Drug therapy of Anaemias

March 2006

Anaemia

- Defined as a reduced number of circulating red blood cells
- Due to reduced production or increased loss of red blood cells

Mean Cell Volume (MCV)

- Low MCV <80fl – microcytic

  eg iron deficiency

- Normal MCV 80-100 fl – normocytic

  eg acute bleeding; chronic disease

- High MCV >100 fl – macrocytic

  eg B12/Folate deficiency

Differential Diagnosis of the Anemic Adult†

Low mean corpuscular volume (microcytic anemia: MCV <80 fL)

- Iron deficiency anemia
- Thalassemic disorders
- Anemia of chronic disease (late; uncommon)
- Sideroblastic anemia (eg, congenital, lead, alcohol, drugs; uncommon)
- Copper deficiency, zinc poisoning (rare)

Normal mean corpuscular volume (normocytic anemia: MCV 80 to 100 fL)

- Acute blood loss
- Iron deficiency anemia (early)
- Anemia of chronic disease (eg, infection, inflammation, malignancy)
- Bone marrow suppression (may also be macrocytic)
  - Bone marrow invasion (eg, leukoerythroblastic blood picture)
  - Acquired pure red blood cell aplasia
  - Aplastic anemia
- Chronic renal insufficiency
- Endocrine dysfunction
  - Hypothyroidism
  - Hypopituitarism

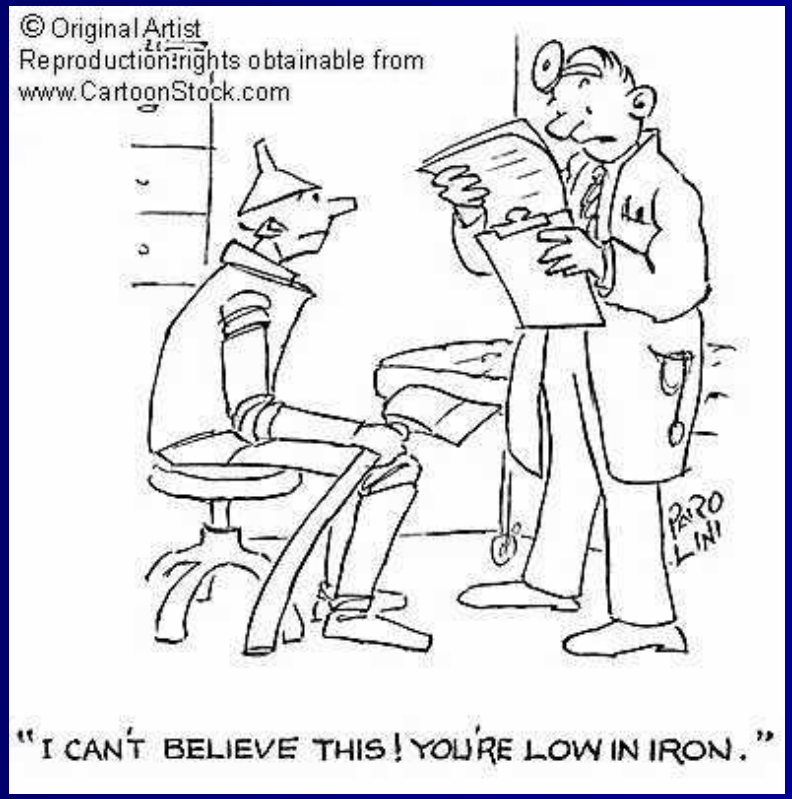
Increased mean corpuscular volume (macrocytic anemia: MCV >100 fL)

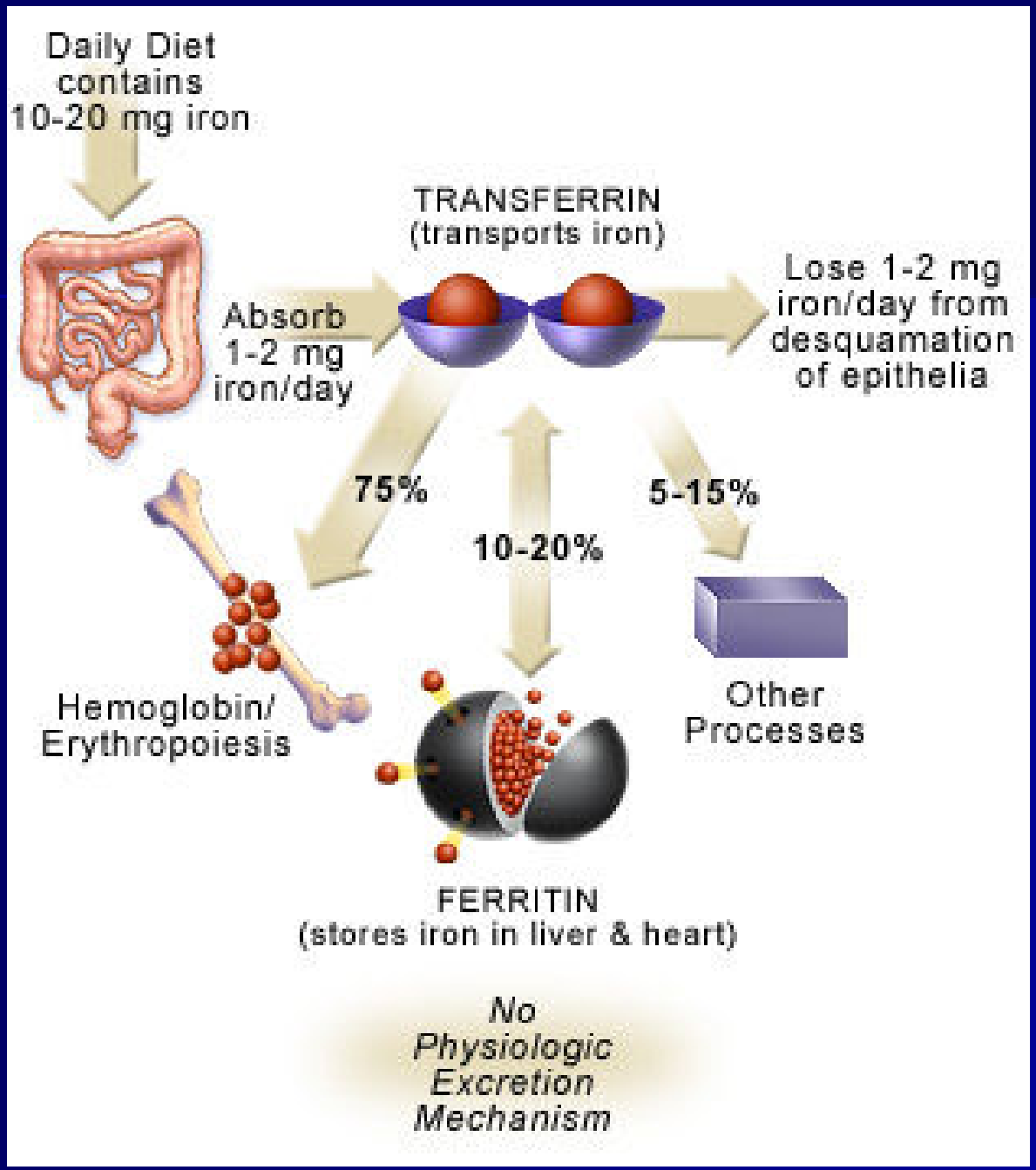
- Ethanol abuse
- Folic acid deficiency
- Vitamin B12 deficiency
- Myelodysplastic syndromes
- Acute myeloid leukemias (eg, erythroleukemia)
- Reticulocytosis
  - Hemolytic anemia
  - Response to blood loss
  - Response to appropriate hematinic (eg, iron, B12, folate)
- Drug-induced anemia (eg, Hydroxyurea, AZT, chemotherapeutic agents)
- Liver disease

† This list is not meant to be exhaustive; only the most common causes are mentioned. In addition, two or more of these conditions may be present (eg, combined iron and folic acid deficiencies), resulting in a misleadingly normal mean corpuscular volume.

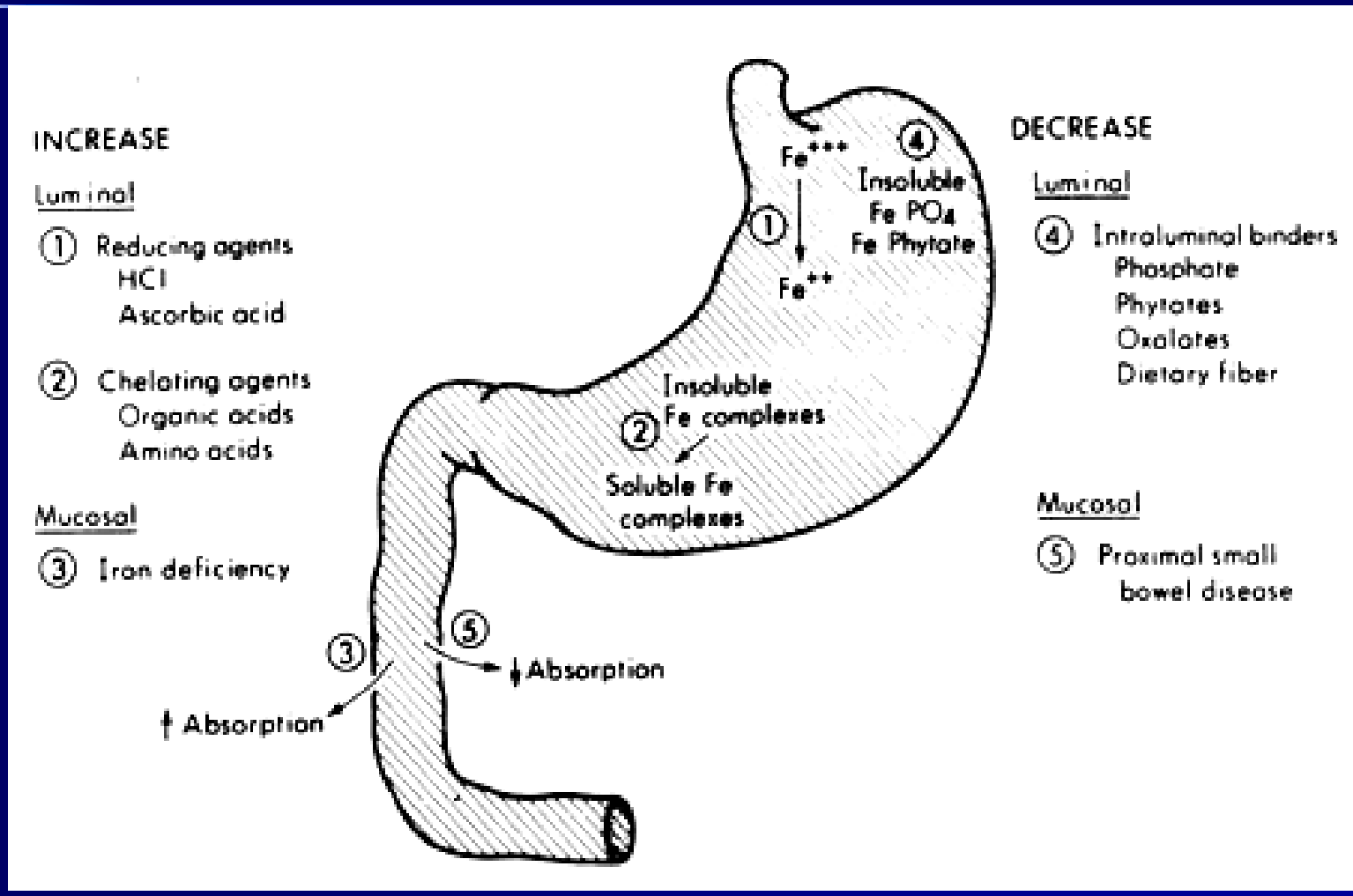
Iron deficiency anaemia

Determine and treat underlying cause




Daily Diet contains 10-20 mg iron
TRANSFERRIN (transports iron)
Absorb 1-2 mg iron/day
Lose 1-2 mg iron/day from desquamation of epithelia
75%
10-20%
5-15%
Hemoglobin/ Erythropoiesis
Other Processes
FERRITIN (stores iron in liver & heart)
No Physiologic Excretion Mechanism

Factors affecting absorption



Iron therapy

- Iron is absorbed best from the duodenum and proximal jejunum
- Enteric coated or sustained release capsules may be counterproductive
- Iron salts should not be given with food because the phosphates, phytates, and tannates in food bind the iron and impair its absorption
- Iron is best absorbed as the ferrous (Fe^{2+}) salt
- Acidic environment favors ferrous over ferric state
- Ascorbic acid can enhance iron absorption
- antacids impair absorption

Iron therapy

- The recommended daily dose for the treatment of iron deficiency in adults is in the range of 150 to 200 mg/day of elemental iron eg 200mg (=65mg elemental iron) ferrous sulphate tds
- No evidence that one iron preparation is more effective than another
- Reticulocytosis begins in approx 7 days and a rise in Hb of approximately 2 g/dL over three weeks

Iron therapy

- The iron preparation used should be based on cost and effectiveness with minimal side effects. The cheapest preparation is iron sulfate
- Upper gastrointestinal tract discomfort is directly related to the amount of elemental iron ingested
- Titrate the dose down to the level at which the gastrointestinal symptoms become acceptable

Side effects

- 10 to 20 percent of patients complain of nausea, epigastric distress and/or vomiting after taking oral iron preparations
- Constipation
- Black stools (can confuse with melaena)
- Try smaller dose of elemental iron
- switch from a tablet to a liquid preparation

Duration of treatment

- Some physicians stop when the hemoglobin level becomes normal, so that further blood loss will cause anemia and alert the patient and physician to the return of the problem which caused the iron deficiency in the first place

- Others believe that it is wise to treat for about six months after the hemoglobin normalizes, in order to completely replenish iron stores

Failure to respond to oral iron

- Incorrect diagnosis (eg, thalassemia)
- Presence of a coexisting disease interfering with response

  (eg, anemia of chronic disease, renal failure)
- Patient is not taking the medication
- Medication is not being absorbed

  (eg, enteric coated tablets, concomitant use of antacids, malabsorption)
- Iron (blood) loss or need is in excess of the amount ingested (eg, severe continuous GI bleeding, dialysis patient)

Parenteral Iron Therapy

- Parenteral iron, given IM or IV, is used in the rare patient who is unable to tolerate even modest doses of oral iron, or in patients whose level of continued gastrointestinal bleeding exceeds the ability of the gastrointestinal tract to absorb iron (eg, hereditary hemorrhagic telangiectasia)

Intramuscular iron

- Mobilization of iron from intramuscular sites is slow and occasionally incomplete
- As a result, the rise in the hemoglobin concentration is only slightly faster then that which occurs with oral iron
- s/e pain, muscle necrosis, and phlebitis
- Anaphylactic reactions occur in about 1% of patients

Iron overload

- Venesection eg haemochromatosis
- Iron chelators
- Complex with trivalent ions (ferric ions) to form ferrioxamine, which is excreted by the kidneys
- Desferrioxamine iv or s/c infusion
- Deferiprone po s/e blood dyscrasias

Macrocytic Anaemia

Causes and Mechanisms of Macrocytosis

Abnormalities of DNA metabolism
- Vitamin B12 (cobalamin) deficiency
- Folate deficiency
- Drugs
  - Hydroxyurea
  - Zidovudine
  - Cytosine arabinoside
  - Methotrexate
  - Azathioprine or 6-mercaptopurine
  - Cladribine
  - Capecitabine

Shift to immature or stressed red cells
- Reticulocytosis
- Action of erythropoietin – skip macrocytes, stress erythrocytosis
- Aplastic anemia
- Pure red cell aplasia

Primary bone marrow disorders
- Myelodysplastic syndromes
- Congenial dyserythropoietic anemias
- Large granular lymphocyte leukemia

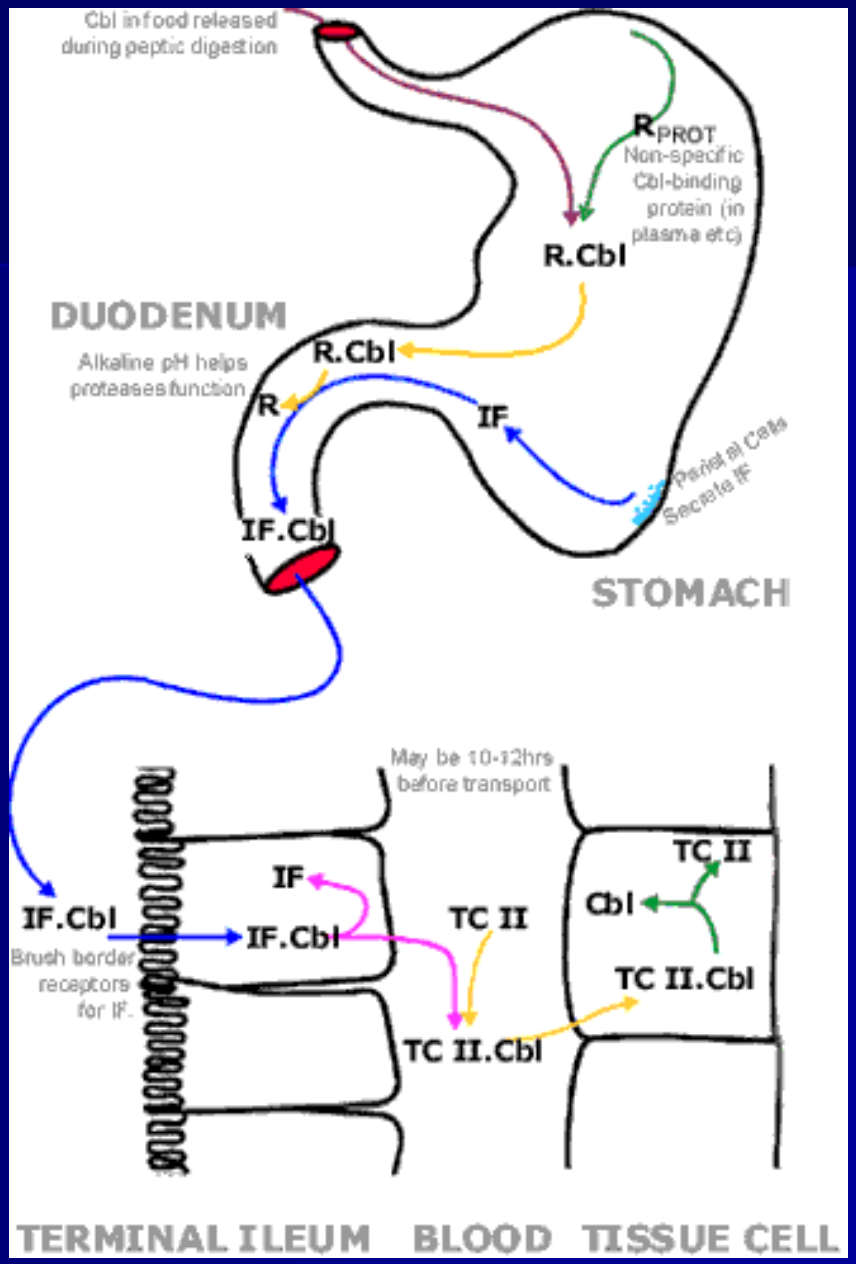
Lipid abnormalities
- Liver disease
- Hypothyroidism
- Hyperlipidemia

Mechanism unknown
- Alcohol abuse
- Multiple myeloma and other plasma cell disorders

B12 & Folate deficiency

- Macrocytosis, with or without anemia
- Examination of the peripheral blood smear, looking specifically for oval macrocytic red cells and hypersegmented neutrophils
- Pancytopenia (anemia, thrombocytopenia, neutropenia) of uncertain cause
- Unexplained neurologic signs and symptoms, especially dementia
- Special populations, such as the elderly, alcoholics, and patients with malnutrition

- Vitamin B12 absorption



Vitamin B12 deficiency

- Pernicious anemia
- Gastrectomy
- Terminal ileal disease
- Bacterial overgrowth
- Nutritional (rare)
- Increased requirement

Treatment

- Hydroxocobalamin dose of 1000 µg (1 mg) IM every day for one week, followed by 1 mg every week for four weeks and then, if the underlying disorder persists, as in PA, 1 mg every 3 months for life
- s/e allergic reactions; hypokalaemia
- high dose oral cobalamin is an alternative but requires much greater patient compliance

Folate deficiency

- Nutritional
- Malabsorption
- Drug related – impaired absorption (eg. Anticonvulsants) folate antagonists (eg. methotrexate)
- Increased Folate Requirements

Folate deficiency

- Folic acid (1 to 5 mg/day PO) for one to four months, or until complete hematologic recovery occurs. A dose of 1 mg/day is usually sufficient, even if malabsorption is present.
- These doses are in excess of those recommended for disease prevention (eg, recommended daily allowance in normal adults, alcoholics, the elderly, prevention of neural tube defects) 200-500mcg/day

An Important Point!

- Folic acid can partially reverse some of the hematologic abnormalities of Vitamin B12 deficiency, although the neurologic manifestations will progress.
- Thus, it is important to rule out Vitamin B12 deficiency before treating a patient with megaloblastic anemia with folic acid

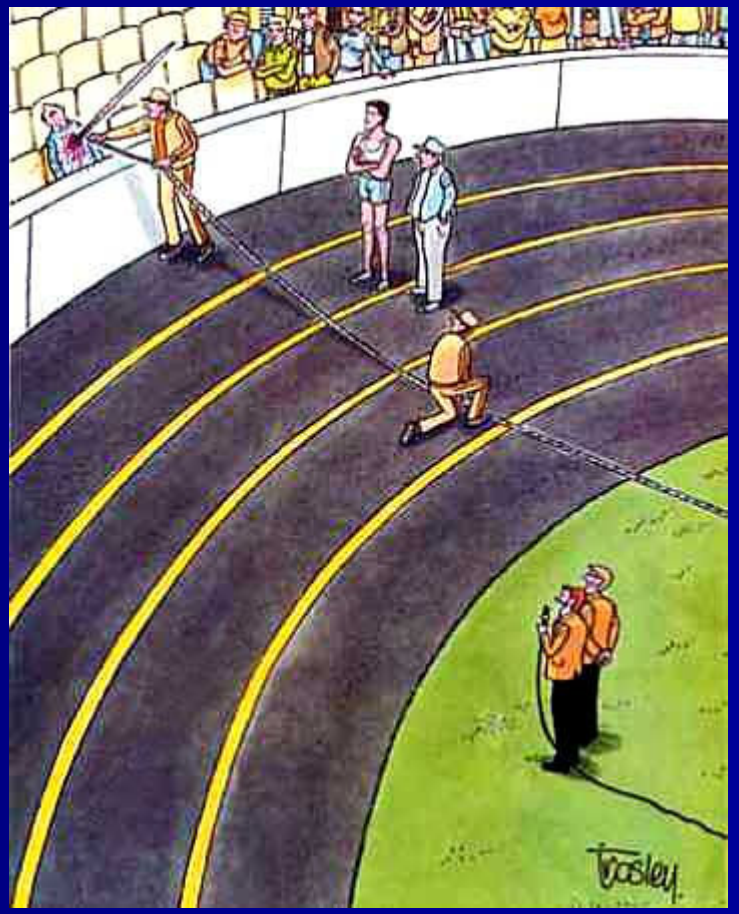
Blood transfusion

- In patients who are severely anemic at presentation, the decision to transfuse can be a difficult one, particularly in elderly patients at risk for congestive heart failure due to volume overload
- If the anemia is extreme and the patient is critically ill, one unit can be given initially at a slow rate, in combination with a diuretic, if fluid status is a concern
- In extreme circumstances, isovolemic exchange can be performed

Anaemia of Chronic Disease

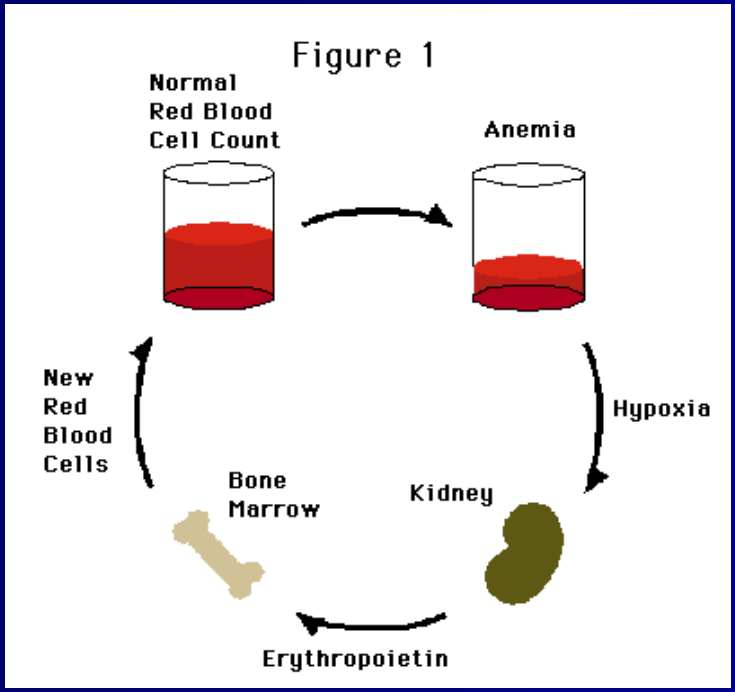
Erythropoietin

- Chronic renal failure
- Cytototic chemotherapy
- ↑ autologous blood yield
- Prematurity



Prior to treatment

- Important to ensure any concomitant deficiencies are treated



Erythropoietin

- Epoetin alpha
- Epoetin beta
- Darbepoetin hyperglycosylated long t1/2
- Aim to ↑ Hb 2g/dl per month
- Monitor Blood pressure; hemoglobin/hematocrit; iron stores

Factors affecting response

- dose-dependent, but varies among patients
- dependent on the route of administration (iv/sc) and the frequency of administration (daily, twice weekly, three times weekly)
- response may be limited by low iron stores, bone marrow fibrosis, inflammation, inadequate dialysis

Adverse effects

- Dose dependent ↑ BP
- Hypertensive crisis
- Dose dependent ↑ platelets
- Flu like symptoms
- Red cell aplasia

  rare but necessitates stopping treatment

  antibodies directed against the EPO molecule

  s/c administration contraindicated in chronic renal failure