General Hematology

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@bloodman

GENERAL HEMATOLOGY
OHSU

DISCLOSURE

Relevant Financial Relationship(s)

Speaker's Bureau – none

Editor: UpToDate (Iron Tx)

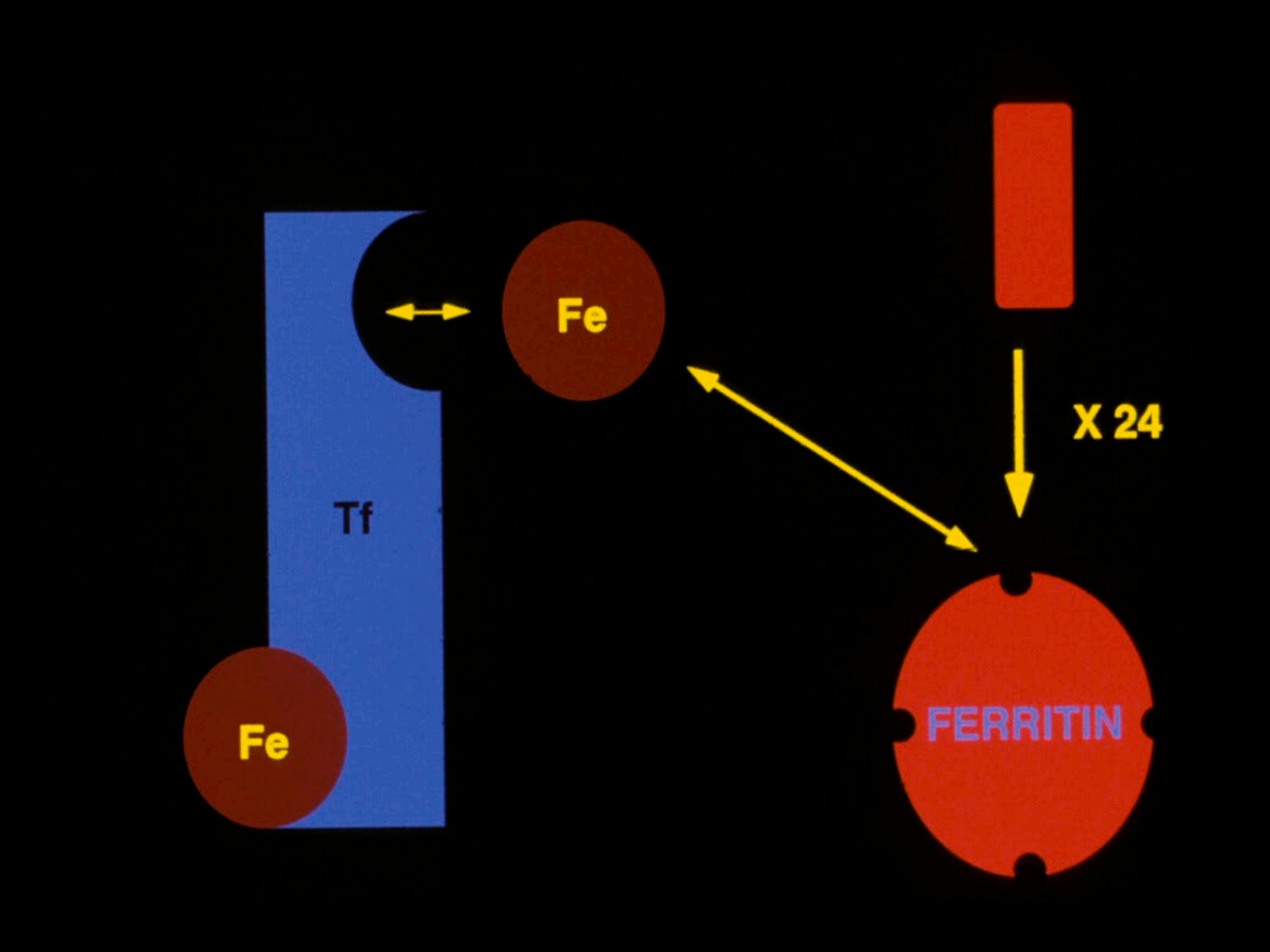
Talk

- Ferritin cut-offs
- Oral Iron
- IV Iron

What is Ferritin?

Ferritin

- Storage molecule of iron
- Composed of 24 subunits
- Can store up to 4500 iron atoms
- Protein synthesis tightly controlled by iron stores


Fe
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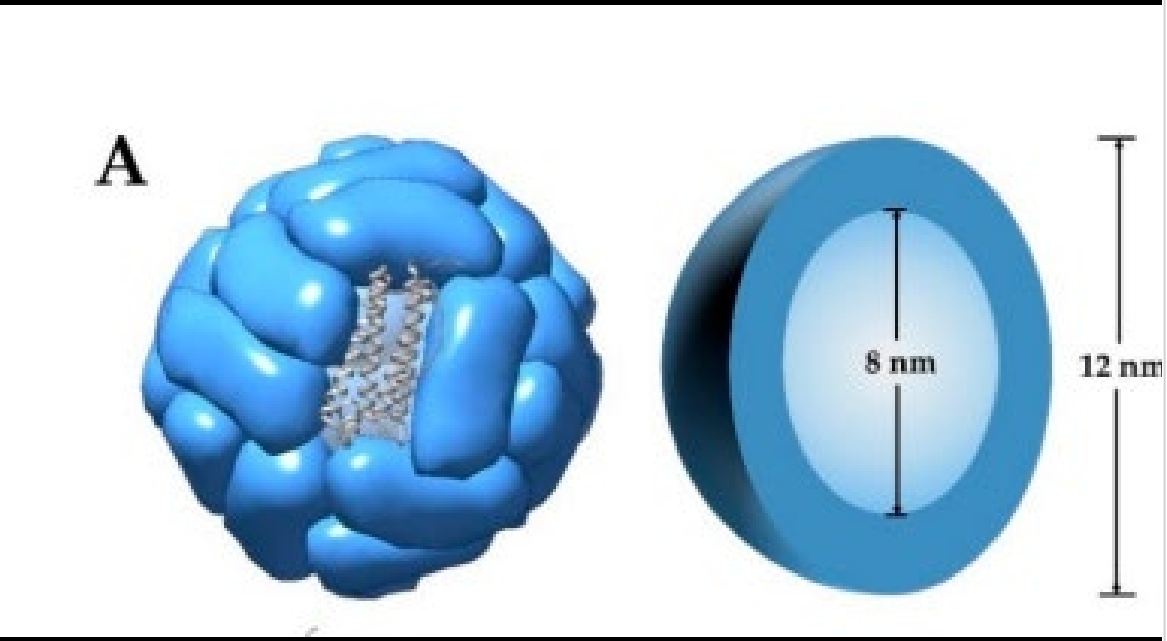
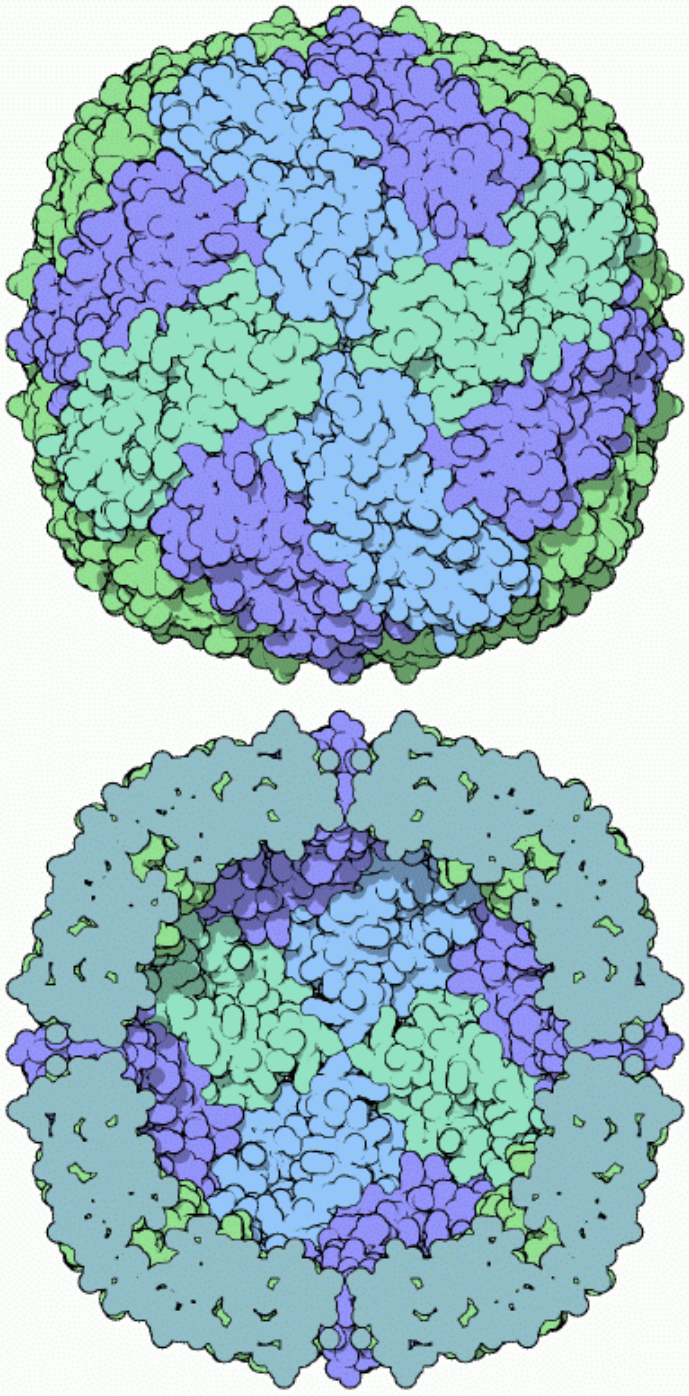
Fe
X 24
FERRITIN



Nanomaterials **2020**, *10*, 1894; doi:10.3390/nano10091894

https://pdb101.rcsb.org/motm/35

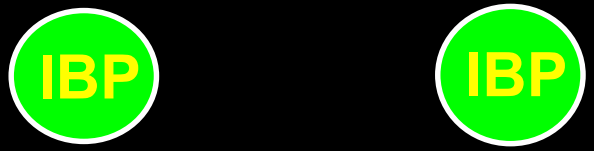


Iron and IRE

- Cellular iron controls production of transferrin receptor and ferritin
- High Iron:
  - High ferritin and low transferrin receptor
- Low Iron:
  - Low ferritin and high transferrin receptor

Iron Deficiency

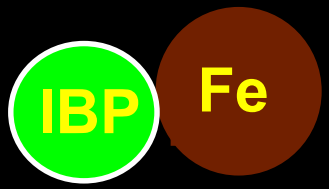
No Protein Synthesis



Stable mRNA

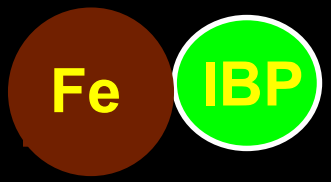
Protein Synthesis

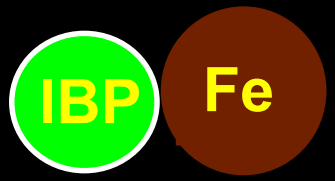
Iron Replete



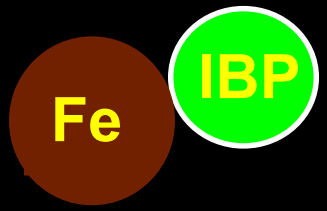
Ferritin

→ Protein Synthesis





Ferritin



Ferritin

→ UNSTABLE mRNA → X

Why is Ferritin Used to Measure Iron Stores?

Tests for Iron Deficiency

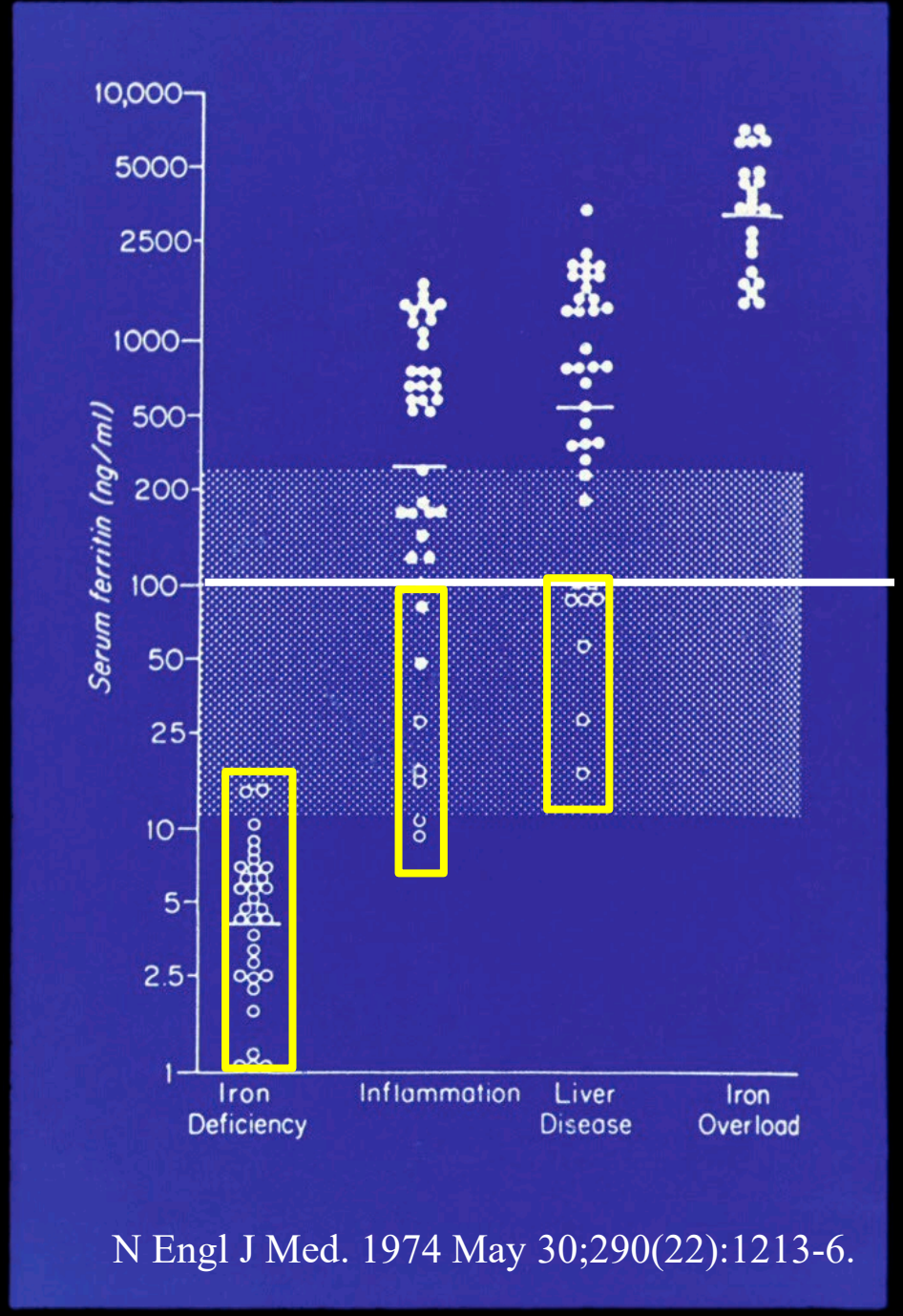
- Hemoglobin – not sensitive
- MCV – not sensitive or specific
- Serum iron – not reliable
- TIBC – specific not sensitive
- Iron saturation – low in inflammation

Ferritin

- Serum levels correlates with iron stores
  - 1ng/ml = 8-10 mg storage iron
- Acute phase reactant only with good iron stores

Ferritin Synthesis

	Iron Deficiency	Inflammation	Both
Ferritin mRNA	+	++++	++++
Ferritin protein	-	++++	-



N Engl J Med. 1974 May 30;290(22):1213-6.

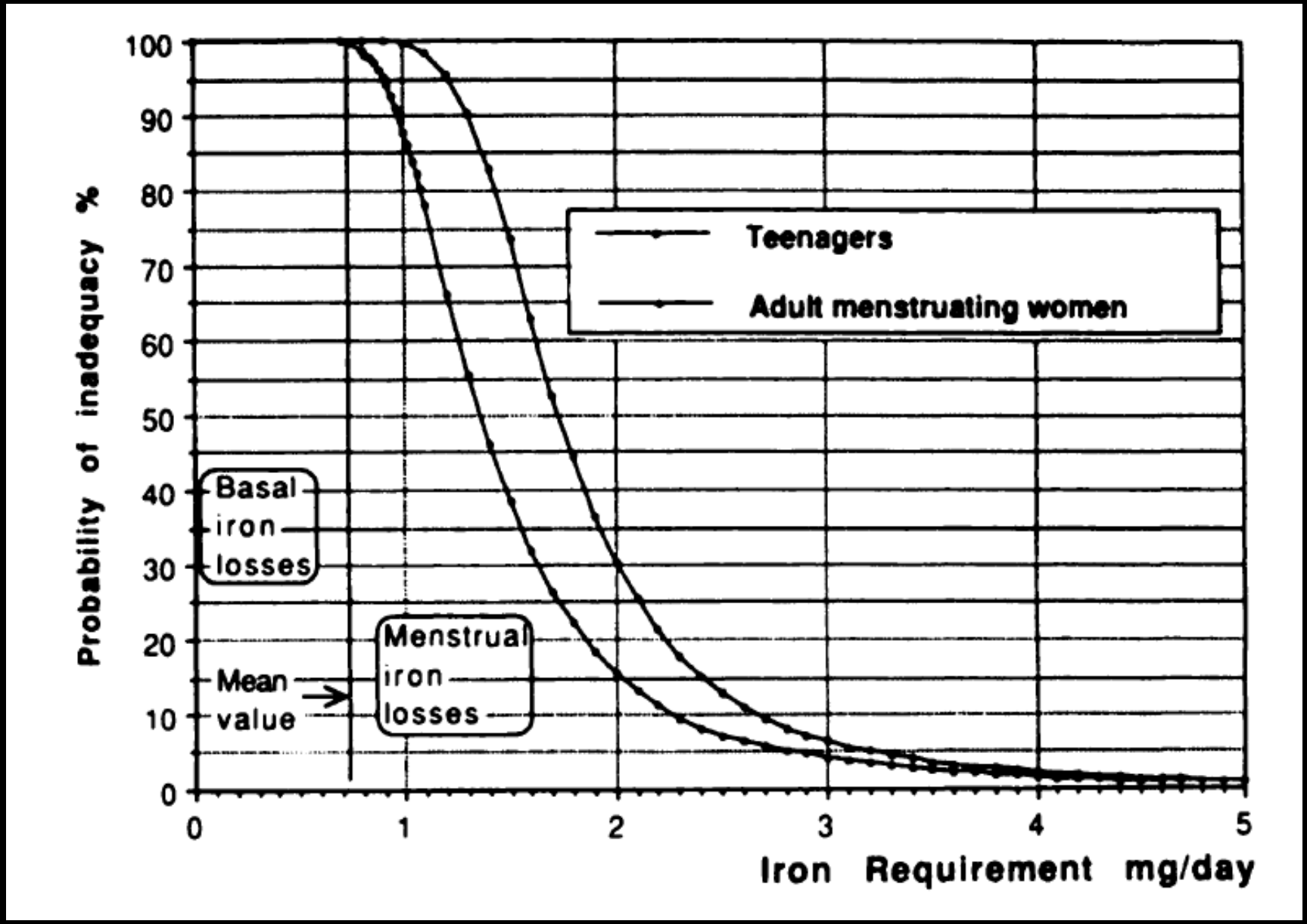
“while a [ferritin] value of >100 ug/L rules out iron deficiency”

J Gen Intern Med;7(2):145-53. 1992

Should Women have a Different Ferritin Reference Range than Men?

Women and Iron

- No physiologic reason that women should have different ranges of normal for ferritin
  - 85% of 20 year old men have ferritin over 50 ng/mL
  - 25% of 20 year old women do



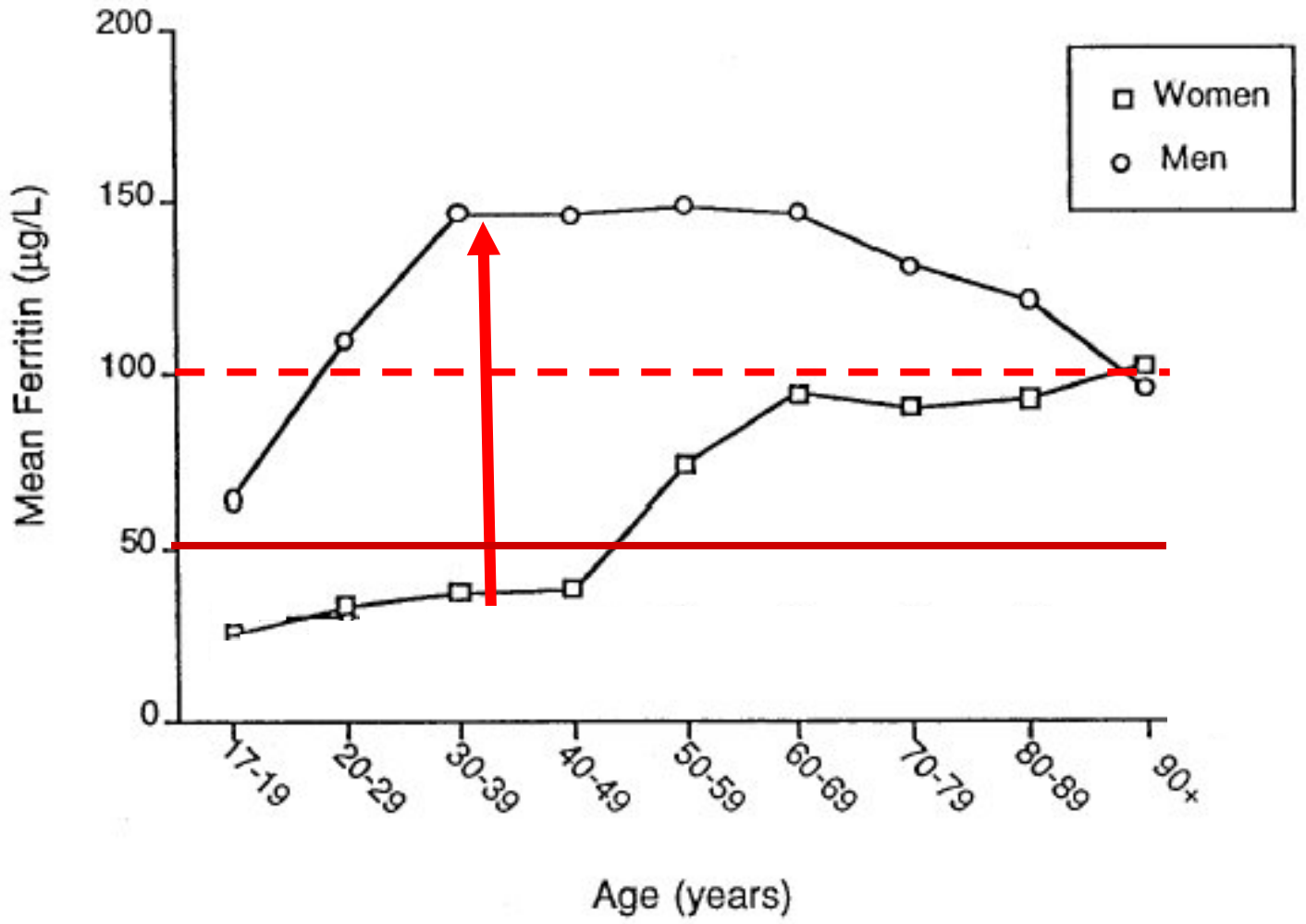
Am J Clin Nutr 54:1047, 1991

Iron Requirements

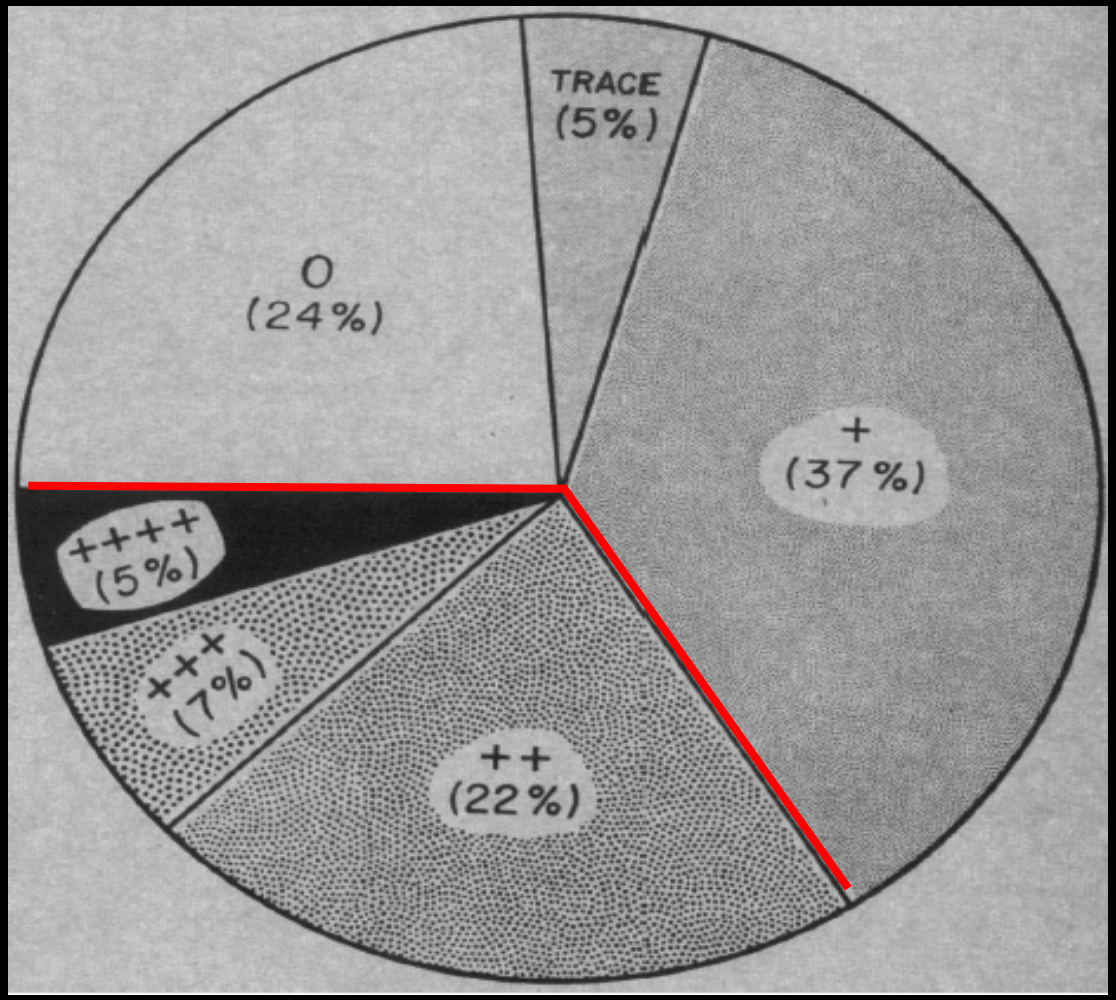
- **Men:**
  - ~ 1mg/day loss
  - RDA: 8mg iron
  - Daily intake: 16-18 mg/day
- **Women:**
  - ~2.4-3.4 mg/day loss
  - RDA: 18 mg iron
  - Daily intake: 12.6-13.5 mg/day

Sex and Ferritin

Figure 1



Most Women have Low Iron Stores



JAMA, Mar 1967; 199: 897 - 900

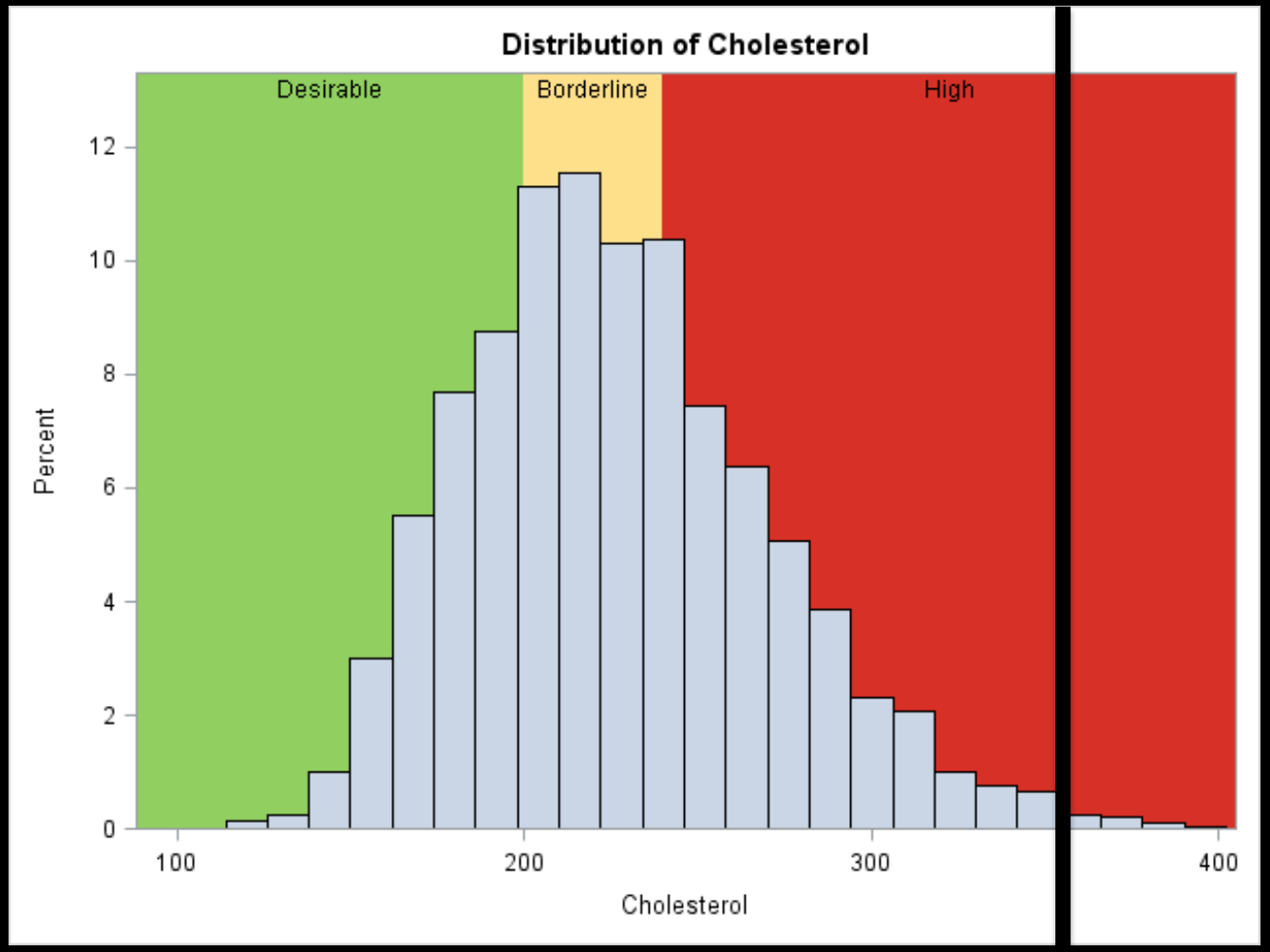
Most Women have Low Iron Stores

- Puolakka: 50% absent iron stores, 15% scant stores
- Hallberg: 34% absent iron stores
- Rybo: 31.5% absent iron stores, 14.3% scant

Acta Obstet Gynecol Scand Suppl. 1980;95:35-41
Br J Haematol. 1993;85(4):787-798
Scand J Haematol Suppl. 1985;43:5-39

Reference Ranges

- “Normal” defined 95% individuals in sample population
- Given 30-50% of women are iron deficient this will grossly underestimate presence of iron lack
- Need cut-offs that reflect physiology



https://blogs.sas.com/content/iml/2015/12/09/categories-histogram-block-plot.html

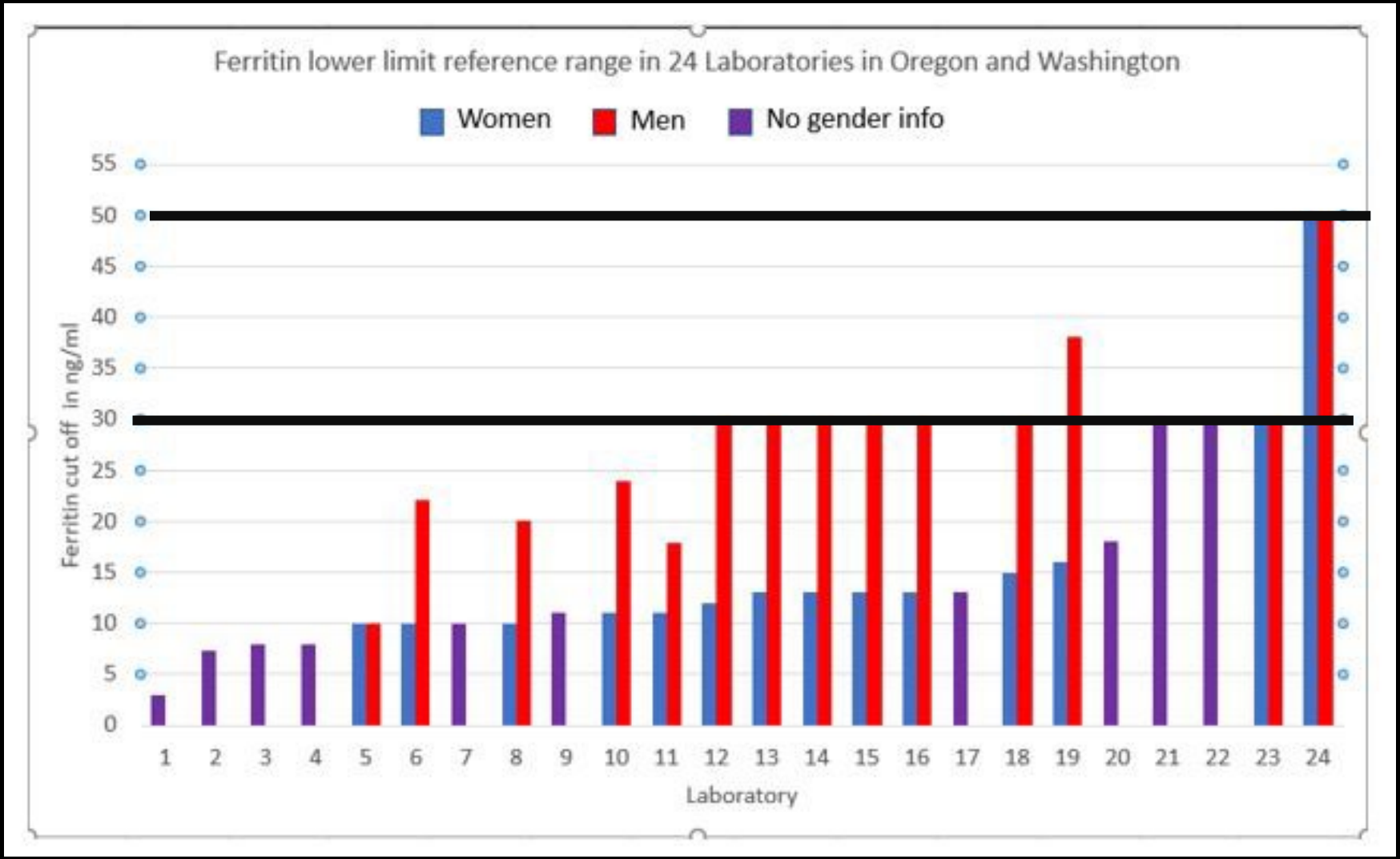
What Should the Ferritin Cut-off Be?

What is a Normal Ferritin?

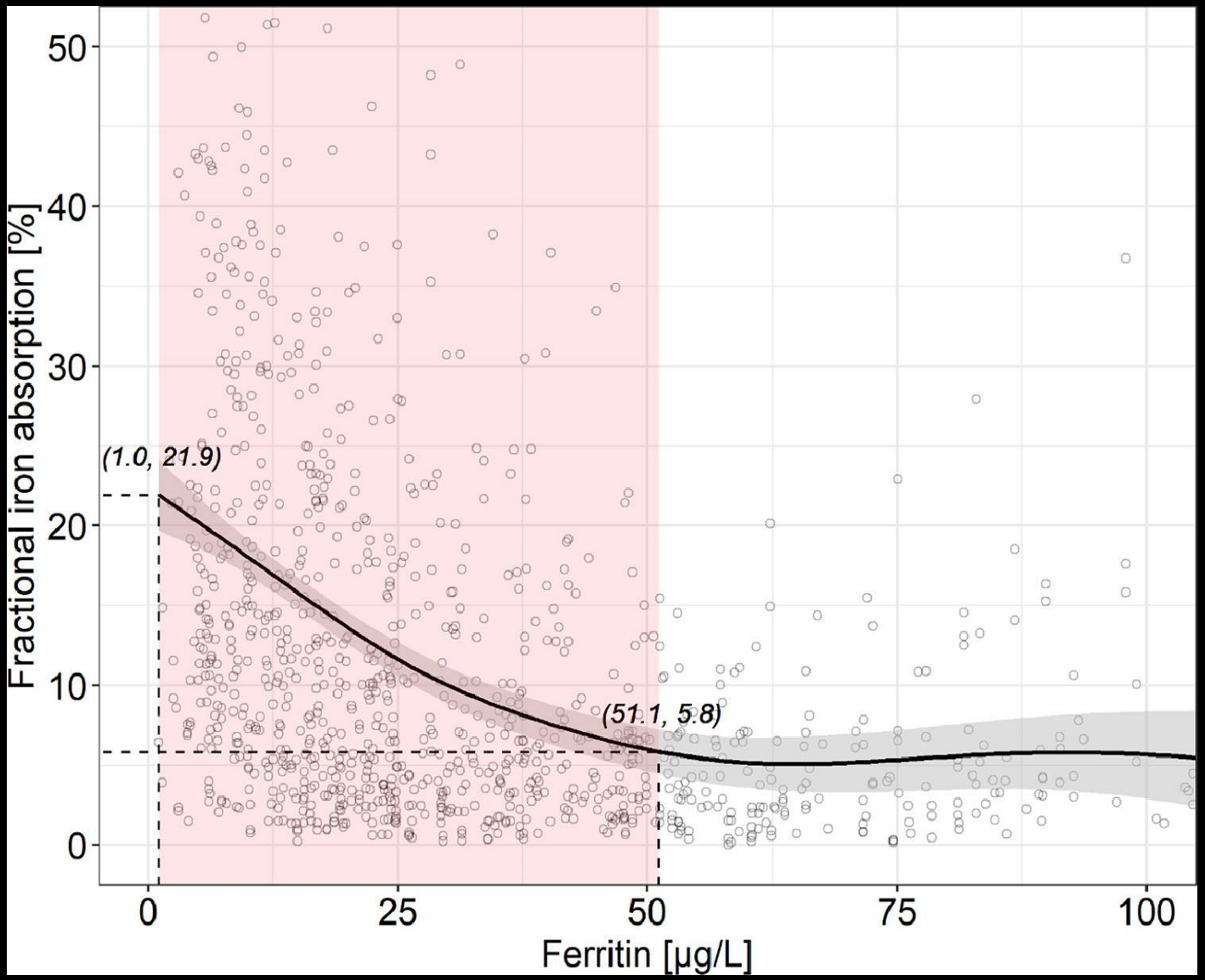
- Most labs have obscenely low normal for ferritin
  - Based on statistics and not physiology
- What should be the cut-off?

FERRITIN, SERUM Latest Range: 11-264 ng/mL

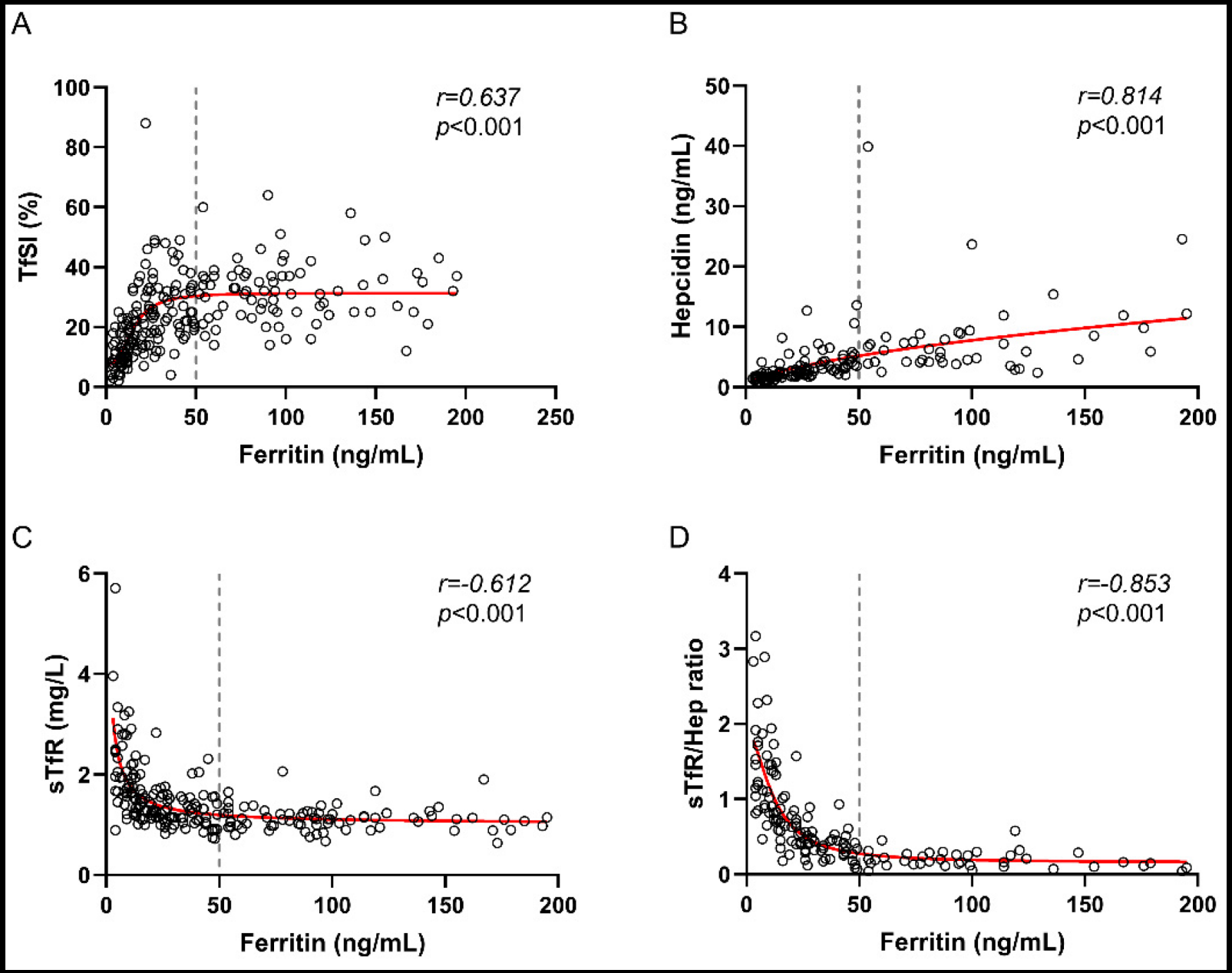
Age:	Male:	Female:
0-6 months	6-400 ng/mL	6-430 ng/mL
7-35 months	12-57 ng/mL	12-60 ng/mL
3-14 years	14-80 ng/mL	12-73 ng/mL
15-19 years	20-155 ng/mL	12-90 ng/mL
20-29 years	38-270 ng/mL	12-114 ng/mL
30-39 years	48-420 ng/mL	12-160 ng/mL
40-49 years	30-490 ng/mL	12-240 ng/mL
50 years and older	30-530 ng/mL	18-340 ng/mL



Drs Merav Sendowski, Alaska Rosenfeld



EClinicalMedicine 2021 39DOI: (10.1016/j.eclinm.2021.101052)



Nutrients 2022 Nov 10;14(22):4739

Ferritin Lower Limit

- Two RCT show treatment < 50 ng/dl improves outcomes
- GI iron absorption only returns to baseline at ferritins of 50-60 ng/dl
- 50 ng/dl natural cut-off?

BMJ. 2003 May 24;326(7399):1124
CMAJ 184:1247-1254, 2012
Am J Clin Nutr. 66(2):347-56, 1997
EClinicalMedicine Jul 31:39:101052, 2021
Nutrients 10;14(22):4739, 2022

What are the Implications?

Iron Deficiency – Common!

- Prevalence of iron deficiency
  - 12-21 yo women
- 15 µg/L: 17% (15.4%-19.2%)
- 30 µg/L: 38.6% (35.8%-40.9%)
- 50 µg/L: 77.5% (75.7%-79.3%)

- JAMA. 2023;329(24):2191-2193.

Most Women have Low Iron Stores

	< 12 ng/dl	<20 ng/dl	< 35 ng/dl	< 50 ng/dl
Women Athletes	6.8%	23.3%	52.1%	72.8%
Control Women	9.2%	25.9%	57.4%	78.8%
Male Athletes	0.8%	3.5%	14.8%	28.9%
Control Men	0.4%	2.4%	9.3%	19.3%

J Sci Med Sports 23:554, 2020

Implications

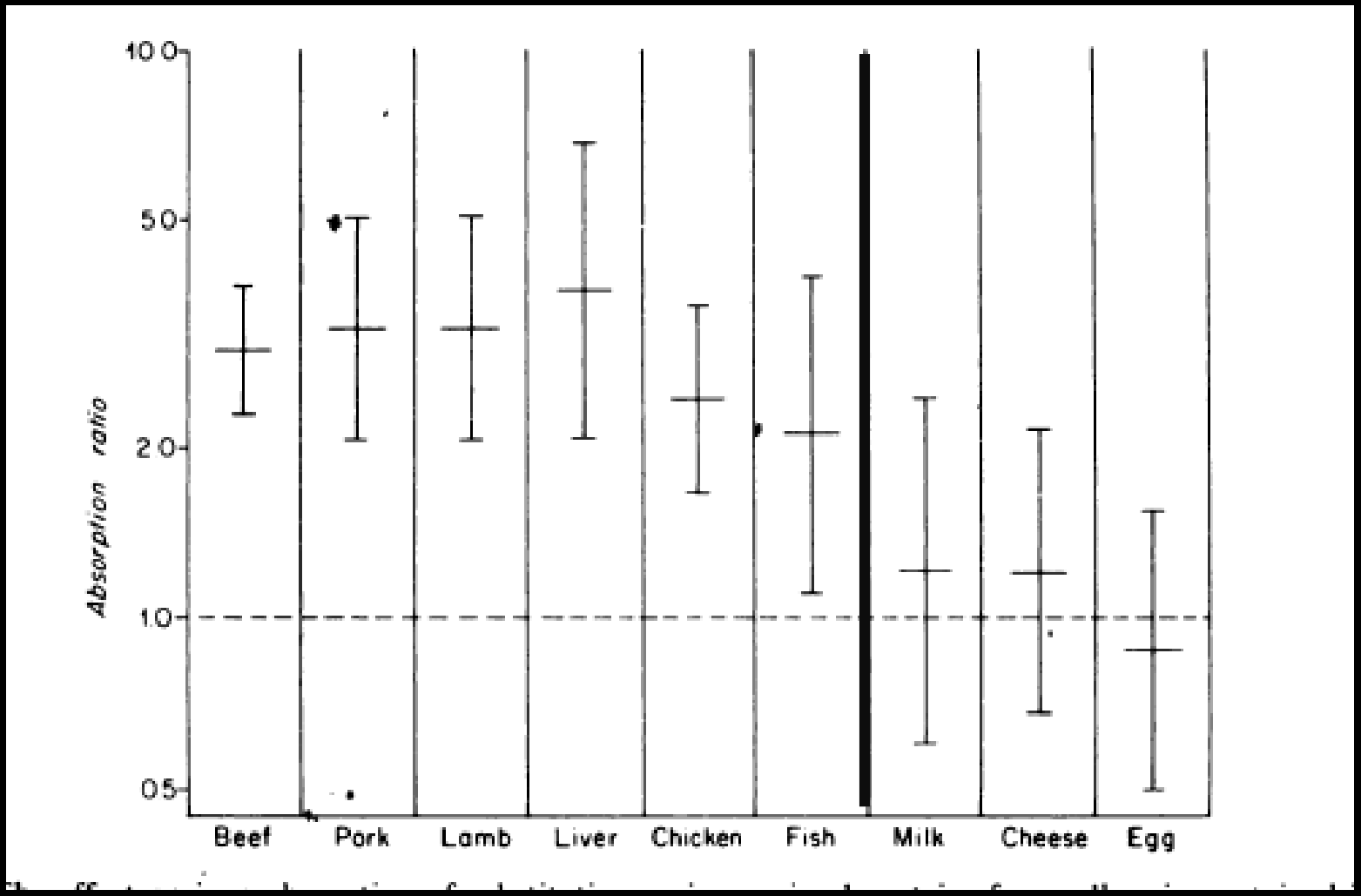
- Under recognition of iron deficiency
- Trivialization of symptoms
- Under treatment
- Denial of treatment

IF YOU WANT YOUR CHILDREN
TO BE
HEALTHY & STRONG

GIVE THEM
IRON BITTERS

Dietary Iron

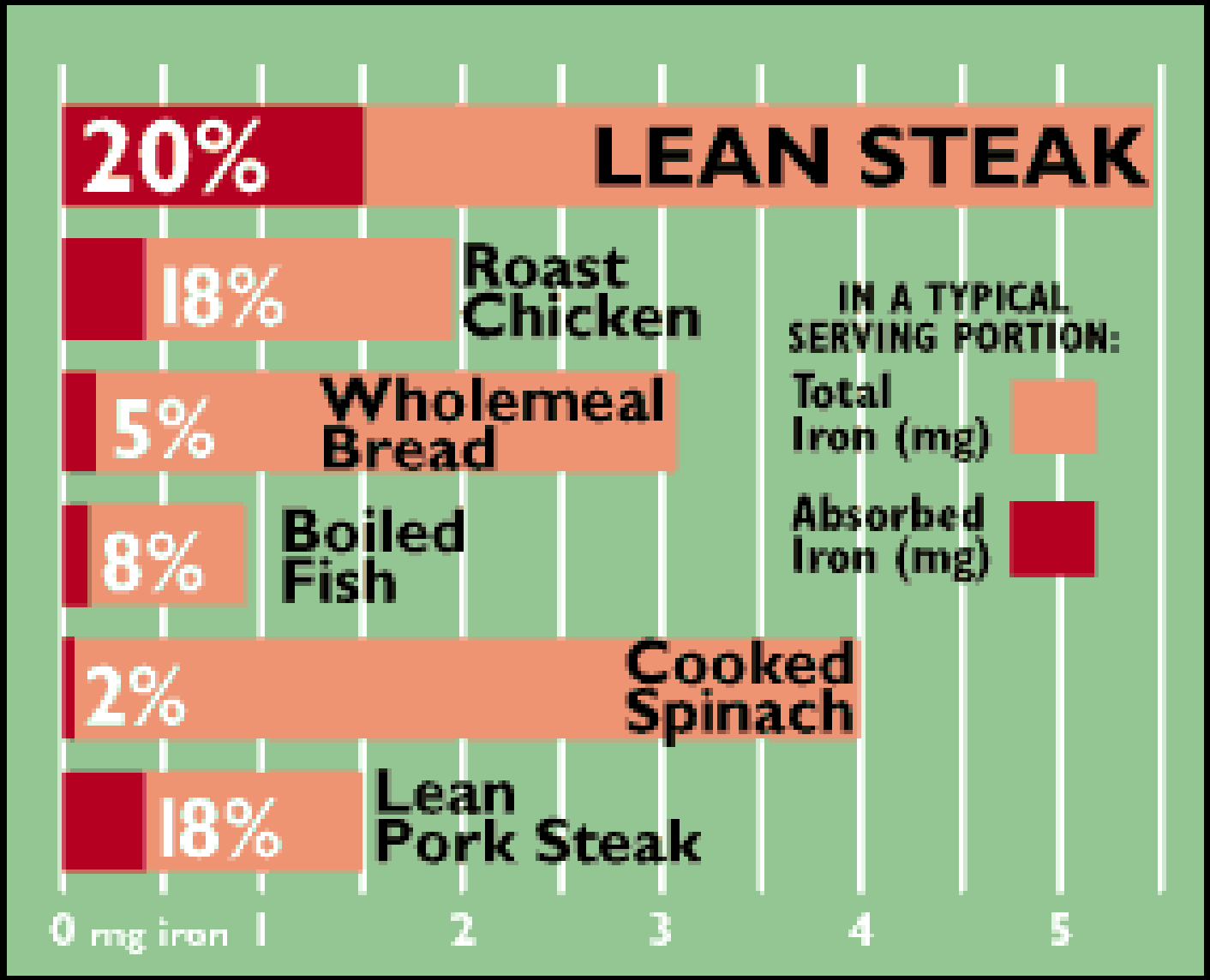
- Heme iron 10x better absorbed than non-heme iron
- Meat protein improves iron absorption



Am J Clin Nutr **August**
1976 vol. 29 no. 8
859-867

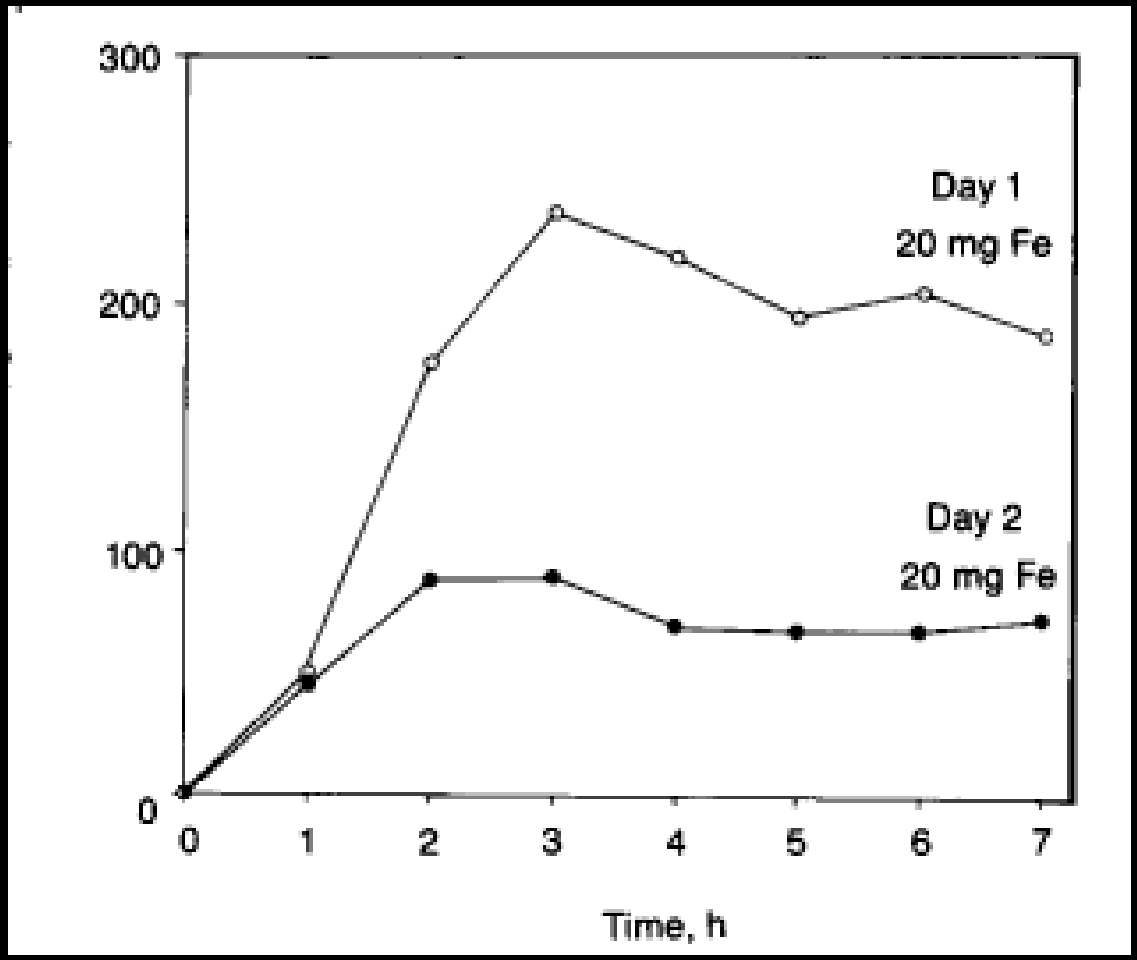
Dietary Iron

- Calcium, fiber can block iron absorption
  - Overcome by vitamin C
- Tea decreases 75-80%
- Coffee decreases 60% (5 oz!)


20%
LEAN STEAK
18%
Roast Chicken
5%
Wholemeal Bread
8%
Boiled Fish
2%
Cooked Spinach
18%
Lean Pork Steak
IN A TYPICAL SERVING PORTION:
Total Iron (mg)
Absorbed Iron (mg)
0 mg iron
1
2
3
4
5

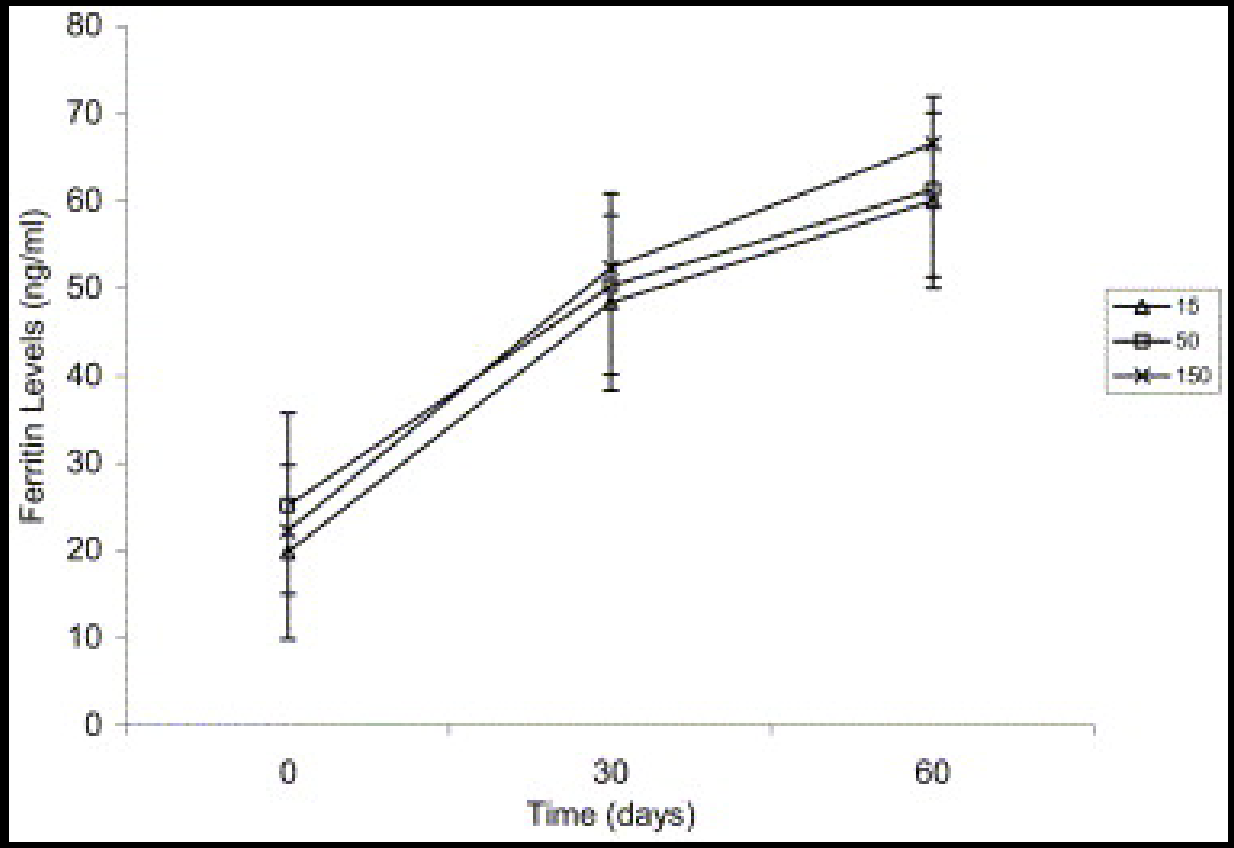
Oral Iron Pills

- Gut can only absorb a limited amount of iron
- Maxed out at ~ 10mg



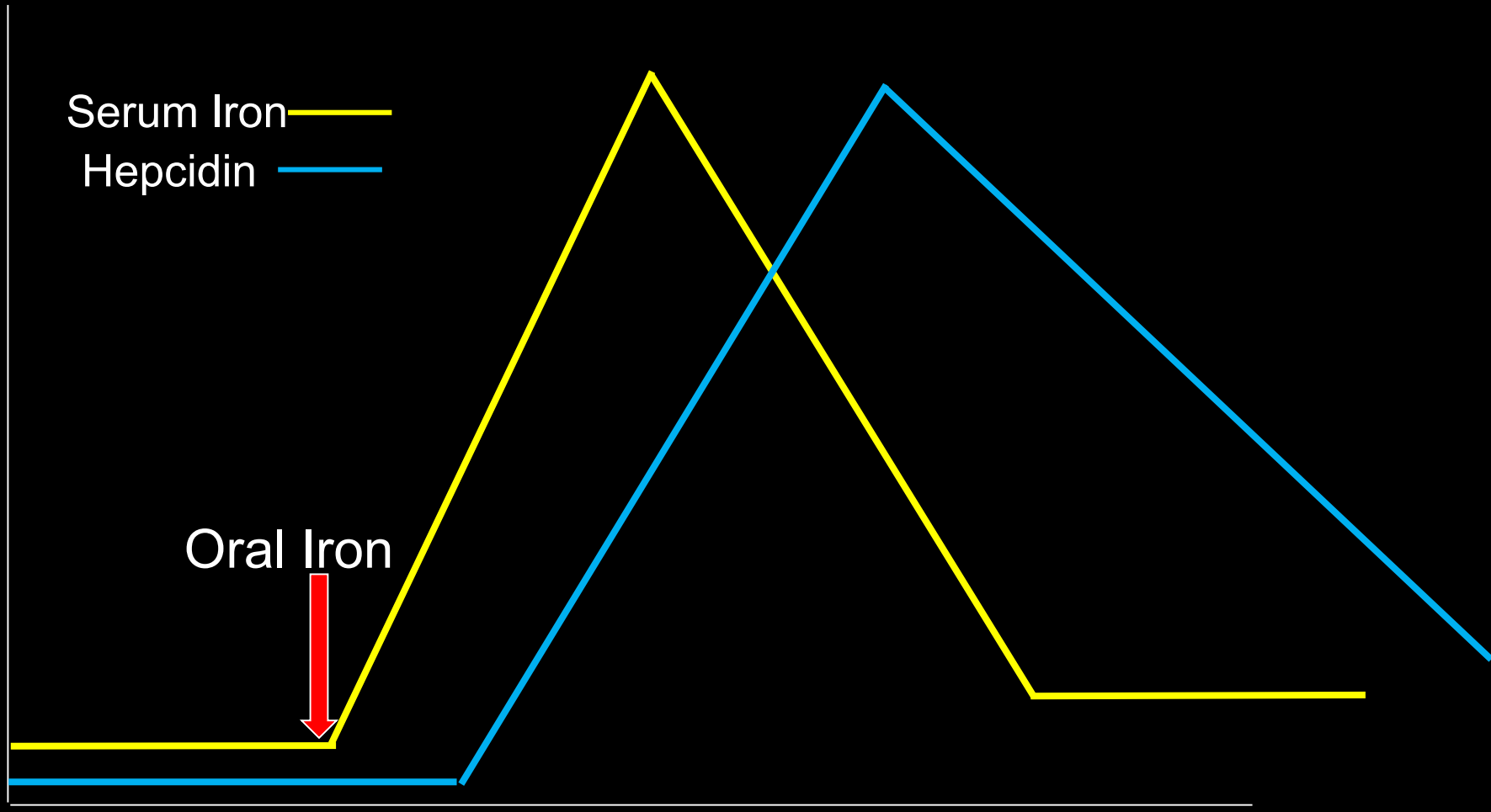
(*Arch Intern Med* 1987;147:489-491)

15 vs 50 vs 150mg Oral Iron



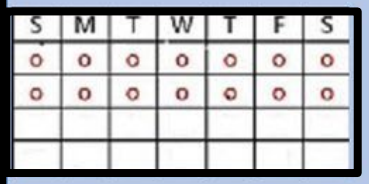
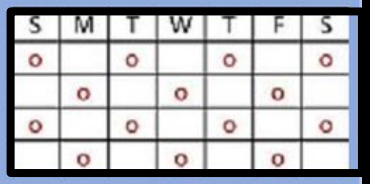
Am J Med. 2005 Oct;118(10):1142-7.

Hepcidin Response to Iron



Does Alternate-Day Dosing of Oral Iron Therapy Improve Iron Absorption?

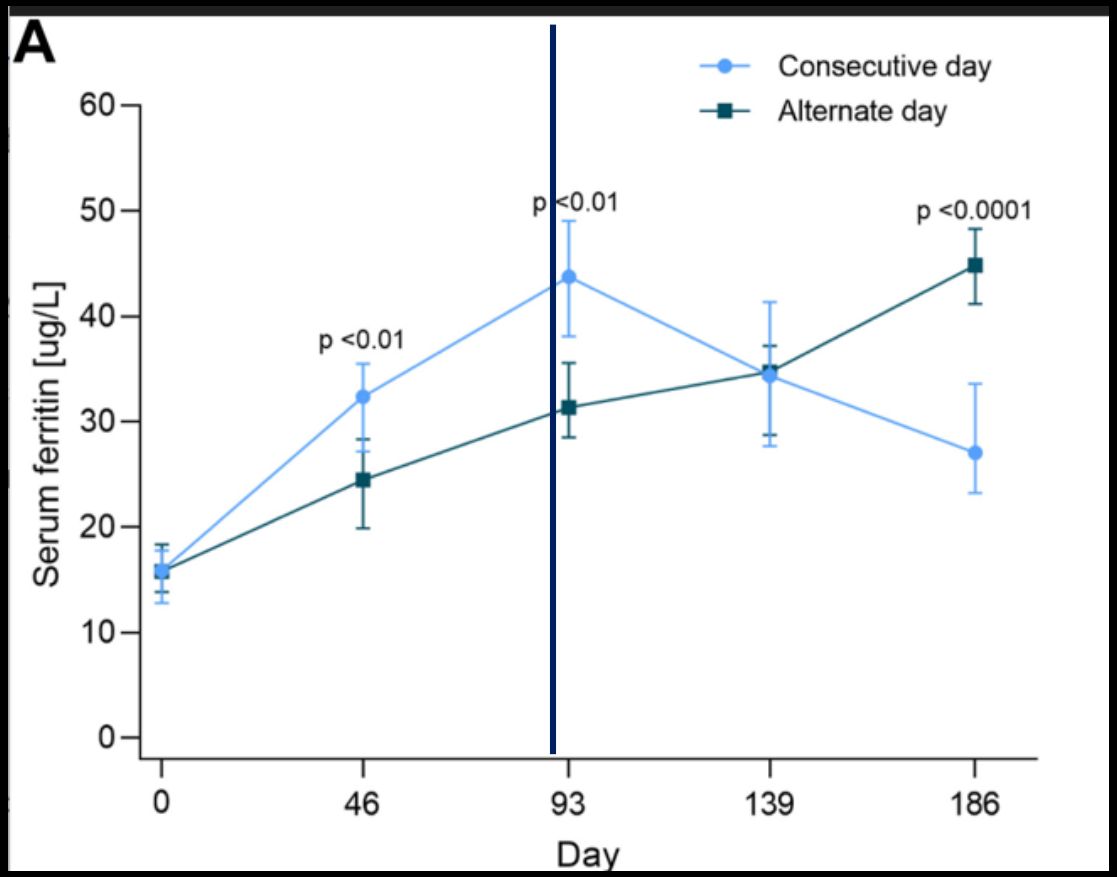
Allan S. Brett, MD, reviewing Stoffel NU et al. *Lancet Haematol* 2017 Oct 9

Daily Dosing 14 days		Alternate-Day Dosing 28 days
		
16%	Fractional Absorption	21%
131 mg	Total Absorption	175 mg

Comment: Fractional absorption was better with alternate-day dosing, but total absorption would still have been better with daily dosing if that group had received 28 days of iron. Alternate-day dosing likely enhanced gastrointestinal tolerability.

NEJM Journal Watch

But 28 days of daily iron = 262 mg absorbed



EClinicalMedicine. 2023 Nov 3;65:102286

Alternate Day Iron

- Better tolerated
- Slower to build up iron stores
- Start with everyday then move to alternate day if not tolerated

Pregnancy

- Iron deficient singleton pregnancy
- Oral iron 30mg
  - 160 – q day
  - 164 – BID
- No difference in outcomes
  - Blood counts or ferritin rise
- J Perinatology 37:782, 2017

Oral Iron Pills

- Years of studies have shown that the best iron preparation is….

Oral Iron Pills

….the one that the patient can tolerate

- No consistent difference in any brand
- Many patients can’t tolerate any pill on an empty stomach
  - Ok with meals

What I Do

- Cheapest iron pill
  - Ferrous sulfate
- Once a day with meals
  - Vitamin C 500
  - No tea or coffee for one hour after
- If intolerant can try lower dose
  - iron bisglycinate 25 mg

Response to Oral Iron

- Best predictor of response is rise in hemoglobin by 1 g/dl in two weeks

At What Ferritin are Iron Stores Replete?

- GI iron absorption goes back to backline only at ferritin of 60 ng/mL
- Falling from 70 to 35 ng/mL muscle loss iron
- Alopecia and restless legs seen at < 100 ng/mL
- Maybe 50-100 ng/mL a reasonable goal for repletion

Etiology of Iron Deficiency

- All iron deficiency has a cause!
- Blood loss must always be assumed!

Contributors to Iron Deficiency

- GI
  - NSAIA 10-15%
  - Colon Ca 5-10%
  - Gastric Ca 5%
  - Ulcers 5%
  - Angiodysplasia 5%
  - Esophagitis 2-4%
  - Esophageal Ca 1-2%
- Non-GI
  - Menstruation 20-30%
  - Celiac disease 4-6%
  - Bariatric surgery 1%

NSAIDS/ASA

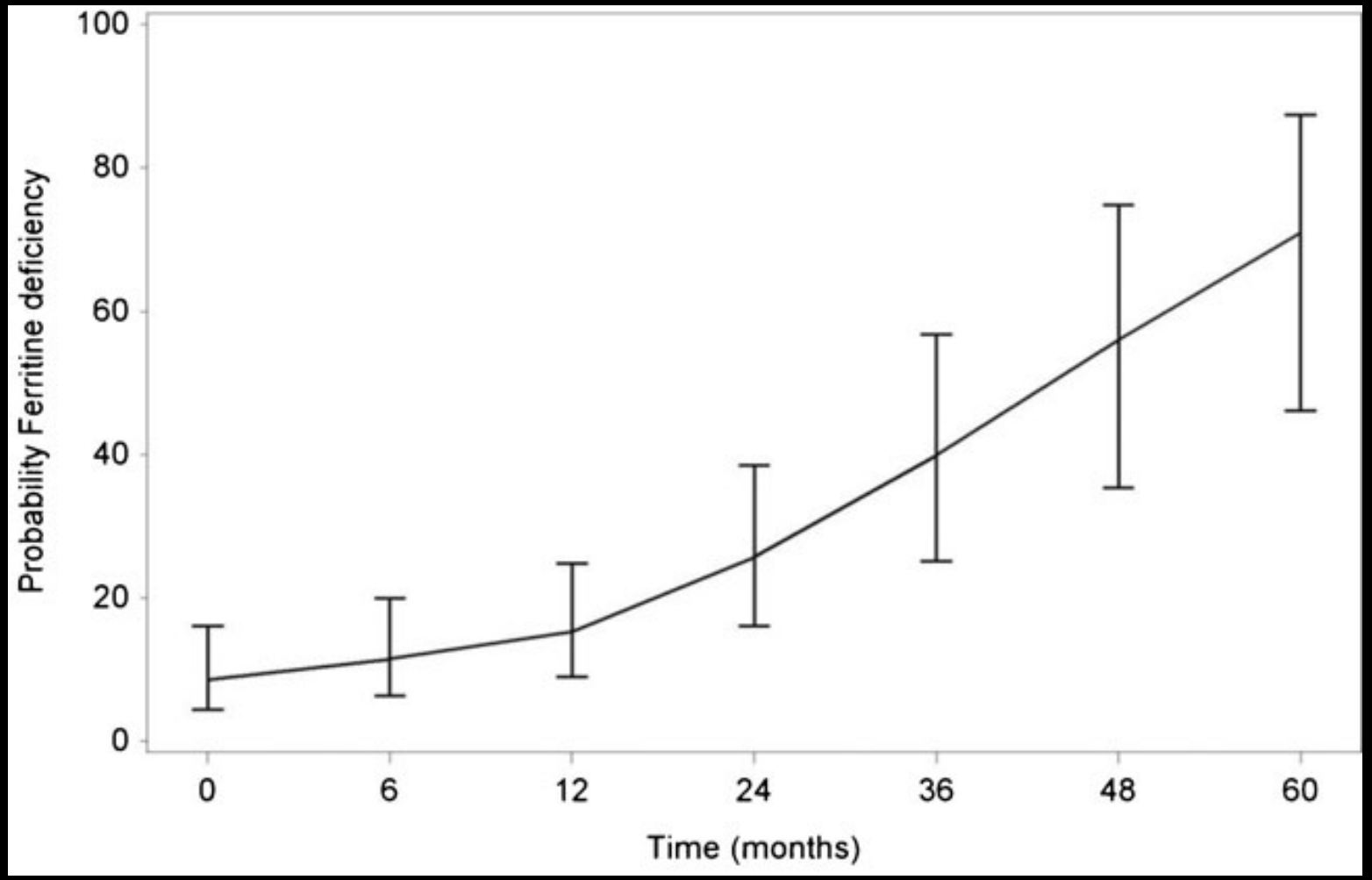
- Multiple mechanisms
  - GI bleeding
  - Small bowel enteropathy
- Even a single 81mg ASA enough to lead to iron deficiency

Celiac Disease

- Common in whites
- Mechanism
  - Blood loss
  - Villous atrophy
  - Inflammation
- Even with gluten free diet may have persistent iron deficiency

Obesity

- Decrease iron absorption
  - Increased hepcidin
- Obesity in pregnancy
  - 43% less iron absorption
  - 17% less fetal iron transfer
  - Am J Clin Nut 115:116, 2022



Gesquiere et al, *Obesity Surgery* 2014;24:56-61

HMB

- European survey
  - 27.2% with 2 or more HMB symptoms
  - 46% never consulted physician
- Runners
  - 22% HMB
    - 48% with severe iron deficiency
- Athletes
  - 43.5% HMB
    - 51% with iron deficiency

Int J Ob GYN 128:196, 2015, Anaeth 76(s4)56, 2021, Medicine 100:1, 2021

Periods

1. How long do your periods last?
2. How often do you change your pad/tampon?
3. Do you have/have you had iron deficiency?
4. Do you pass clots larger than a quarter in diameter?

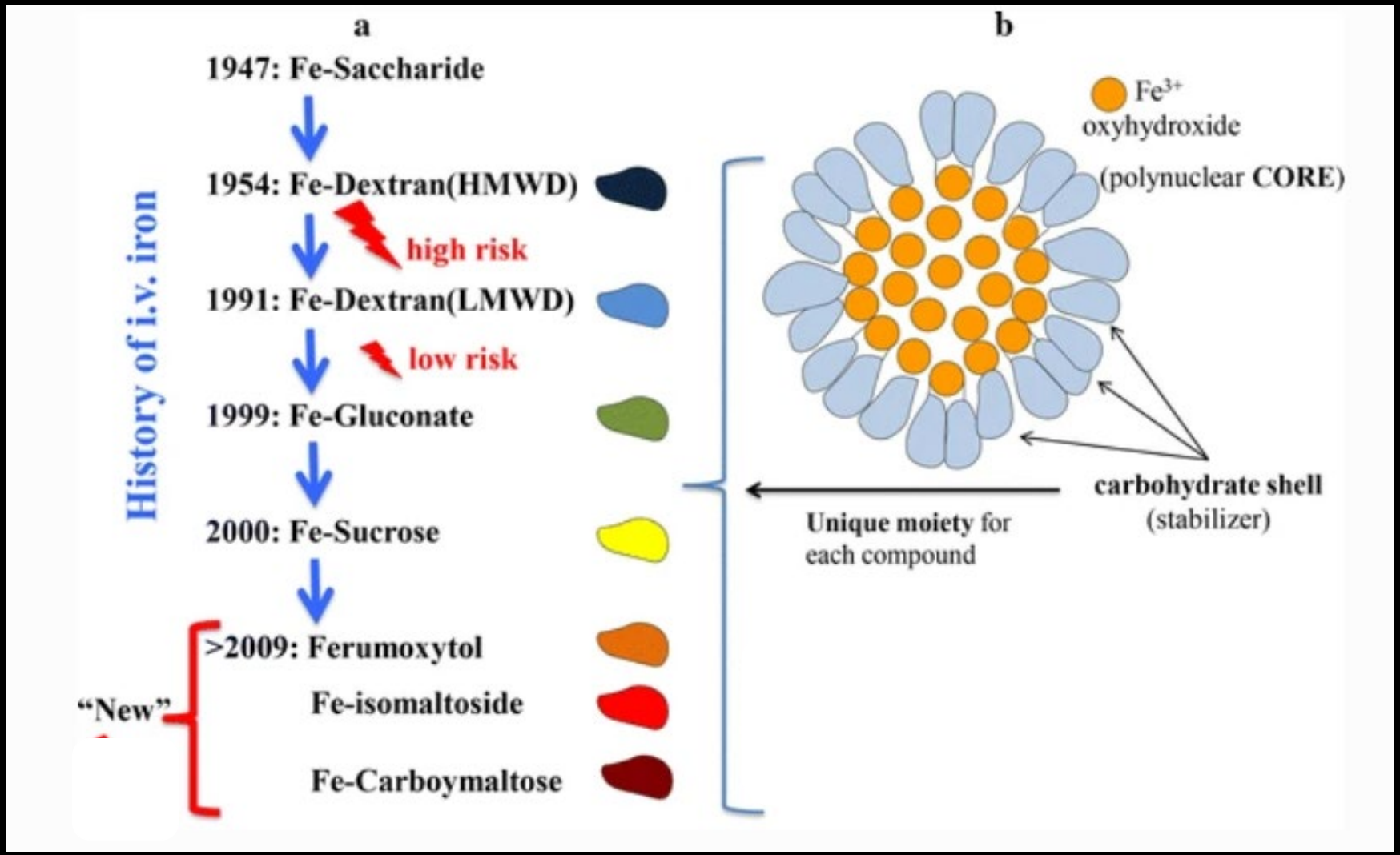
Dr Samuelson-Bannow

Iron Deficiency: GI Evaluation

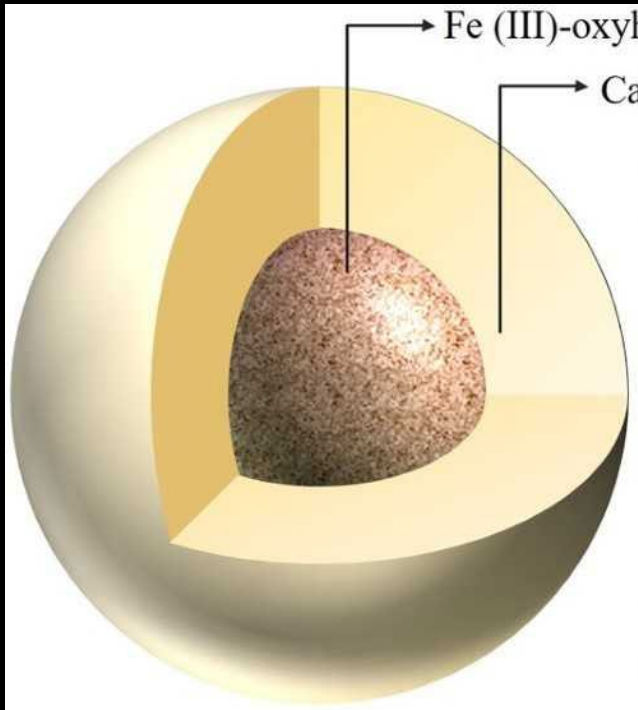
- Most patients with identifiable source of GI blood loss
- Very high number with tumors
- Most common cause of missed cancer diagnosis
- Who to evaluate?
  - 2021 AGA guidelines “any iron deficiency anemia”

What is IV Iron

- Free iron very toxic
- IV iron preparation “coated” with carbohydrate
- Uptaken by macrophages to increase iron stores

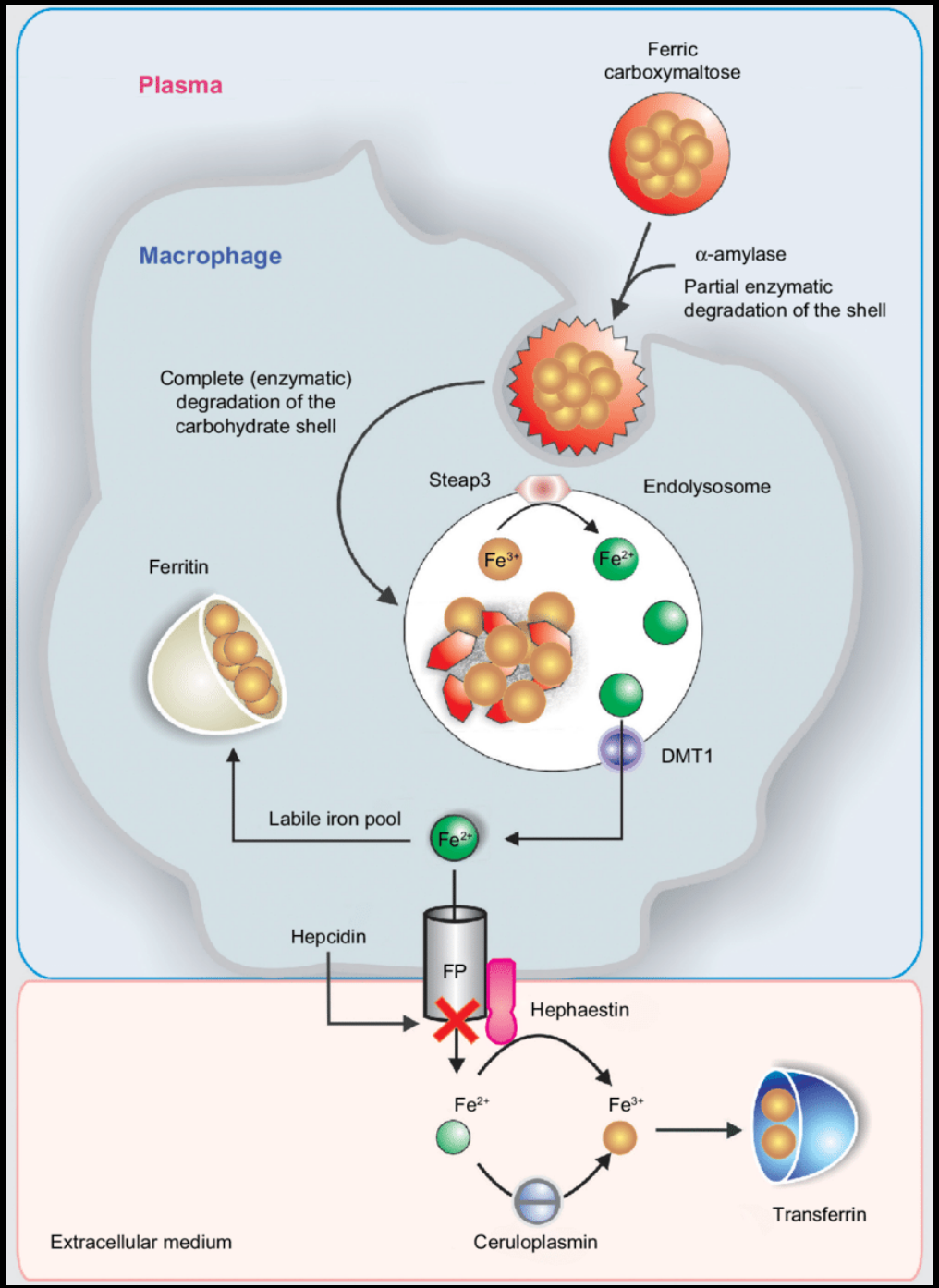


International Journal of Hematology volume 107, pages16–30(2018)



Trade name	Carbohydrate shell
InFeD	Low molecular weight dextran
Ferrlecit	Gluconate
Venofer	Sucrose
Ferinject	Carboxymaltose
FeraHeme	Polyglucose sorbitol carboxymethyl ether
Monofer	Isomalto-oligosaccharides
Maltofer	Polymaltose

Nanomedicine . 2020 Jun;26:102178.


Plasma
Ferric carboxymaltose
Macrophage
α-amylase
Partial enzymatic degradation of the shell
Complete (enzymatic) degradation of the carbohydrate shell
Steap3
Endolysosome
Ferritin
Fe3+
Fe2+
DMT1
Labile iron pool
Fe2+
Hepcidin
FP
Hephaestin
Fe2+
Fe3+
Transferrin
Extracellular medium
Ceruloplasmin

Parental Iron Therapy

- When to use
  - Refractory to oral iron
  - Unable to take oral iron
  - Cannot keep up with blood loss
    - Bariatric surgery
    - Inflammatory bowel disease
    - Chronic GI bleeding

Inflammatory Bowel Disease

- Never give oral iron!
- Worse
  - Microbiome
  - Quality of life
  - Inflammation
  - Most likely won't work!

Pregnancy

- Meta-analysis 11 studies
- IV iron
  - Achieved target Hgb OR 2.66
  - Increased Hgb after 4 weeks
  - Less adverse reactions OR 0.35
- Am J Perinatol 2019 Mar;36(4):366-376

Safety

- Minor infusion reactions common (~1-4%) but true anaphylaxis very rare
- OHSU: 35,737 iron infusions
  - ~ 3.9% minor reactions
  - ~ 1: 18,000 major reactions
  - Reactions 23x with premeds

JAMA Netw Open. 2022;5(3):e224488

Reactions

- Complement mediated pseudo-allergy
- Drug non-specific activated complement
  - Similar to rituximab etc.
- True anaphylaxis very rare
  - Negative tryptase > 300 reactions

Implication

- No value test dose
- Premedication often doesn't help
- Diphenhydramine makes things worse
- Treat as infusion reaction not allergy
- Studies show risk same with all iron preparations

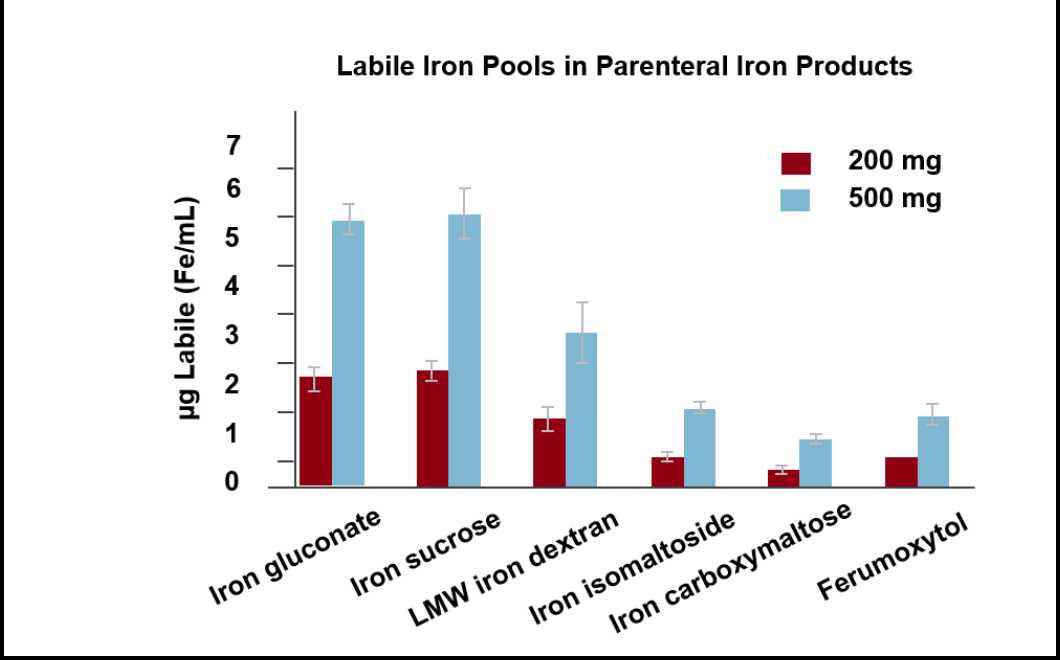
Dosing IV Iron

- Replacement formulas inaccurate
- Give ~1000mg
  - Recheck in 4 weeks
  - If severe anemia recheck in two weeks

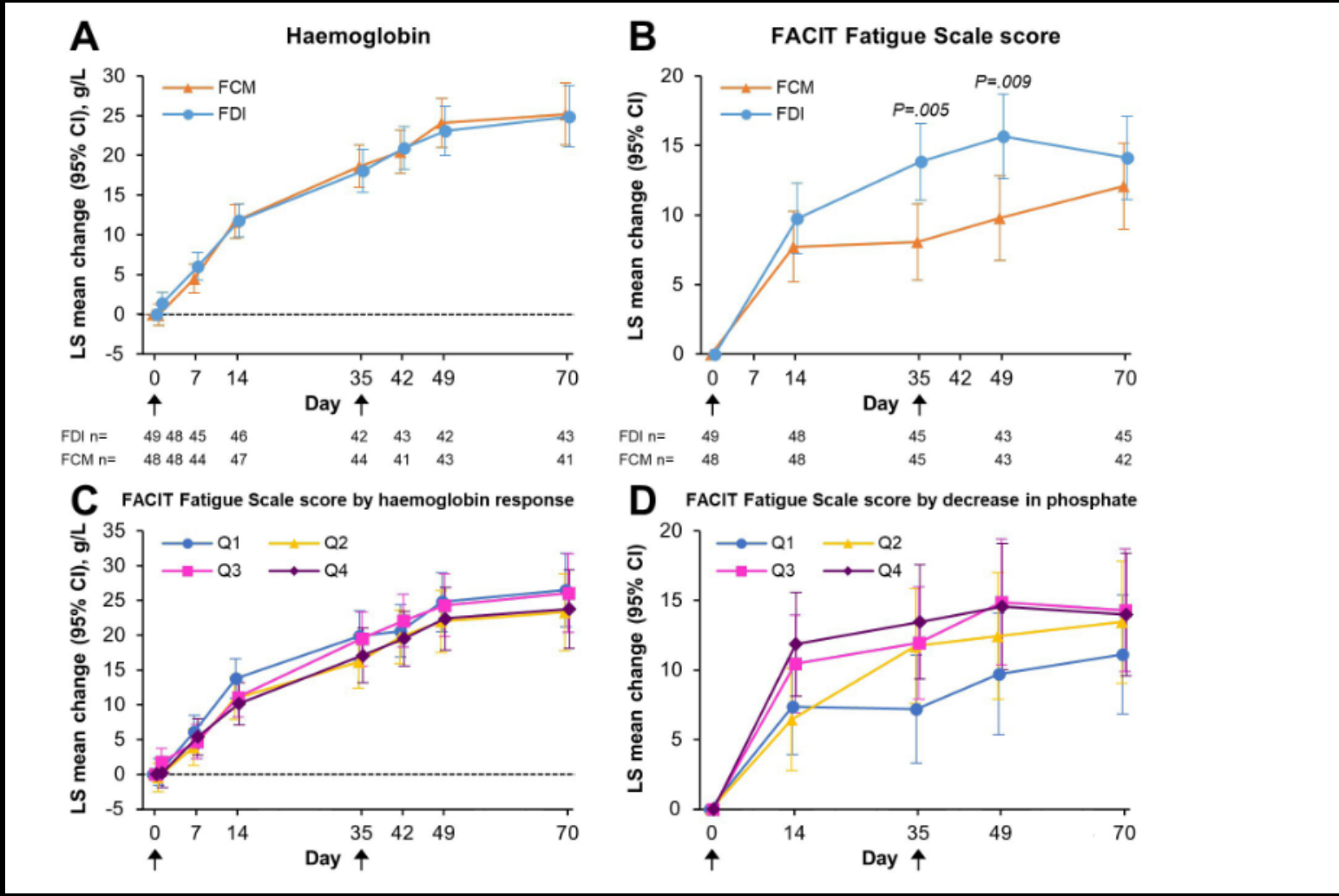
Iron Preparations

- Iron salts overrated
  - Venofer/Ferrlecit
  - Not safer and more infusions/reactions
- Single dose therapy best
- Ferric carboxymaltose
  - High incidence hypophosphatemia
  - <2.0 mg/dl: 50.8%: <1.3 mg/dl, 10.0%
  - Osteomalacia reported

Labile Iron Content in Parenteral Iron Products



Used with permission from: Jahn MR, Andreasen HB, Fütterer S, Nawroth T, Schünemann V, Kolb U, Hofmeister W, Muñoz M, Bock K, Meldal M, Langguth P. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. Eur J Pharm Biopharm. 2011 Aug;78(3):480-91.



Gut. 2023 Apr;72(4):644-653

IV Iron Dosing

Formulation	Recommended Dose
LMW Iron dextran	1000mg over 1 hr
Ferumoxytol	510 x 2 or 1020 over 15 min
Ferric carboxymaltose	1000mg over 15 min or 750 mg x 2
Iron isomaltoside	1-2000 mg over 15 min

Refractory Iron Deficiency

- Patient is “refractory” to IV iron
- Not getting enough iron
- Frequent ferritin checks
  infusions
- Goal ferritin > 100

Remember!

- Iron is good!
- Ferritins > 50 ng/mL are good
- Oral iron
  - One pill/day
  - With vitamin C
  - With meat if feasible