Erythropoietin and the Treatment of Anemia in ESRD

Introduction

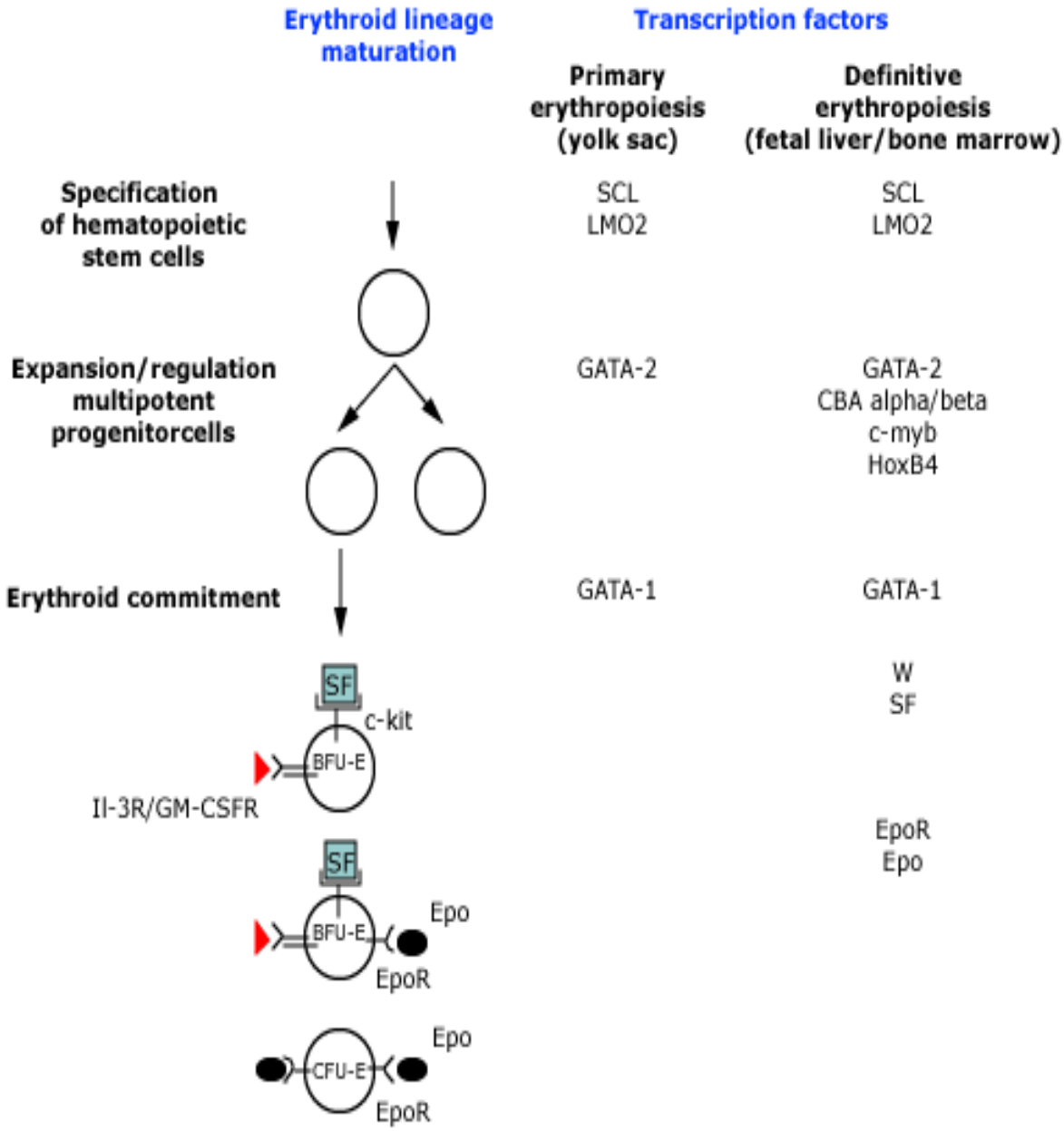
- If left untreated, the anemia of CKD is associated with **reduced cardiac function**, decreased cognition/mental acuity, fatigue, weakness, lethargy, anorexia, and sleep disturbances. In addition, anemic patients commonly lack the stamina needed to perform normal daily activities or to work.
- Anemia may also, in part, underlie the **high cardiovascular mortality** observed in the CKD population as a low hematocrit (Hct) is an independent risk factor for death in this population. In one study a 3 % decrease in Hct was associated with a 7 % increased risk of death.
- This is likely due to an **increase in left ventricular hypertrophy (LVH) The result of untreated anemia is maladaptive cardiac remodeling**. Every 1 g/dL decrease in hemoglobin (Hb) is associated with a 6 percent increase in risk of LVH.

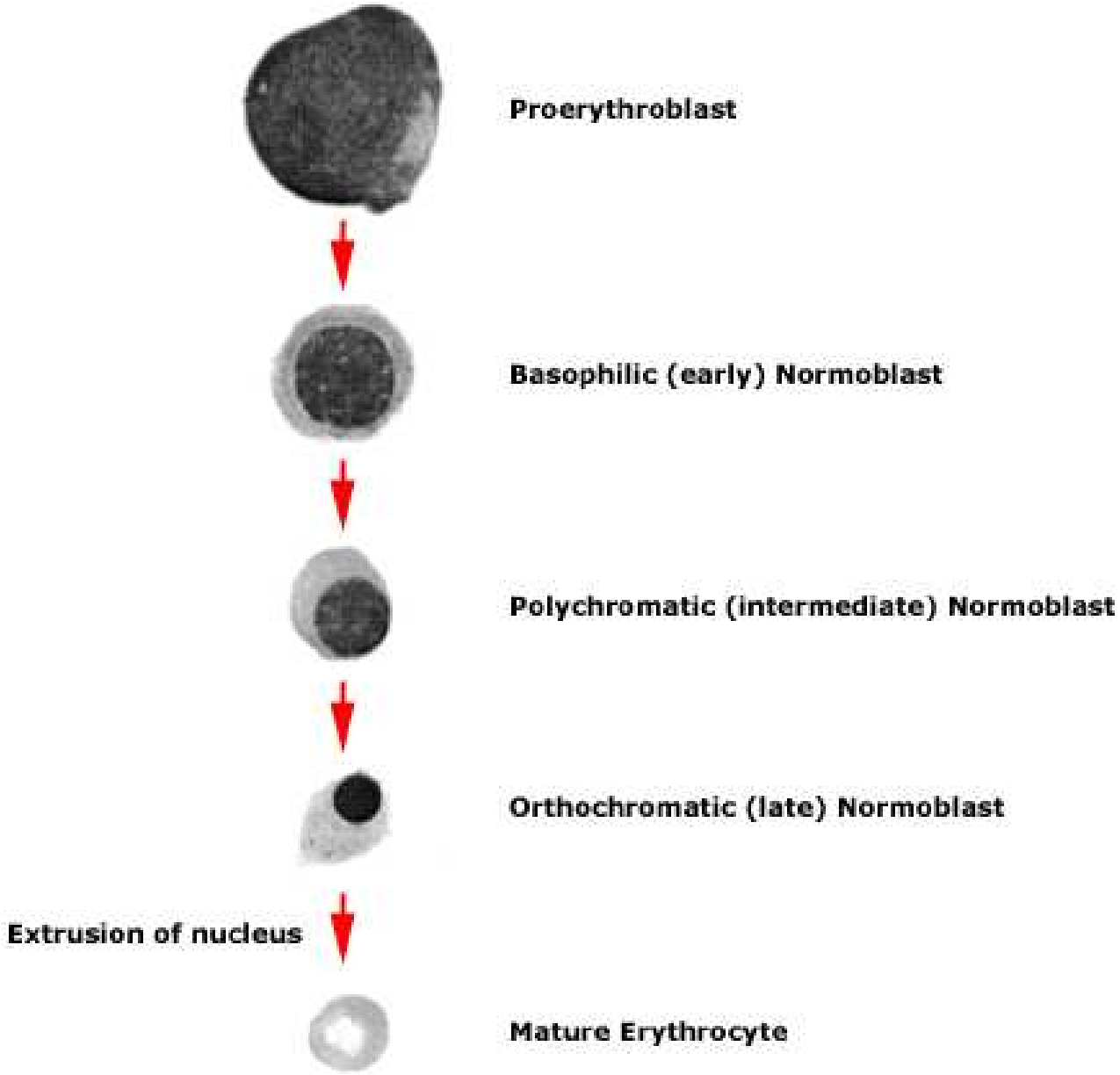
Outline

- General review of erythropoiesis
- Anemias associated with renal disease
- Erythropoietin- Indications, dosing, route of administration, side effects
- Pure Red Blood Cell Aplasia due to anti-EPO antibodies
- Erythropoietin Resistance
- Darbepoetin alfa
- Review of current EPO protocol for home patients
- Review of EPO calculator

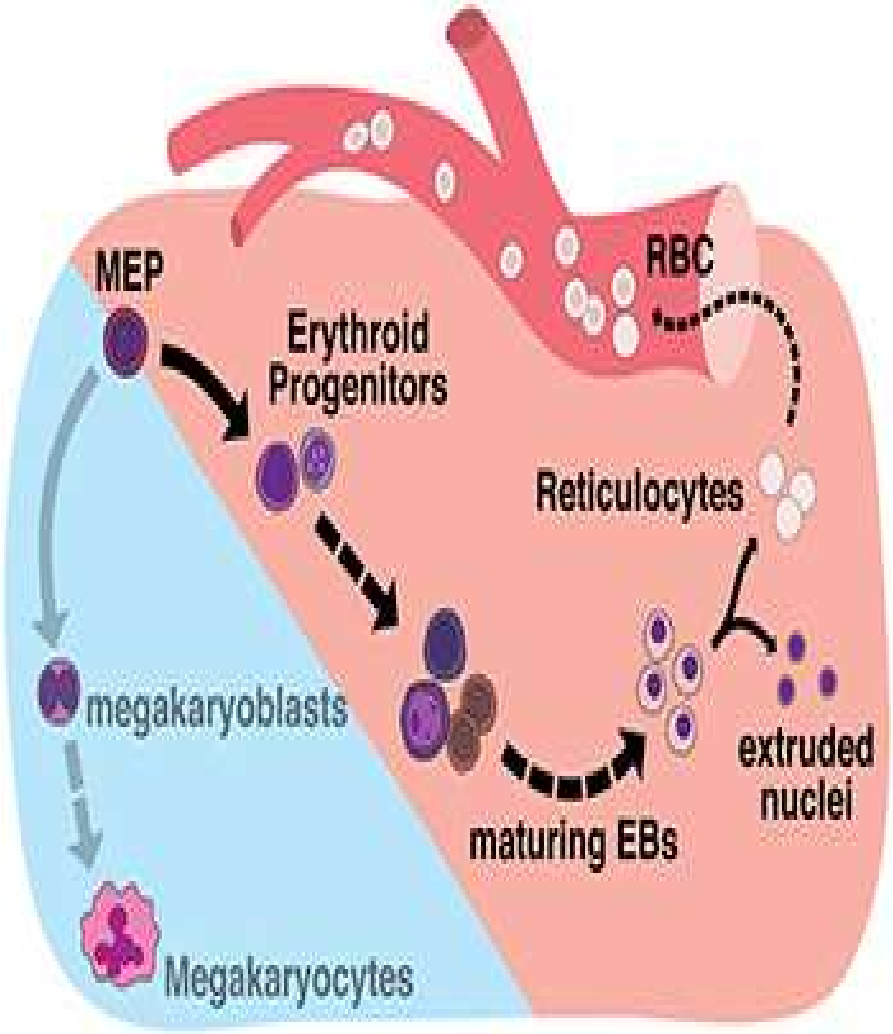
Red Blood Cell Life Cycle

- RBC's (erythrocytes) are produced through the process of erythropoiesis in the bone marrow.
- The process involves many factors and EPO plays an integral role.
- EPO is a hormone produced in the kidney by cells that sense low tissue oxygenation
- It is produced and travels to the bone marrow where it differentiates 2 progenitors called BFU-E and CFU-E into normoblasts.
- Once the nucleus is lost it is called a reticulocyte or immature RBC


Erythroid lineage maturation
Transcription factors
Primary erythropoiesis (yolk sac)
Definitive erythropoiesis (fetal liver/bone marrow)
Specification of hematopoietic stem cells
SCL
LMO2
SCL
LMO2
Expansion/regulation multipotent progenitorcells
GATA-2
GATA-2
CBA alpha/beta
c-myb
HoxB4
Erythroid commitment
GATA-1
GATA-1
SF
c-kit
BFU-E
Il-3R/GM-CSFR
W
SF
SF
BFU-E
Epo
EpoR
EpoR
Epo
CFU-E
Epo
EpoR

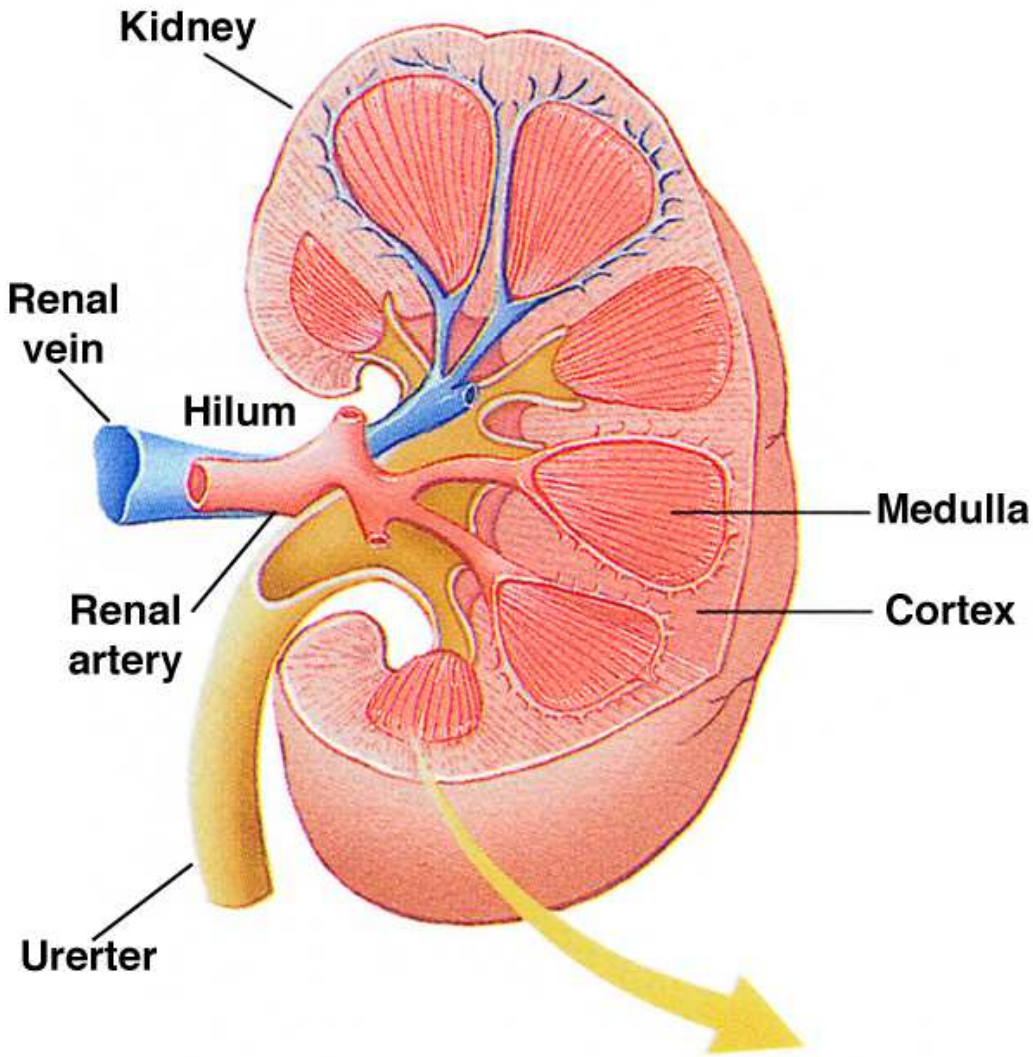

Proerythroblast
Basophilic (early) Normoblast
Polychromatic (intermediate) Normoblast
Orthochromatic (late) Normoblast
Extrusion of nucleus
Mature Erythrocyte

- The reticulocyte stays about 3 days in the bone marrow and one day in the blood before it is fully matured
- Normal retic count is 0.5 – 2% and the bone marrow must produce 50,000 retics/microL of blood each day or anemia will occur.
- High levels of EPO will increase production greatly
- After about 110-120 days the RBC is removed from circulation by macrophages sensing that the cell is aged.

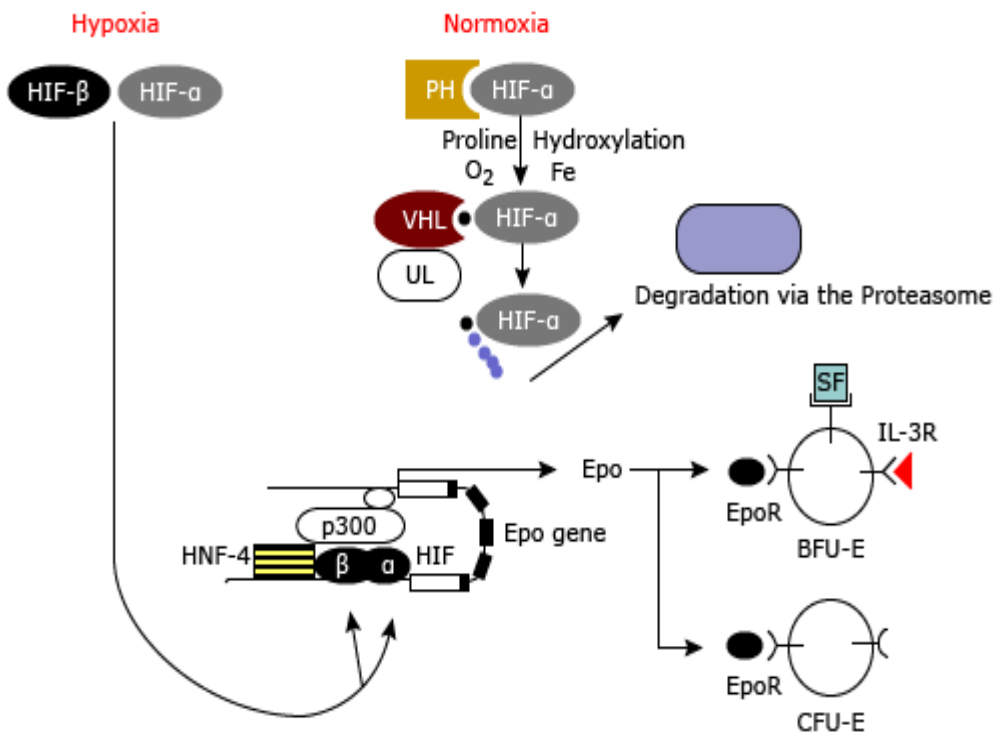

MEP
Erythroid
Progenitors
RBC
Reticulocytes
megakaryoblasts
maturing EBs
extruded
nuclei
Megakaryocytes

The Kidney and EPO Physiology

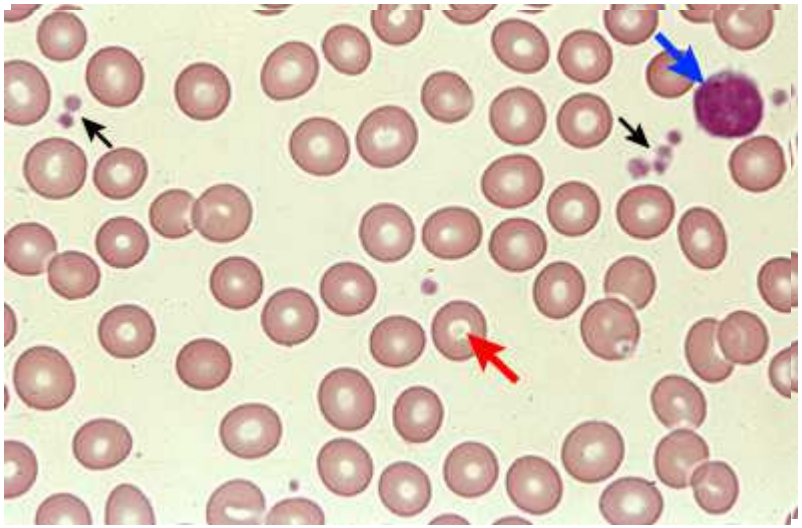
- The kidney is the main site of EPO production.
- The interstitial cells positive for EPO mRNA are found in the deep cortex and outer medulla in the unstimulated kidney.
- With increasing anemia the number of positive cells increase and spread to the superficial cortex.


Kidney
Renal vein
Hilum
Medulla
Renal artery
Cortex
Urerter

- Epo is not stored in the kidney and is released as it is formed
- Transcription of the EPO gene is regulated by a Hypoxia-Inducible Factor

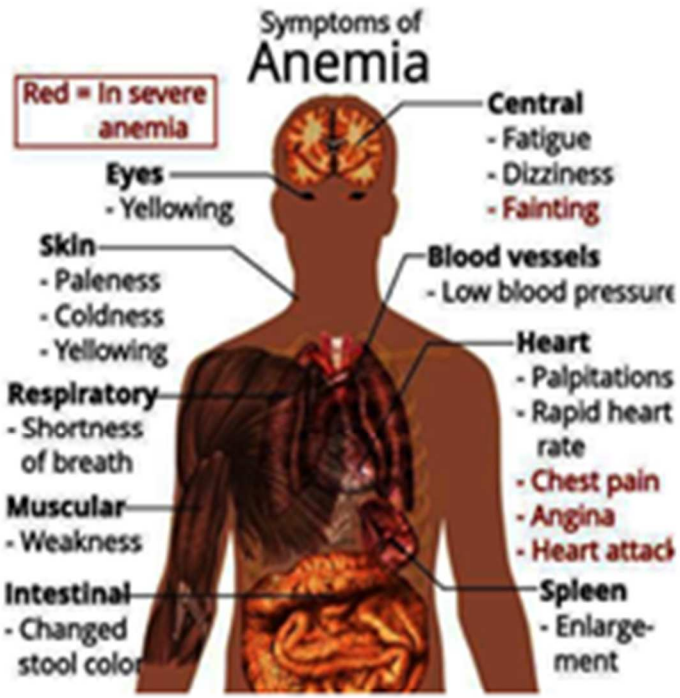

Hypoxia
Normoxia
HIF-β
HIF-α
PH
HIF-α
Proline Hydroxylation
O_2 Fe
VHL
HIF-α
UL
HIF-α
Degradation via the Proteasome
SF
IL-3R
Epo
EpoR
BFU-E
p300
HNF-4
β α
HIF
Epo gene
EpoR
CFU-E

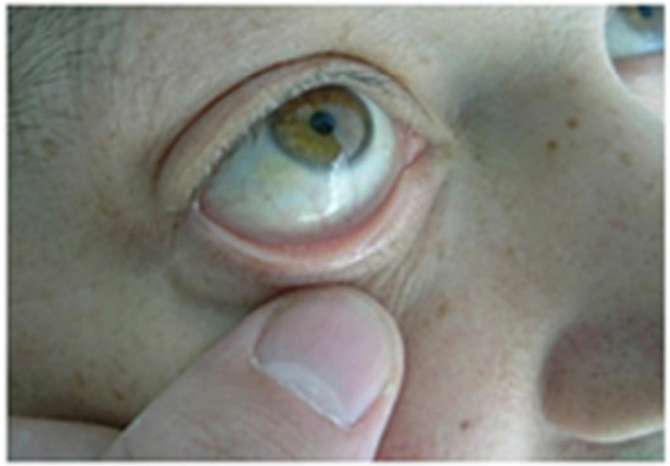
Normal RBCs



Anemia
Normocytic

- The corrected reticulocyte count is decreased but WBC lines and platelets are usually normal
- Etiology:
- Chronic Inflammation
- Moderate Iron Deficiency
- Renal Failure
- Endocrine problems (thyroid)


Symptoms of
Anemia
Red = In severe anemia
Central
- Fatigue
- Dizziness
- Fainting
Eyes
- Yellowing
Skin
- Paleness
- Coldness
- Yellowing
Blood vessels
- Low blood pressure
Heart
- Palpitations
- Rapid heart rate
- Chest pain
- Angina
- Heart attack
Respiratory
- Shortness of breath
Muscular
- Weakness
Intestinal
- Changed stool color
Spleen
- Enlarge-ment

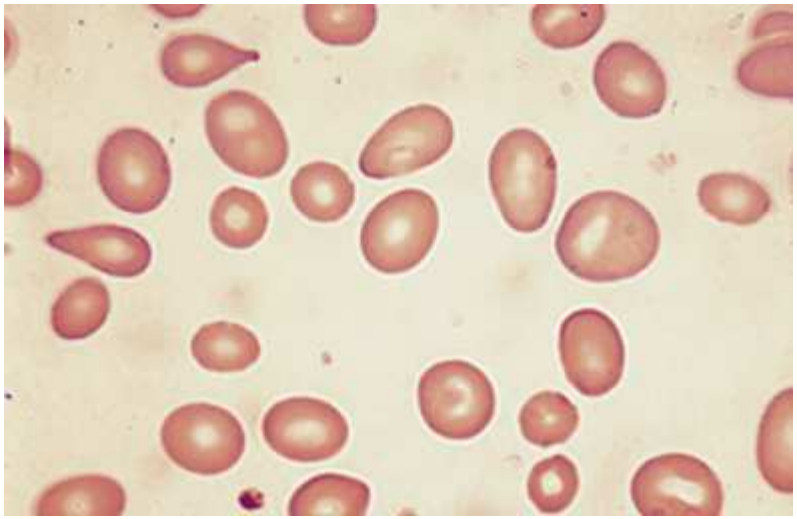


Anemia in Renal Failure

- The anemia of ESRD is mostly normocytic and normochromic
- It is due to reduced renal EPO production (because of reduced renal mass)relative to the degree of anemia. It is a “relative” deficiency
- EPO levels fall as eGFR falls especially below 30 ml/min
- It is also due to shortened RBC survival

Other Factors

- Blood loss from GI bleed
- Blood loss through the hemodialysis process
- Folate and Vitamin B 12 deficiency
- Chronic inflammation
- Vasculitis and microangiopathic hemolytic anemia
- Hemolytic anemia



Lab Tests Used in Diagnosis and Management of Anemia

- Peripheral smear
- CBC which includes MCV/RDW
- Vitamin B12 level
- RBC Folate level
- Reticulocyte count
- Iron studies


PORGES

Use of ESAs
General Principles

-The response to EPO is dose-dependent AND varies GREATLY among patients

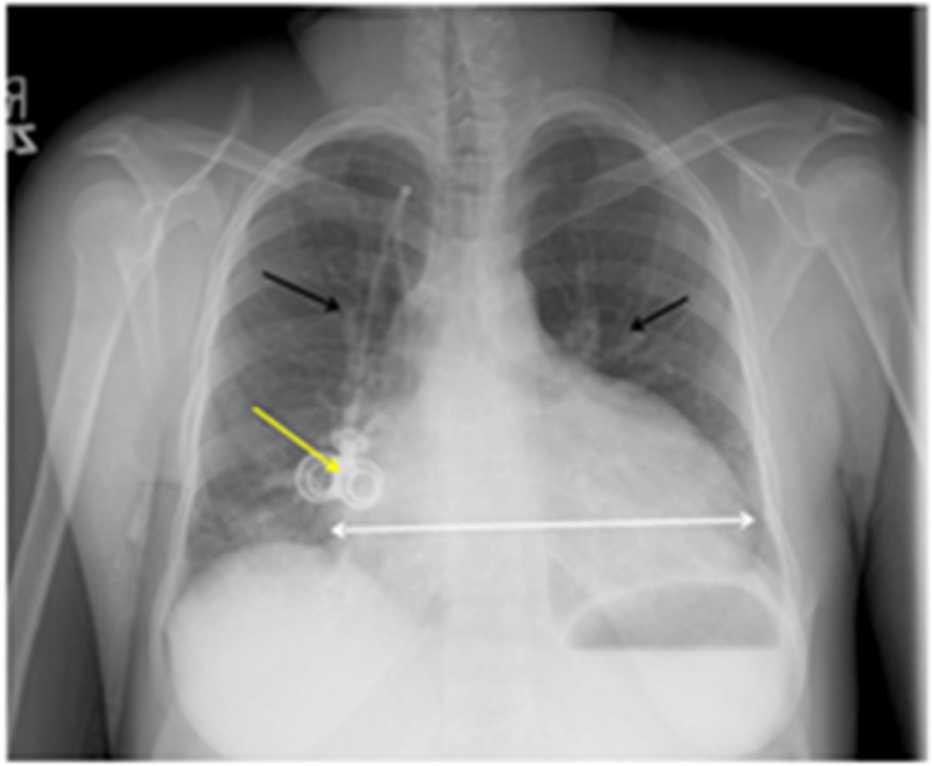
-The response is dependent on the route and frequency of administration

-The response may be limited by low iron stores, bone marrow fibrosis, infection, or other co-factor deficiency

-Stroke, mortality and HTN may complicate therapy

Benefits of ESAs

- Use has almost eliminated severe anemia as a major cause of morbidity in dialysis patients
- Improvement in LVH
- Normalization of cardiac output and SVR
- Relief of impaired carbohydrate and cortisol metabolism
- Improved QOL
- Increased cerebral blood flow and cognitive function


PA

Route of Administration

- K/DOQI guidelines previously recommended the use of subcutaneous route (EPO) because of greater efficacy and 30% less dose requirement
- At 26 weeks the average SC EPO dose was 95 versus 140 units/kg per week in the IV group of one study.
- Despite this over 90% of patients receive ESA's IV in the US

Dosing

- The initial dose of EPO is based upon:
- Baseline Hgb value
- Clinical setting
- Mode of administration
- Target Hgb level
- For SC administration – initial dose is about 80-120 units/kg/week (around 6000 units)

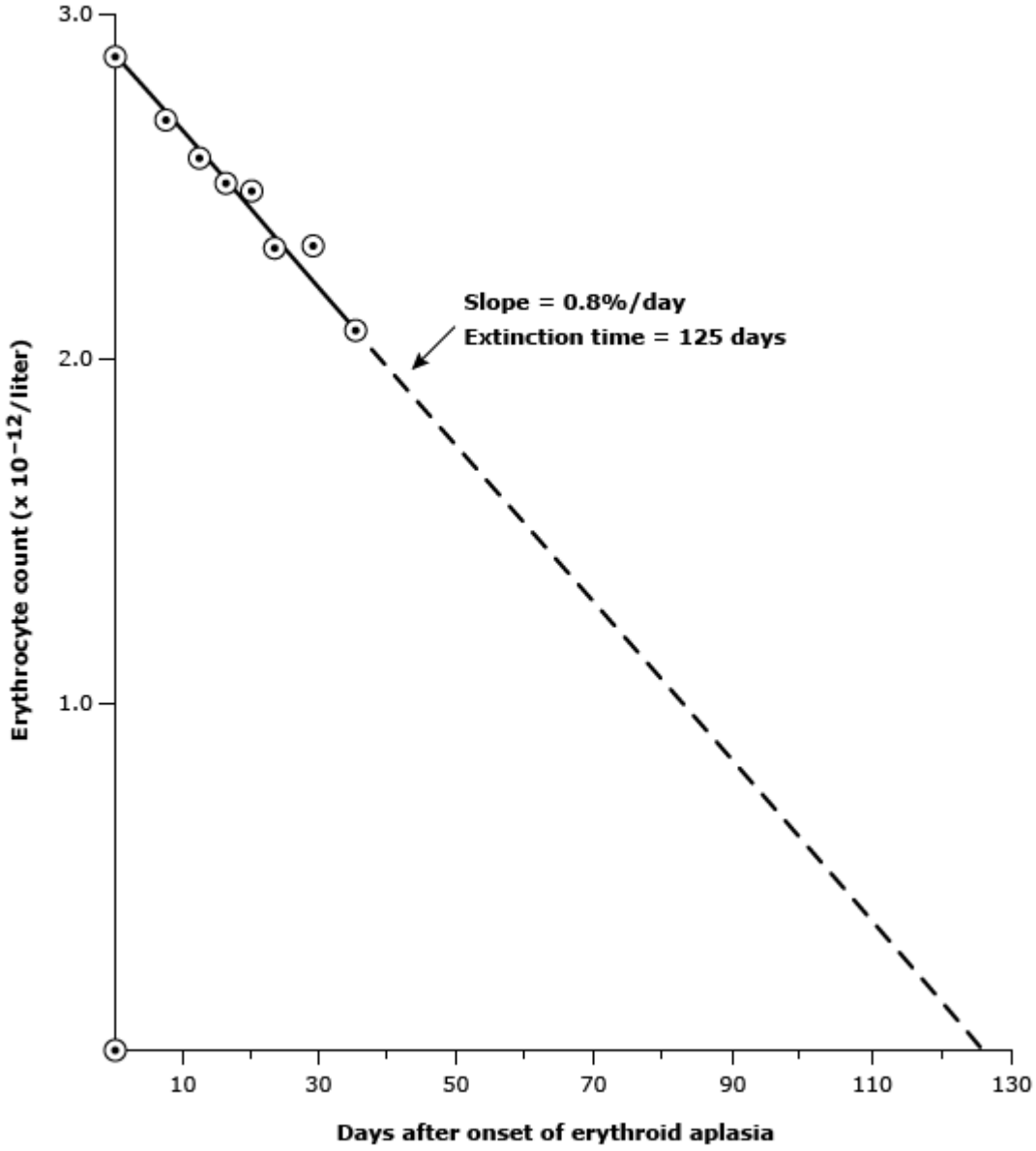
Side Effects of ESAs

- The most recent boxed warning on ESAs recommends that clinicians and patients with CKD weigh the benefits of ESAs to decrease the need for transfusions against the increased risks for serious, adverse cardiovascular events. One should individualize dosing and use the lowest dose of ESA sufficient to reduce the need for transfusion. For patients on dialysis, one should initiate ESA treatment when the Hgb level is <10 g/dL and reduce or interrupt the ESA dose if the Hgb level approaches or exceeds 11 g/dL [15].

- Adverse effects — The US NHT was terminated prematurely because the group targeted to normal values of Hgb had a higher mortality that was approaching statistical significance. Similar findings were noted in the CHOIR study of pre-dialysis patients with CKD. Increased mortality has also been observed in patients with malignancy who have received erythropoietic agents

Pure Red Cell Aplasia Due to Anti-EPO Antibodies

- PRCA is a rare condition characterized by profound anemia and a very low retic count
- There is an absence of erythroid precursors in the bone marrow
- It has occurred in patients treated with EPO when antibodies directed against the EPO molecule develop.


3.0
2.0
1.0
Erythrocyte count (x 10⁻¹²/liter)
Slope = 0.8%/day
Extinction time = 125 days
10
30
50
70
90
110
130
Days after onset of erythroid aplasia

PRCA continued

- The vast majority of cases of PRCA related to EPO use have occurred in patients treated with a particular product – Eprex in single dose syringes by the SC route. It is thought that altered antigenicity of this product was the cause and could be due to the polysorbate used as a stabilizing agent.

- There have been over 200 reported cased related to Eprex mainly between 2001-2003.
- 11 cases have been attributed to NeoRecormon – EPO beta (Roche) in Europe
- Less than 10 cases have been reported in patients on EPO/Procrit Amgen products
- There are 2 published cases attributed to Aranesp
- Screening for Anti-EPO Antibodies is not justified but testing should occur if there is a decline in the Hgb level of greater than 1 g/dl/week, absolute retic count less than 10,000/ microL, with normal other cell lines

- Treatment of PRCA is:
- Stop all ESA’s
- Provide blood transfusions as necessary
- Rechallenging may incite anaphylaxis

ESA Resistance

- Definition: No increase in the Hgb after one month of appropriate weight-based dosing or after two increases in the ESA dose up to 50% beyond the dose at which the patient had originally been stable.
- 300 units/kg/wk SC or 450 units/kg/week IV EPO
- 1.5 mcg/kg/wk Darbepoetin
- Poor Response to EPO may be associated with increased mortality
- Higher doses of ESA's have been associated with increased mortality

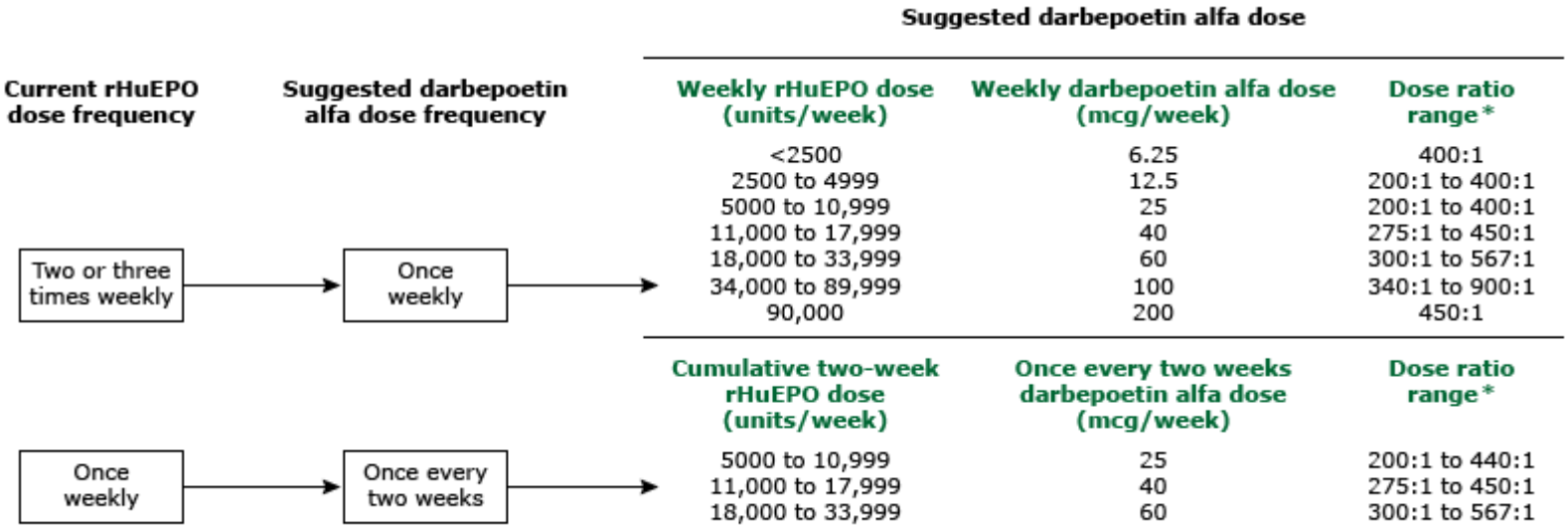
Causes

- Iron Deficiency
- Secondary Hyperparathyroidism
- Malignancy
- Multiple myeloma or MDS
- Chronic inflammation
- Aluminum toxicity
- Hemoglobinopathy
- ACEI’s
- PRCA
- B12 /Folate deficiency

Darbepoetin Alfa

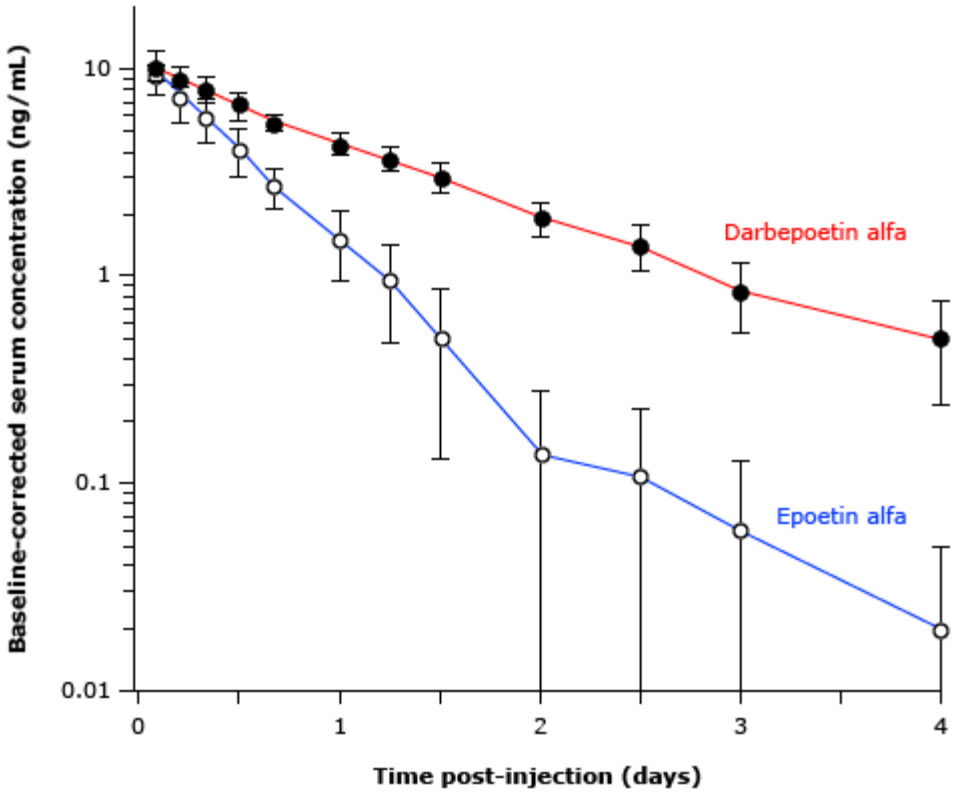
- Though distinct from rHuEPO it binds to the EPO receptor and has the same mechanism of intracellular signaling as rHuEPO
- It has higher potency and longer t ½.
- Several large trials have confirmed that patients on rHuEPO can be switched to darbepoetin.
- It is well tolerated and has a safety profile similar to rHuEPO.

- In the TREAT trial 2012 patients were assigned to receive darbepoetin to a target of 13 Hb or to placebo and treatment with darbepoetin if Hb was less than 9. No benefit found in the higher target group and there was an increased risk of stroke.
- Recommended starting dose is 0.45 mcg/kg once per week in naïve patients.

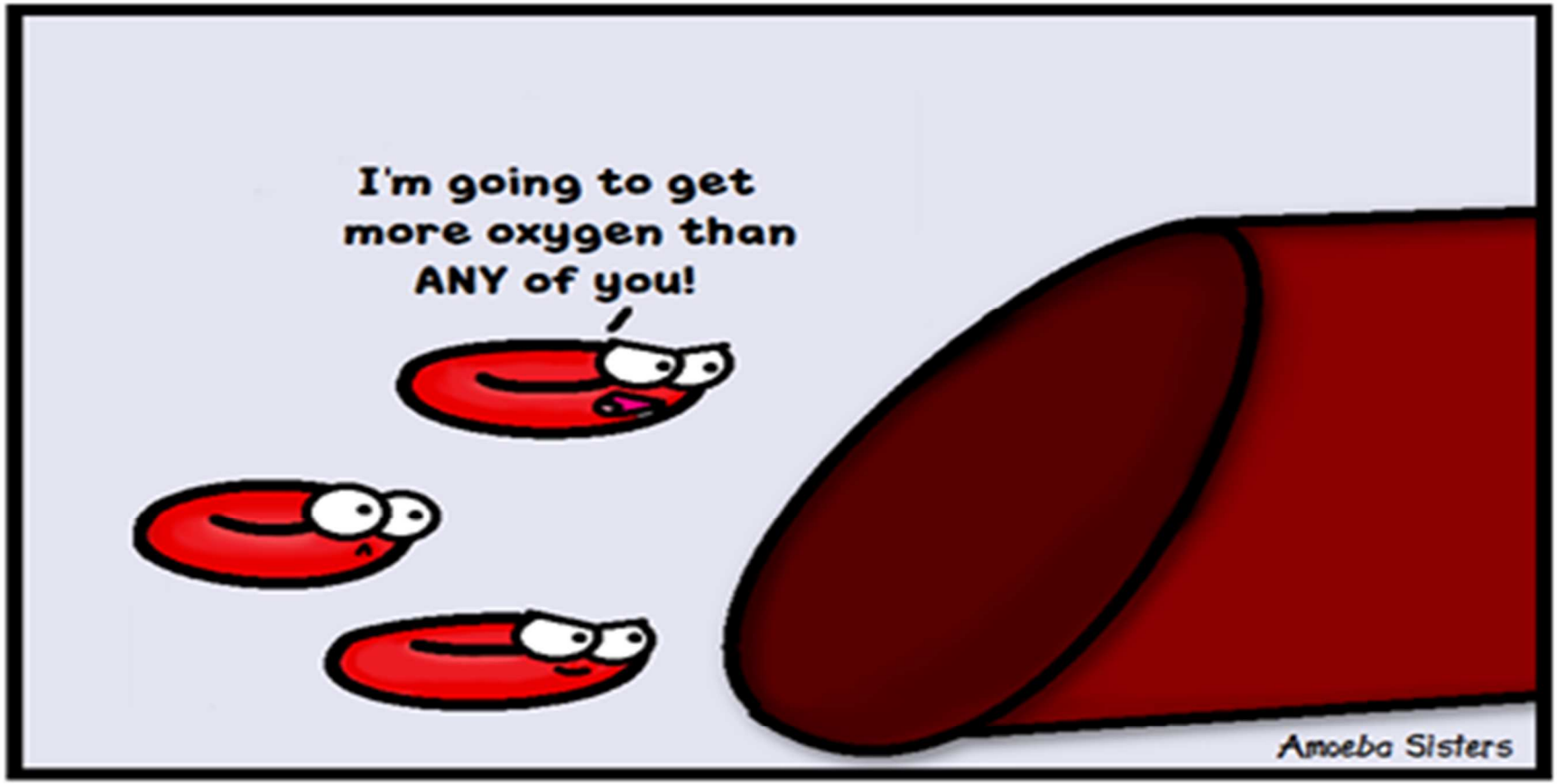


- Dose adjustment should not be more than once per month
- If Hb levels are approaching the upper target the dose should be reduced by 25% (or if the increase in Hb exceeds 1/g/dL over 2 weeks.
- The dose should be increased by 25 % if the rise in Hb is less than 1g/dL over 4 weeks.

Pharmacokinetics of EPO and Darbepoetin



The Paramecium Parlor



Frank was starting to wonder if there was more to life than transporting oxygen.