portions of the South: starting prevalence of 43%, 39% prevalence at the time of disbandment
- Prevalence did decline greatly over time but was likely due to
  - Increased use of indoor plumbing
  - Availability of cheap, safe food
  - Introduction of mechanized agriculture
- Hookworm was still prevalent in the South well into 60s and 70s and is still VERY common in underdeveloped countries worldwide

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HOOKWORM SOLUTIONS

- Prevention!
  - Avoid skin contact with larvae
  - Effective sewage disposal systems
- Anti-helminthic drugs
  - Aldendazole
  - Mebendazole
- Iron supplements if needed
- Vaccine?

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HOW DOES HOOKWORM MAKE YOU ANEMIC?

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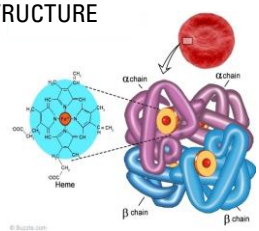
OVEREVIEW: HGB STRUCTURE

- 1 Hgb = 4 porphyrin rings
  + 4 globin chains
  + 4 iron atoms
- 1 hemoglobin carries 4 O_2 molecules



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DEFECTIVE HGB PRODUCTION

- Due to disturbances in either heme or globin synthesis
- Often reflected by a microcytic, hypochromic anemia
- **Defective heme synthesis**
  - ***Iron deficiency anemia (IDA)***
  - Anemia of chronic disease (ACD)/Anemia of inflammation (AOI)
  - Sideroblastic anemia (SA)
- **Defective globin synthesis**
  - Thalassemias
  - Hemoglobinopathies

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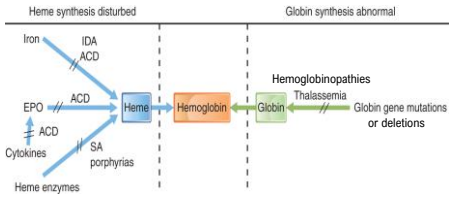

FIGURE LEGEND: SITES OF DEFECTIVE HEMOGLOBIN SYNTHESIS THAT CAN RESULT IN ANEMIA. SOME OF THESE ANEMIAS ARE HEREDITARY OR CONGENITAL AND OTHERS ARE ACQUIRED. ACD = ANEMIA OF CHRONIC DISEASE; IDA = IRON-DEFICIENCY ANEMIA; SA = SIDEROBLASTIC ANEMIA; EPO = ERYTHROPOIETIN; // = DEFECTIVE OR DISTURBED

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IRON METABOLISM

- Iron is required by every cell in the body
  - Generation of ATP
  - Cellular growth and proliferation
  - Oxygen transport
- Iron toxicity results if body's capacity is exceeded
- Factors that ↑ iron requirements
  - Chronic blood loss (menstruation or GI bleed most common)
  - Pregnancy
  - Infancy/Children

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IRON ABSORPTION

- Iron homeostasis depends on balance of
  - Total body requirements
  - Absorption of iron
- Absorption occurs in the gut (duodenum)
- 2 forms of dietary iron
  - Non-heme iron (Fe^{3+})
  - Heme iron (Fe^{2+})

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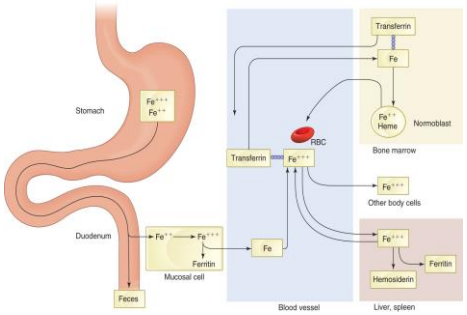

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FACTORS AFFECTING GI IRON ABSORPTION

- Availability of iron
- Condition of GI tract
- Activity of bone marrow
- Tissue iron stores
- Oxygen content of blood
- Systemic inflammation or infection
- Hgb concentration in blood

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IRON DISTRIBUTION

- Total iron concentration in the body
  - 40-50 mg of iron/kg of body weight
- Found primarily in RBCs, macrophages, hepatocytes, enterocytes
- Major fraction of body iron comes from Hgb in RBCs
  - Hgb is degraded in macrophages of spleen, liver, BM
  - ~ 85% of this iron is recycled
- Bound to transferrin, delivered to developing normoblasts in the BM
- Excess iron stored in tissues and organs

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IRON TRANSPORT

- Transferrin (Tf)
  - Primary plasma iron transport protein, made in the liver
  - Is a single polypeptide
    - 2 homologous lobes
    - Each lobe contains an iron-binding site for Fe^{3+}
  - Mediates iron exchange between the tissues
- Total iron binding capacity (TIBC)
- Serum iron
  - Almost all is complexed to transferrin; Fe^{3+} required

$$\frac{\text{Serum iron}}{\text{TIBC}} \times 100 = \%\text{ saturation of transferrin}$$

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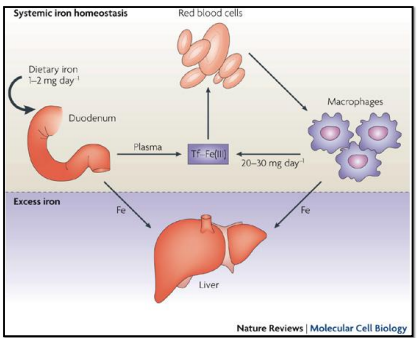

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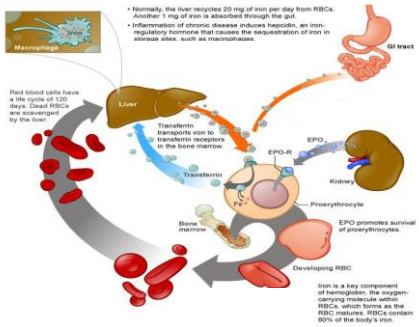

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IRON STORAGE

- Normally, most iron taken up by erythroid precursors is either incorporated into heme within the RBC mitochondria or stored.
- **Ferritin**
  - Protein that stores iron in the ***short-term***
  - Allows iron to be readily available for erythropoiesis
  - Controls amount of iron released for cellular activity
  - Found in the BM, liver, spleen – stains with Perl's Prussian Blue
  - Serum levels reflect tissue storage
  - Caution: APR!

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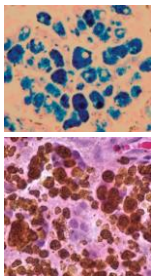
IRON STORAGE, CONT.

- **Hemosiderin**
  - ***Long-term*** **storage for iron**; iron released more slowly
  - BM and liver macrophages primarily contain hemosiderin
    - Yellow to brown refractile inclusions
    - Stains with Prussian blue



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IRON BALANCE

- Daily absorption and loss are small
  - Lose ~1 mg per day
  - 20-25 mL of RBCs are destroyed each day
    - Releases 20-30 mg of iron but most is recycled
  - Daily requirement for iron is 1 mg
- No physiologic route for excreting excess iron

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IRON BALANCE

- Iron deficiency can occur if:
  1. Intake is insufficient
  2. Loss is increased
  3. Absorption is impaired
- Iron overload may occur if:
  1. Individual receives multiple transfusions or iron infusions
  2. Absorption is impaired

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LABORATORY ASSESSMENT OF IRON

- Serum iron – diurnal variation
- Total iron-binding capacity (TIBC)
- Calculation of % saturation of transferrin
- Serum ferritin
- Indirect measure of FEP – *free erythrocyte protoporphyrin*
  - Zinc protoporphyrin (ZPP)

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IRON DEFICIENCY ANEMIA (IDA)

- Most common nutritional deficiency in the world
- Prevalent in countries where
  - Grain major part of diet
  - Meat is scarce
  - Hookworm infestation
- Due to:
  - Dietary deficiency
  - Blood loss
  - Malabsorption

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IDA PATHOPHYSIOLOGY

- IDA develops in sequential stages
  - Due to a negative iron balance: losing more iron than is absorbed
- **Stages**
  - Iron depletion
  - Iron deficient erythropoiesis
  - Iron deficiency anemia (IDA)

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IDA PATHOPHYSIOLOGY, CONT.

- **Stage I – Iron depletion**
  - Iron stores are exhausted: ↓ serum ferritin
  - Serum iron and transferrin saturation in PB still normal.
  - No anemia
  - RBC morphology is normal.
  - RBCs vary in size; RDW is frequently ↑
  - Iron absorption ↑ in gut

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IDA PATHOPHYSIOLOGY, CONT.

- **Stage 2 – Iron deficient erythropoiesis**
  - Ferritin and hemosiderin depleted
  - BM sideroblasts are absent
  - Serum iron and serum ferritin ↓, TIBC ↑
  - Transferrin saturation ↓
  - **Hgb still normal, no anemia**
  - Insufficient iron to insert in to the protoporphyrin ring
    - Protoporphyrin accumulates in cell
    - Complexes with zinc to form ZPP (↑ FEP)
  - **RBCs may be *slightly* microcytic**

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IDA PATHOPHYSIOLOGY, CONT.

- **Stage 3 – IDA**
  - All lab tests for iron status become abnormal
  - Microcytic, hypochromic anemia
  - Represents advanced stage of severe iron deficiency

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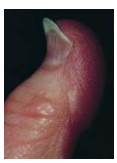
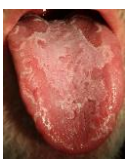
CLINICAL FEATURES





- Onset is insidious
  - Takes months to years (more rapid if blood loss)
  - Symptoms appear as anemia develops
- Variety of other abnormalities appear
  - Concavity of nails (koilonychia)
  - Glossitis
  - Muscle dysfunction
  - Inability to regulate body temperature
  - Gastritis
  - Heart palpitations

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CLINICAL FEATURES, CONT.

- Pica syndrome
  - Unusual craving for ingesting unnatural items
    - Phagophagia (ice-eating)
    - Geophagia (dirt/clay-eating)
    - Amylophagia (starch-eating)
- Infants: perform worse in mental and motor development
- Children: irritability, loss of memory, difficulties in learning

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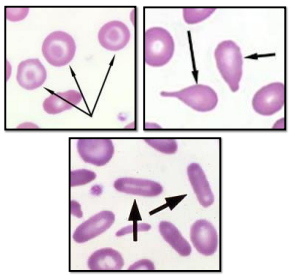
LABORATORY FEATURES

- Peripheral blood
  - MCV: decreased
  - MCH: decreased
  - MCHC: decreased
  - RDW: increased
  - Most frequent poikilocytes: target cells, elliptocytes, teardrop cells
  - PLT count?



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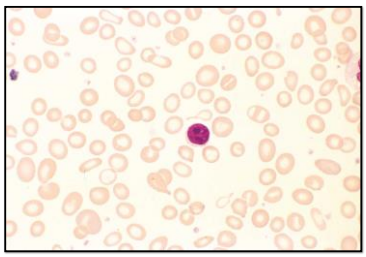
MICROCYTIC, HYPOCHROMIC ANEMIA OF IRON DEFICIENCY. COMPARE SIZE OF RBCS TO NUCLEUS OF SMALL LYMPHOCYTE IN CENTER.



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LABORATORY FEATURES

- Bone marrow
  - Mild to moderate erythroid hyperplasia
  - Ineffective erythropoiesis
  - Erythroblasts poorly hemoglobinized
  - Iron stores
    - Absent hemosiderin in macrophages
    - Sideroblasts are markedly reduced or absent

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THERAPY

- Treat underlying disorder
- Administer iron
  - Oral administration
  - Parenteral administration
  - Observe for response
    - Defined as an ↑ of 1 gm/hemoglobin in 1 month
    - Retic response begins about the 3rd day
    - Hgb normal within 6-10 weeks

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- Podcasts:
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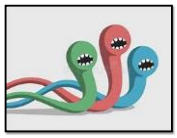
THANKS FOR GETTING HOOKED IN!



Questions or comments?

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