

# HEMATOLOGY/ HEMATOPOIESIS

## Introduction

# HEMATOLOGY

## *Introduction*

- Study of blood & its components
- Window of rest of body

## BLOOD

### *Raison d'être*

- Delivery of nutrients
  - Oxygen
  - Food
  - Vitamins
- Removal of wastes
  - Carbon dioxide
  - Nitrogenous wastes
  - Cellular toxins
- Repair of its conduit
- Protection *versus* invading microorganisms
- Multiple cellular & acellular elements

## HEMATOLOGY

### *Divisions*

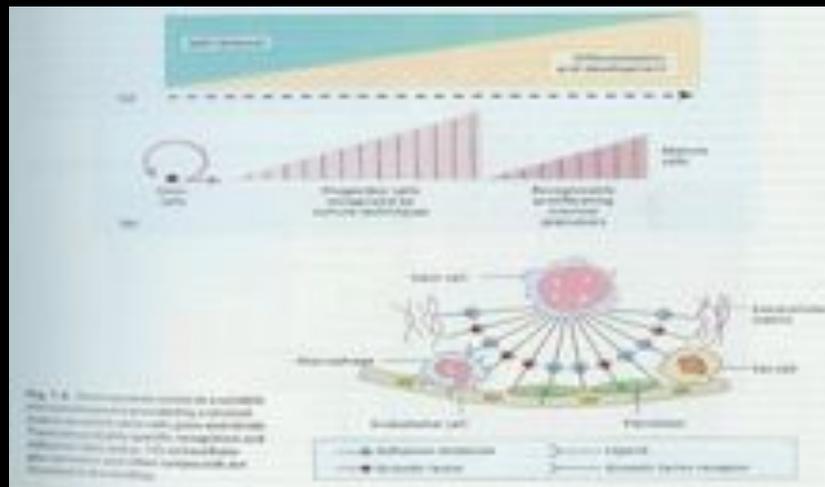
- Red Blood Cells/Oxygen & CO<sub>2</sub> transport
- Coagulation/platelets/Maintenance of vascular integrity
- White Blood Cells/Protection *versus* pathogens/microorganisms

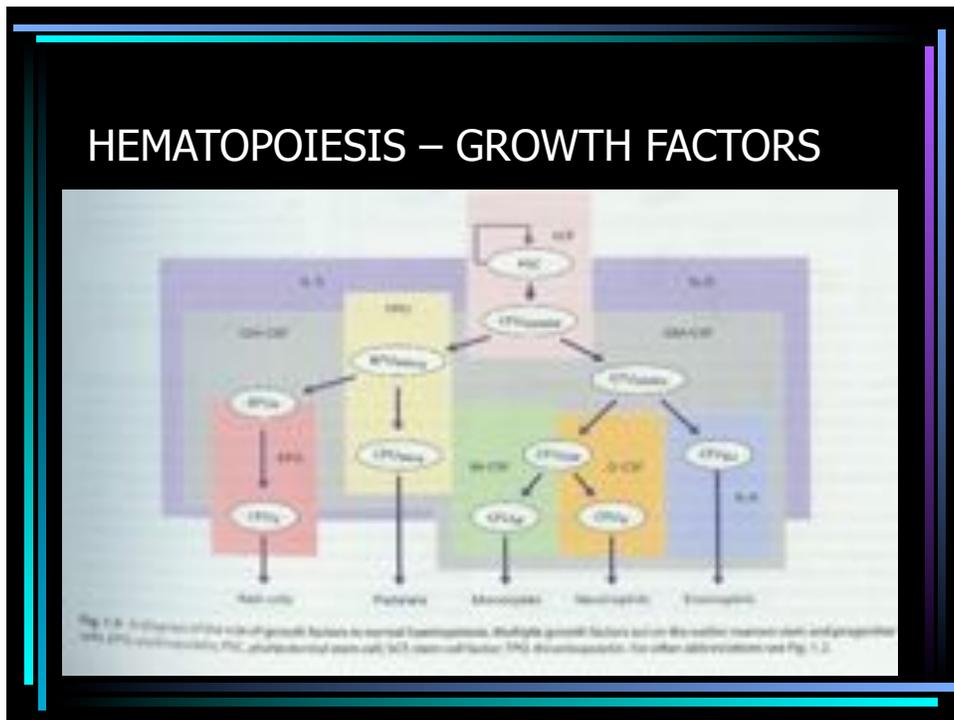
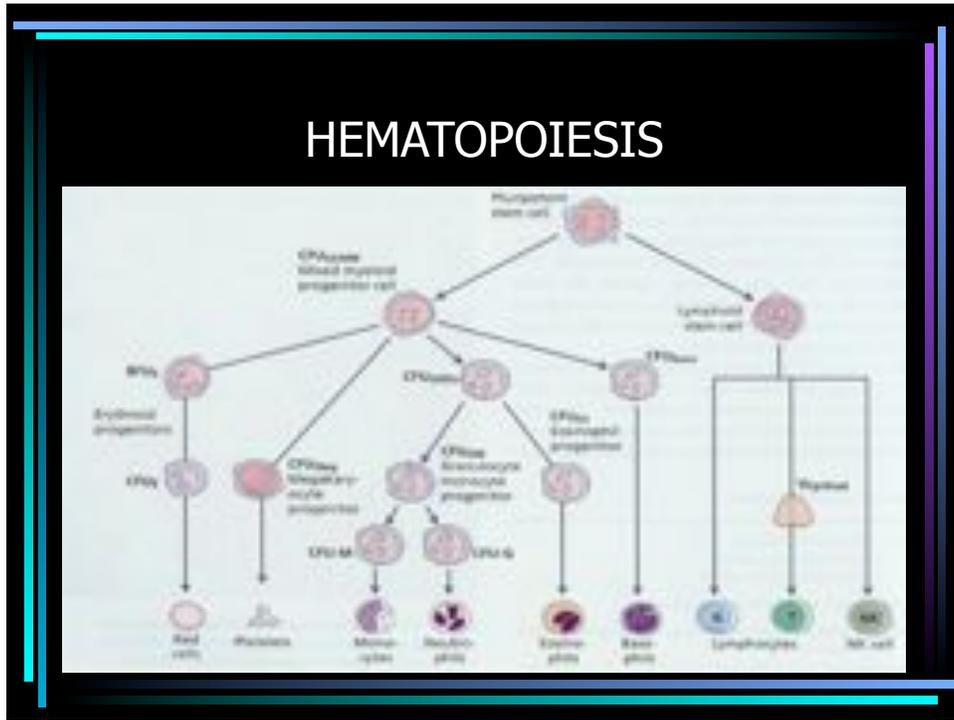
## HEMATOLOGY

### *Hematopoiesis*

- In humans, occurs in bone marrow exclusively
- All cellular elements derived from pluripotent stem cell (PPSC)
- PPSC retains ability to both replicate itself and differentiate
- Types of differentiation determined by the influence of various cytokines

## PLURIPOTENT STEM CELLS

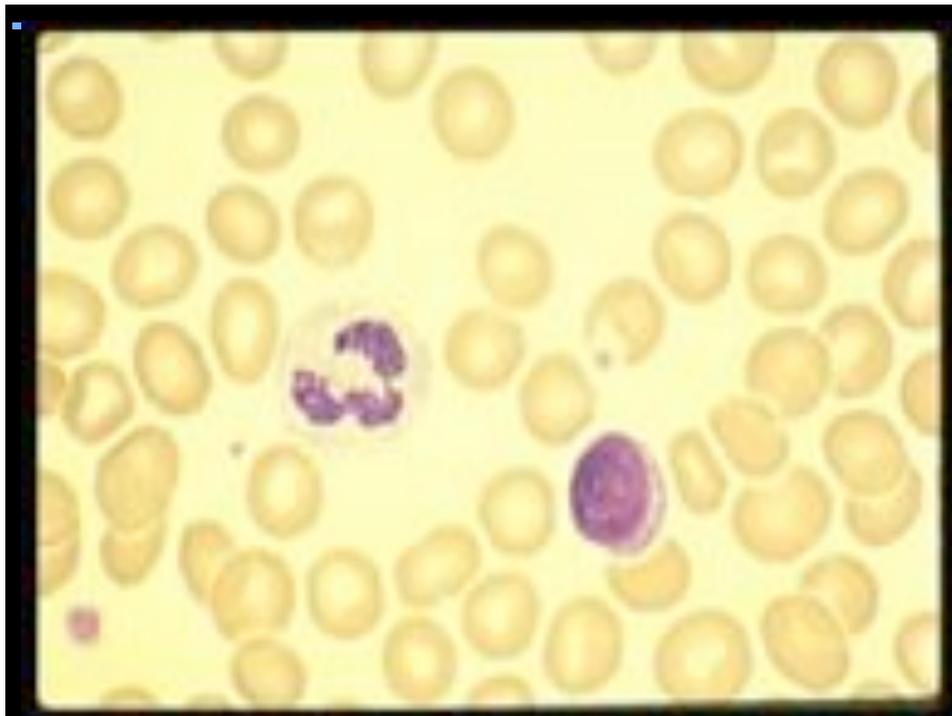




## RED BLOOD CELLS

### *Introduction*

- Normal - Anucleate, highly flexible biconcave discs, 80-100 femtoliters in volume
- Flexibility essential for passage through capillaries
- Major roles - Carriers of oxygen to & carbon dioxide away from cells

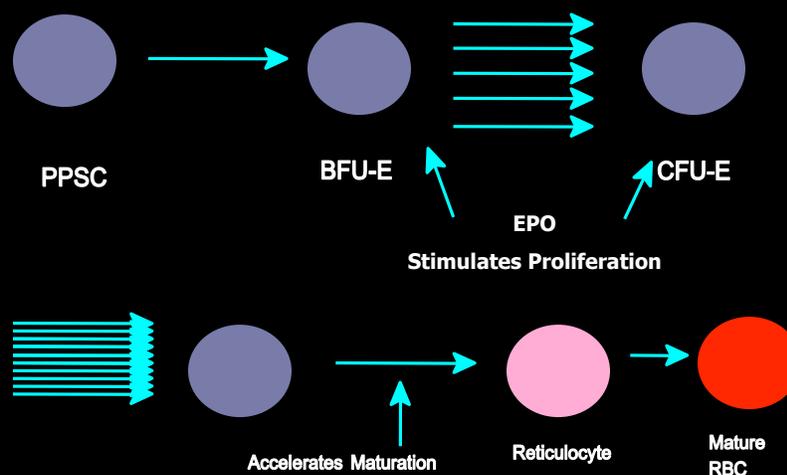


## ERYTHROPOIETIN

- Cytokine - Produced in the kidney
- Necessary for erythroid proliferation and differentiation
- Absence results in apoptosis of erythroid committed cells
- Anemia of renal failure 2° to lack of EPO

## ERYTHROPOIETIN

### *Mechanism of Action*

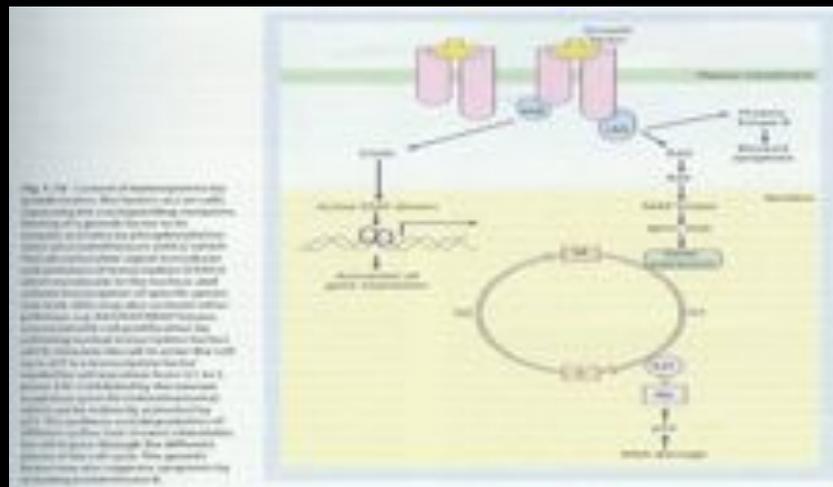


## ERYTHROPOIETIN

### *Mechanism of Action*

- Binds specifically to Erythropoietin Receptor
- Transmembrane protein; cytokine receptor superfamily
- Binding leads to dimerization of receptor
- Dimerization activates tyrosine kinase activity

## GROWTH FACTORS – Mechanisms of Action

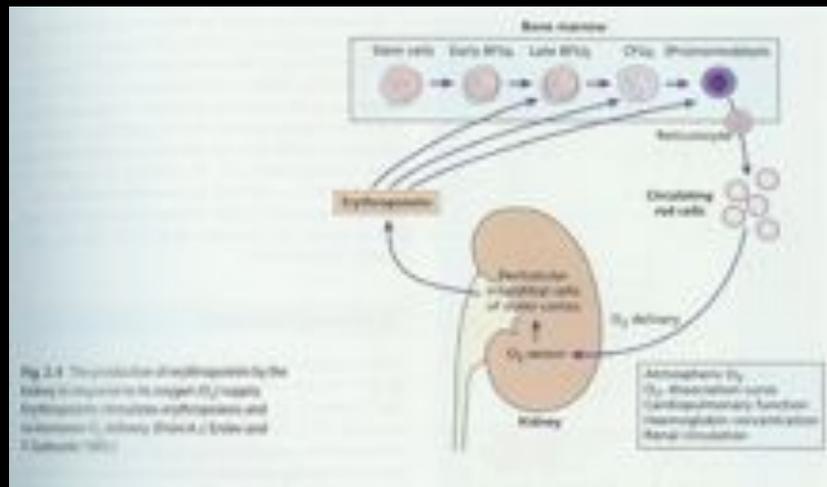


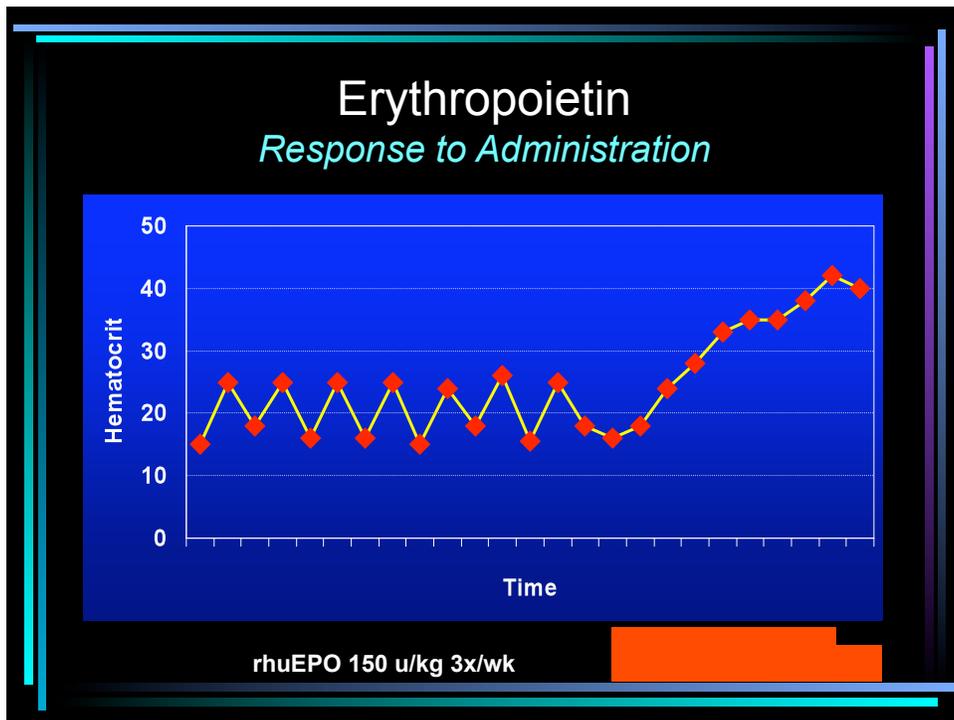
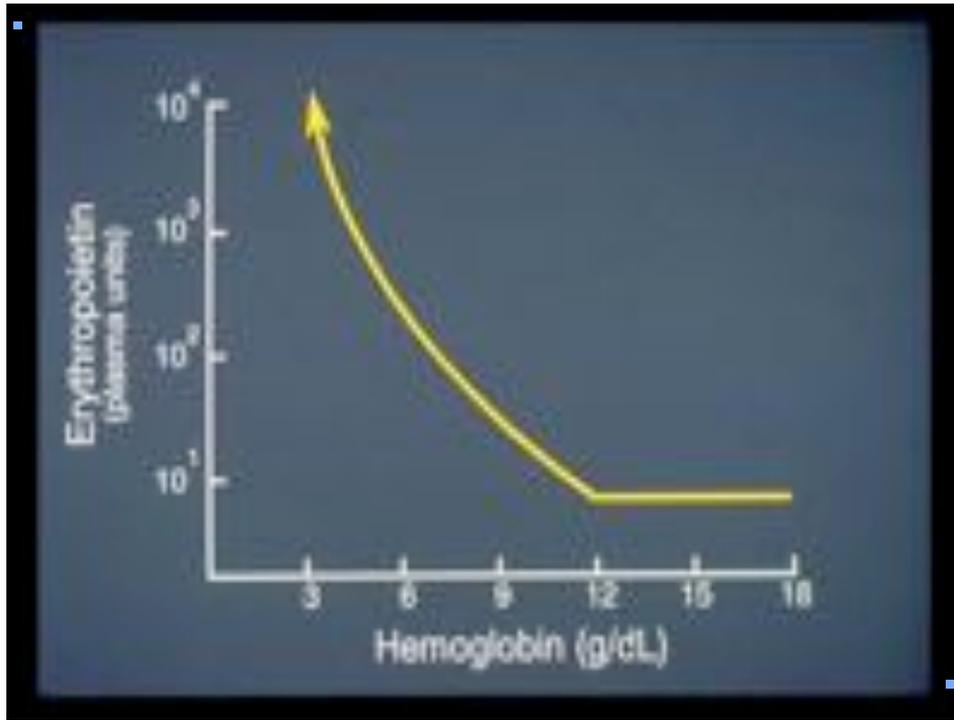
## ERYTHROPOIETIN

### *Mechanism of Action*

- Multiple cytoplasmic & nuclear proteins phosphorylated via JAK-STAT pathways
- Nuclear signal sent to activate production of proteins leading to proliferation and differentiation
- Signal also sent to block apoptosis

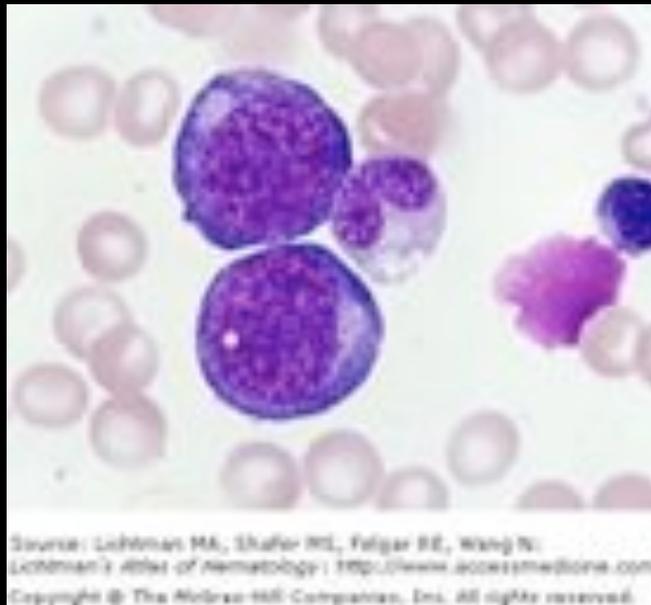
## ERYTHROPOIETIN – Regulation of Production/Mechanism of Action



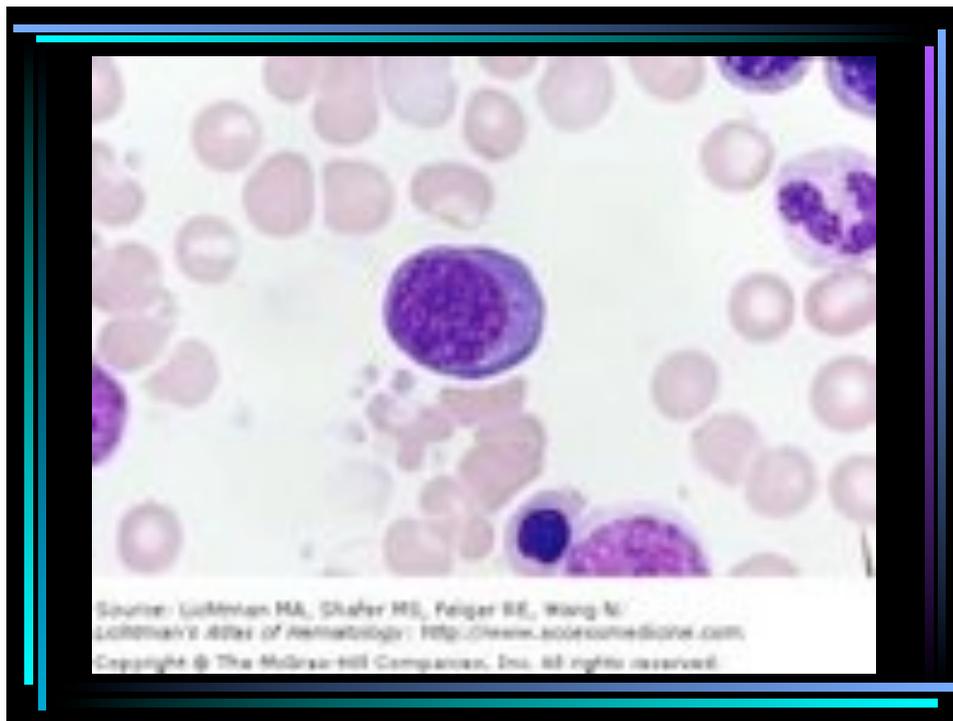


## RBC Precursors

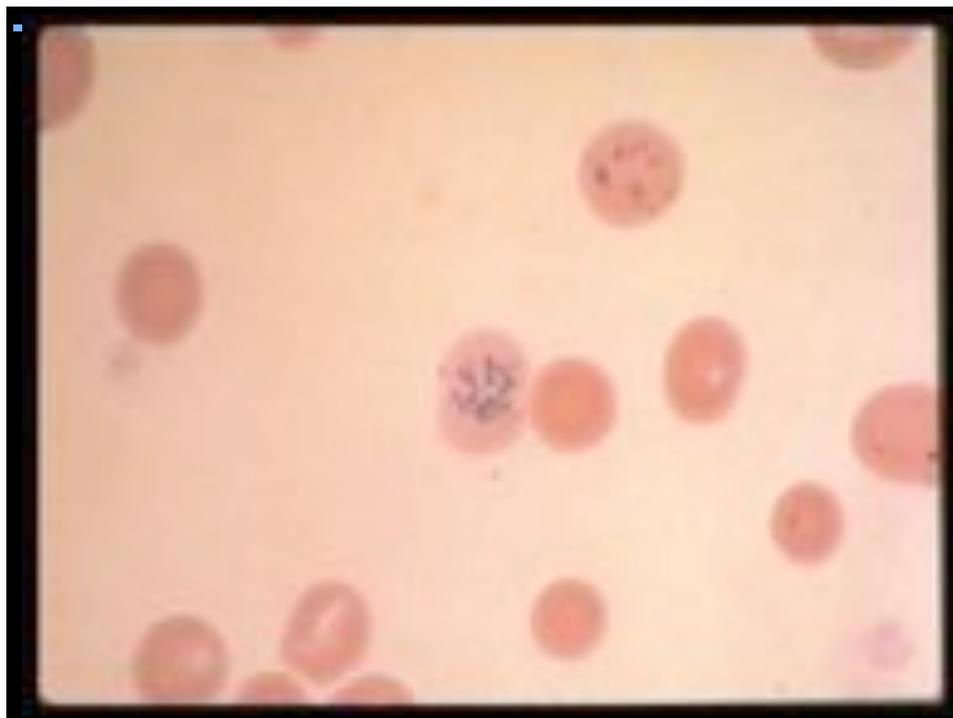
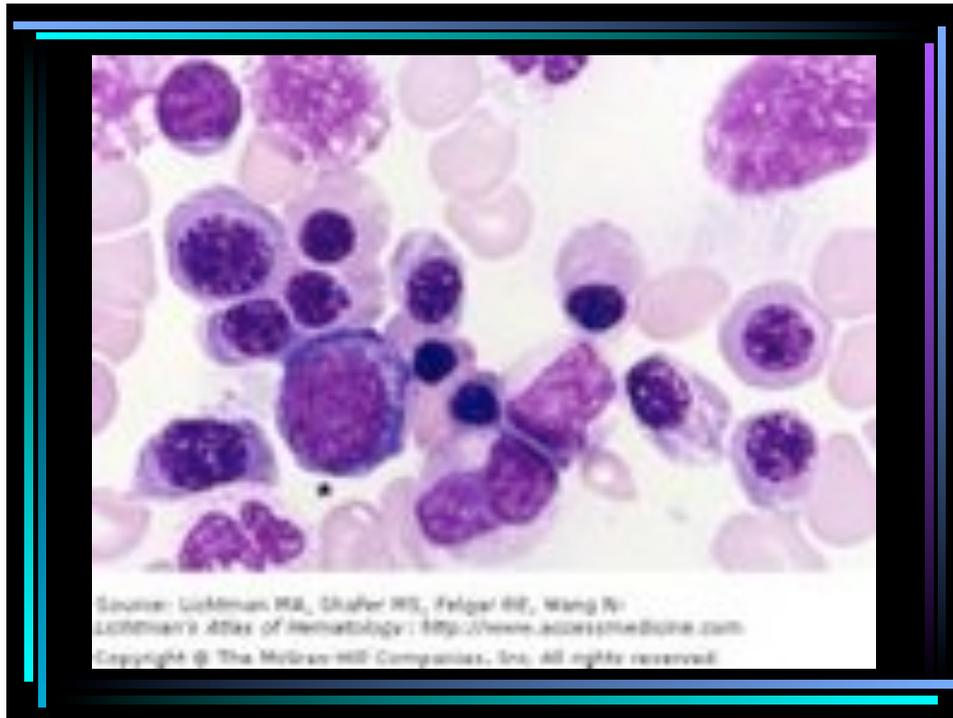
- Pronormoblast
- Basophilic normoblast
- Polychromatophilic Normoblast
- Orthochromatophilic Normoblast
- Reticulocyte
- Mature Red Blood Cell
- 5-7 days from Pronormoblast to Reticulocyte



Source: Lichtman MA, Shafer RL, Felgar RE, Wang N:  
Lichtman's Atlas of Hematology: <http://www.accessmedicine.com>  
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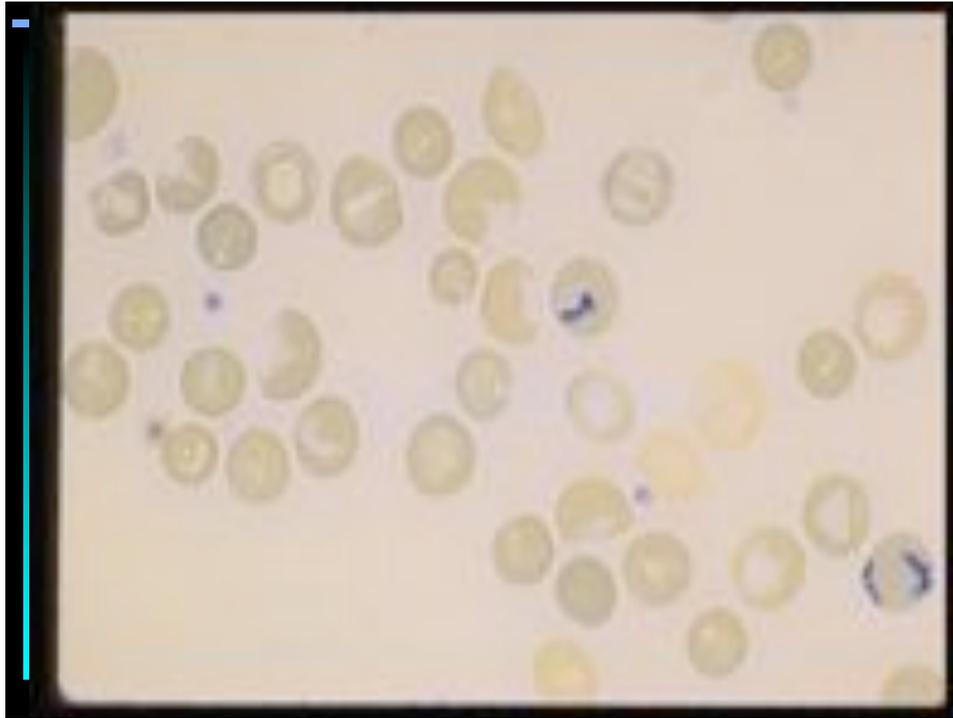
## RETICULOCYTE

- Important marker of RBC production
- Young red blood cell; still have small amounts of RNA present in them
- Tend to stain somewhat bluer than mature RBC's on Wright stain (polychromatophilic)
- Slightly larger than mature RBC
- Undergo removal of RNA on passing through spleen, in 1st day of life
- Can be detected using supravital stain

## RETICULOCYTE COUNT

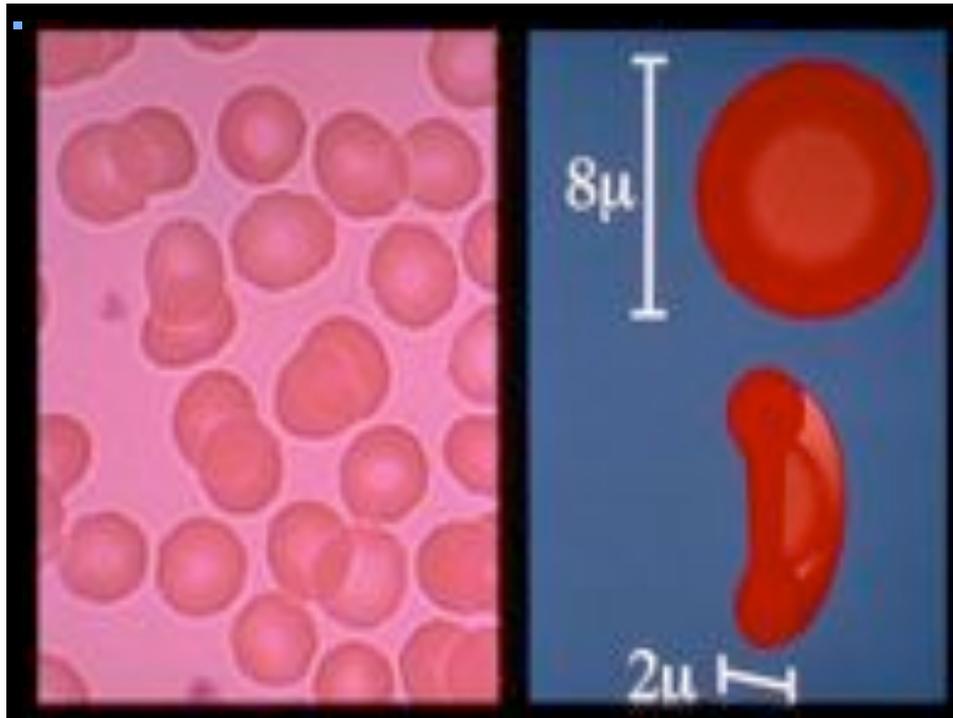
### *Absolute Value*

- = Retic % x RBC Count
  - eg  $0.01 \times 5,000,000 = 50,000$
- Normal up to 100,000/ $\mu$ l
- More accurate way to assess body's response to anemia



## RBC Assessment

- Number - Generally done by automated counters, using impedance measures
- Size - Large, normal size, or small; all same size *versus* variable sizes (anisocytosis). Mean volume by automated counter
- Shape - Normal biconcave disc, *versus* spherocytes, *versus* oddly shaped cells (poikilocytosis)
- Color - Generally an artifact of size of cell



## Red Blood Cells

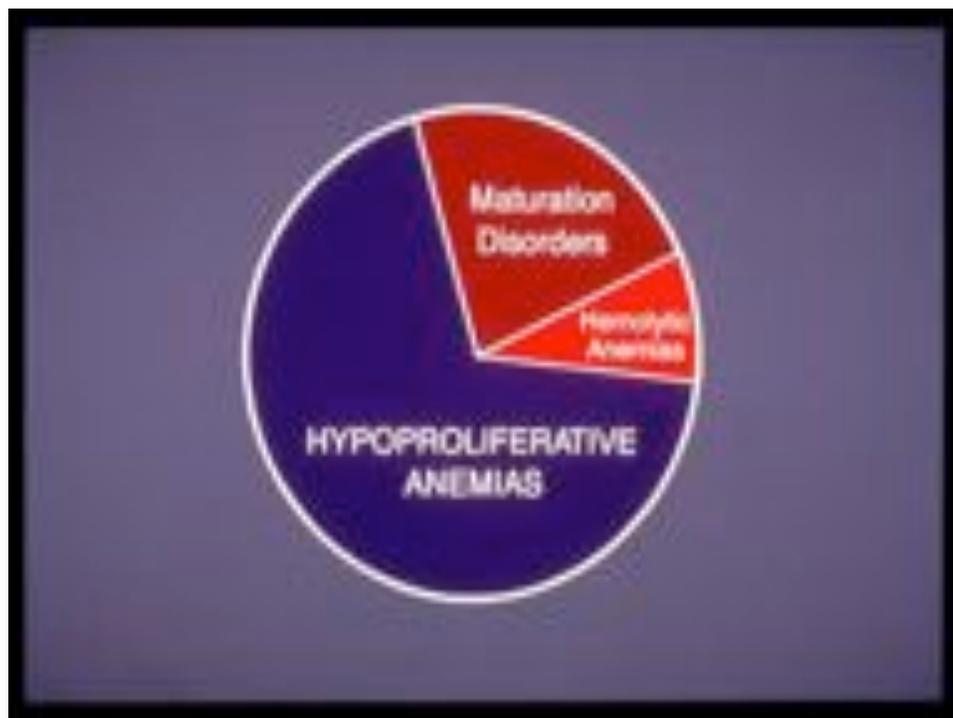
### *Normal Values*

RBC Parameters	Normal Values
Hematocrit	
Females	35-47%
Males	40-52%
Hemoglobin	
Females	12.0-16.0 gm/dl
Males	13.5-17.5 gm/dl
MCV	80-100 fl
Reticulocyte Count	0.2-2.0%

## ANEMIA

### *Causes*

- Blood loss
- Decreased production of red blood cells (Marrow failure)
- Increased destruction of red blood cells
  - Hemolysis
- Distinguished by reticulocyte count
  - Decreased in states of decreased production
  - Increased in destruction of red blood cells



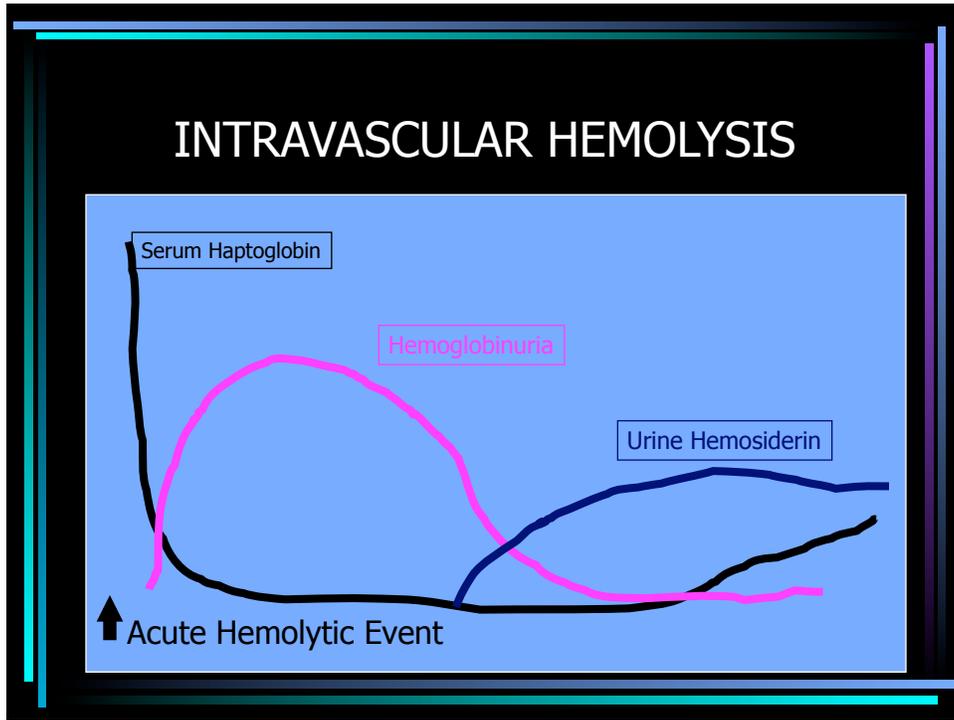
## RBC DESTRUCTION - EXTRAVASCULAR

### *Markers*

- Heme metabolized to bilirubin in macrophage; globin metabolized intracellularly
- Unconjugated bilirubin excreted into plasma & carried to liver
- Bilirubin conjugated in liver & excreted into bile & then into upper GI tract
- Conjugated bilirubin passes to lower GI tract & metabolized to urobilinogen, which is excreted into stool & urine

## RBC DESTRUCTION - INTRAVASCULAR

- Free Hemoglobin in circulation leads to
  - Binding of hemoglobin to haptoglobin, yielding low plasma haptoglobin
  - Hemoglobin filtered by kidney & reabsorbed by tubules, leading to hemosiderinuria
  - Capacity of tubules to reabsorb protein exceeded, yielding hemoglobinuria



### HEMOLYTIC ANEMIA

*Commonly used Tests*

Test	Result
Reticulocyte Count	Increased
Unconjugated Bilirubin	Increased
Lactate Dehydrogenase	Increased
Haptoglobin	Decreased
Urine Hemoglobin	Present
Urine Hemosiderin	Present

**Problems with sensitivity & specificity**