BLOOD DISORDERS

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Development of the Hematopoietic System & Blood Cell Counts

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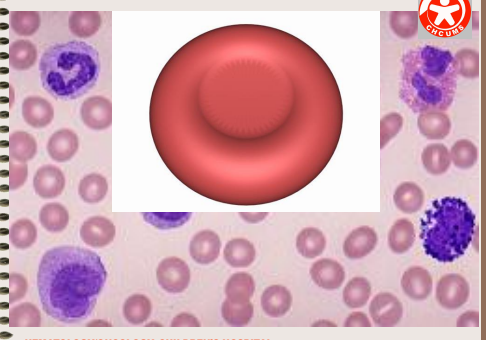
Development of Hematopoietic System

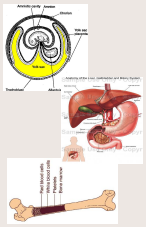


hematopoiesis （造血）

In the embryo and fetus,
constant changes characterize all
phases of hematopoiesis （造血）

Development of Hematopoietic Organs

- **Fetal hematopoiesis**
  - Mesoblastic Hematopoiesis
  - Hepatic Hematopoiesis
  - Myeloid Hematopoiesis
- **Hematopoiesis after birth**



Development of Hematopoietic Organs

Mesoblastic Hematopoiesis
(中胚层造血)

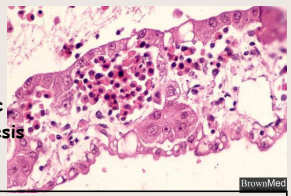
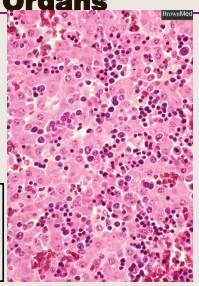


Figure: hematopoiesis in yolk sac, 18th hematopoiesis island

Development of Hematopoietic Organs

Hepatic Hematopoiesis
(肝脏造血)

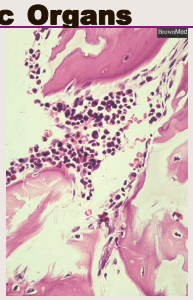
Figure: 17weeks gestations , erythroids are seen in



Development of Hematopoietic Organs

Myeloid hematopoiesis
(骨髓造血)

Figure: Bone marrow in 19weeks gestations



Development of Hematopoietic Organs

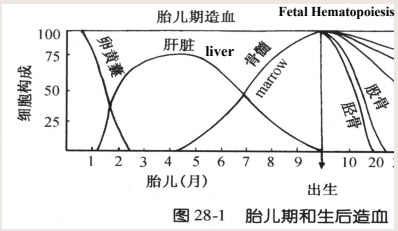


图 28-1 胎儿期和生后造血

Table 1. Fetal Hematopoiesis

	SITES	TIME	PRODUC
Measoblastic hematopoisis	Yolk Sac	10-14th day 3-4wk:primitive blasts 10-12wk:ceased	Erythroid
Hepatic hematopoiesis	Liver Spleen	6-8wk:appear 12-16wk:active 6mo:diminish/ stop at birth	Erythroid
Myeloid hematopoiesis	Bone marrow	4mo:start 6mo:increase/steady after birth: the only	Erythroid Neutrophils Macrophages

Development of Hematopoietic Organs

- Fetal hematopoiesis
- Hematopoiesis after birth
  - Bone marrow hematopoiesis
  - Extrmedullary hematopoiesis

Development of Hematopoietic Organs

- Hematopoiesis after birth
  - Bone marrow hematopoiesis 骨髓造血
    - All blood cells are produced in the marrow after 2nd trimester
    - Newborn and early infancy: red marrow
    - 5-7yr： yellow marrow

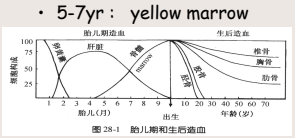
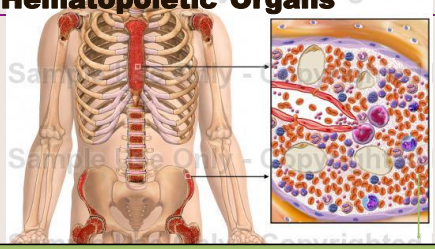


图 28-1 胎儿期和生后造血

Development of Hematopoietic Organs



The site for bone marrow aspiration :
Newborn and early infancy — tibia(胫骨)
After the infancy period — posterior superior iliac spine （髂后上脊）

Development of Hematopoietic Organs

- Hematopoiesis after birth
  - Bone marrow hematopoiesis
  - Extramedullary hematopoiesis 骨髓外造血
    - In disease status: red cell production ↑ hematopoietic tissue↑.
    - blood production expands to replace fatty marrow.
    - blood cells production extends to extramedullary sites (liver and spleen).

Development of Hematopoietic Organs

- Hematopoiesis after birth
  - Bone marrow hematopoiesis
  - Extramedullary hematopoiesis

QA: **When hemolytic anemia occurs, splenomagly is more apparent in infants than that in adults. Why?**

Development of the Hematopoietic Blood Cells

- Pluripotent Stem Cells

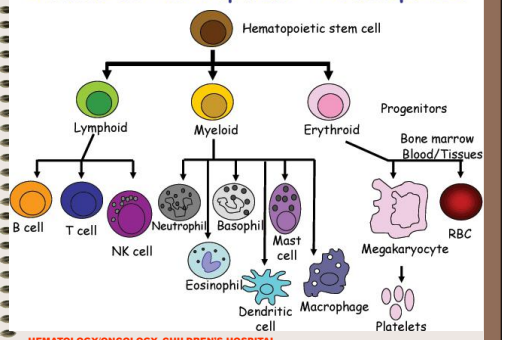
多能造血干细胞：

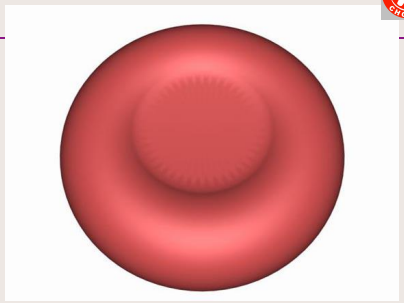
- which are capable of both self-renewal and of clonal maturation into all blood cell lineages.
- Progenitor cells differentiate under the influence of hematopoietic growth factors

Table 2.The Development of Blood Cells

PROGENITOR	CYTOKINES	PRODUC
CFU-GM	G-CSF 粒-集落刺激因子	NEUTROPHIL
CFU-Meg	TPO 血小板生成素	PLT
CFU-E BFU-E	EPO 红细胞生成素	RBC

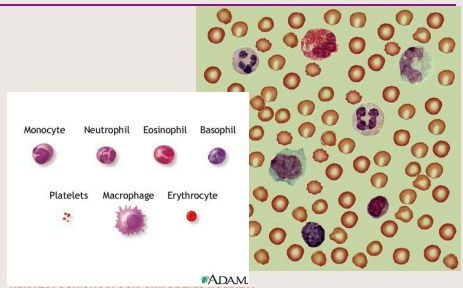
Immune cell development: Hematopoiesis





Blood Cell Counts and Hemoglobin

Fig2. Peripheral Blood Cells



RBC and Hb Level

- **At Birth:**
  - RBC: 5-7x10^{12}/L
  - Hb:150 to 230g/L.

Polycythemia
红血球增多症

Age	Anemia
Newborn	< 145g/L
1-4 mo	< 90g/L
4-6 mo	< 100g/L
6 mo-6 yr	< 110g/L
6-14 yr	< 120g/L

RBC and Hb Level

- At Birth:
- physiological anemia / Postnatal fall
  - Hemoglobin values in term infants drop to their lowest mean of 100g/L at 2-3 mo
  - Preterm infant

Age	Anemia
Newborn	< 145g/L
1-4 mo	< 90g/L
4-6 mo	< 100g/L
6 mo-6 yr	< 110g/L
6-14 yr	< 120g/L

RBC and Hb level

- Physiological Anemia.
  - Causes
    - Erythropoietin production↓
    - Red cell life span (90/120)
    - Blood volume↑

RBC and Hb Level

- At Birth:
- physiology anemia / Postnatal fall
- Infancy – Preschool age:
  - RBC: 4 x 10^{12}/L
  - Hb: 110 g/L
- 7-12yr: adult level
  - Hb: 120 g/L

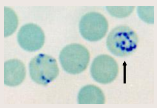
Age	Anemia
Newborn	< 145g/L
1-4 mo	< 90g/L
4-6 mo	< 100g/L
6 mo-6 yr	< 110g/L
6-14 yr	< 120g/L

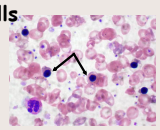
RBC and Hb Level

- At Birth:
  - RBC: 5-7x10^{12}/L
  - Hb:150 to 230g/L.
- Postnatal fall /physiology anemia
- Infancy – Preschool age:
  - RBC: 4 x 10^{12}/L
  - Hb: 110 g/L
- 7-12yr: adult level

RBC and Hb level

- Reticulocytes（网织红细胞）
  - At Birth: 5% / 10%
  - 1-2mo: fall down to 0.3%
  - Later adult level: 0.5-1.5%
- Nucleated Red Blood Cells
  - At birth: 3-10/100 WBC; 10-20/100WBC
  - 1wk: disappear



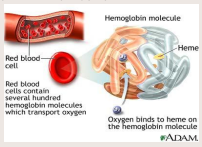


RBC and Hb level

- Reticulocytes（网织红细胞）and nucleated Red Blood Cells
  - Persistence of a high reticulocyte count is abnormal and often suggests a hemolytic process or blood loss.
  - Nucleated RBC present in peripheral blood often suggests active hematopoiesis respond to hemolysis or blood loss

HEMOGLOBIN 血红蛋白.

- **Function**
  - transport oxygen.
- **Construction**
  - iron-containing heme plus globins which is a tetramer made up of two pairs of polypeptide chains,



HEMOGLOBIN 血红蛋白.

血红蛋白是一个纯粹的蛋白吗？

你的血红蛋白有几种组分？

Table3. HEMOGLOBINS

	Hb	Chains	8周	6月	出生	6-12月	2岁
Embry	Gower1	$\zeta_2\varepsilon_2$	8周前，3月消失				
	Gower2	$\alpha_2\varepsilon_2$					
	Portlan	$\zeta_2\gamma_2$					
Fetal	HbF	$\alpha_2\gamma_2$	增加	90%	70%	<5%	<2%
Adult	HbA	$\alpha_2\beta_2$		5-10%	30%	>95%	>95%
	HbA_2	$\alpha_2\delta_2$			<1%	2-3%	<3.5%

HEMOGLOBIN.

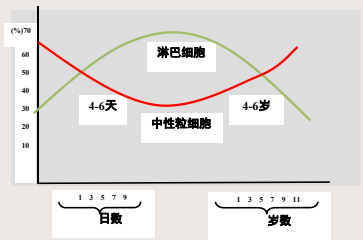
QA：2岁后血红蛋白组分及比例？

- Hb A (α2β2)： >95%
- Hb A2 (α2 δ2): < 3.5%
- Hb F (α2 γ2): < 2.0%

WBC Counts

- At birth: 20 x 10^9/L
- Infant: 12 x 10^9/L
- Preschool: 8.0 x 10^9/L

Fig4. WBC Ratio



WBC Counts

- 简单病例
  - 男孩，2岁2月，因发热1天就诊
  - 查体发现：T38℃,面色红润，咽部充血，扁桃1度，肺心（-）
    - WBC 10 x 10^9/L, N 0.30, L 0.68 ？
    - WBC 18 x 10^9/L, N 0.70, L 0.28 ？

PLT & Blood Volume

- **PLT:** 100-300 x 10^9/L
- **Blood Volume:**
  - Term newborn: 85ml/kg
  - Premature infant: 95ml/kg
  - Adult: 75ml/kg
  - Young children: 75-80ml/kg

The Introduction of ANEMIA

Prevalence of anemia in children 0-5 years old WHO region, 1998

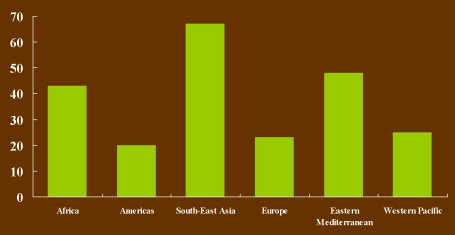
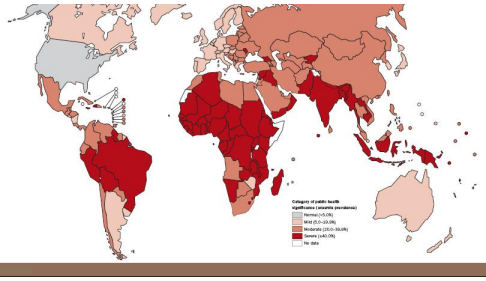


Table 2.3 ***Classification of anaemia as a problem of public health significance***

Prevalence of anaemia (%)	Category of public health significance
≤4.9	No public health problem
5.0–19.9	Mild public health problem
20.0–39.9	Moderate public health problem
≥40.0	Severe public health problem

Source: adapted from reference (2)



Definition of Anemia

- *A reduction of the red blood cell volume or hemoglobin concentration below the range of values occurring in healthy persons*
- *是指单位容积内的红细胞数、血红蛋白量或红细胞比容低于正常值。*

Table 4. The definition of Anemia

年龄	贫血值
neonate	< 145g/L
1-4月	< 90g/L
4-6月	< 100g/L
6月-6岁	< 110g/L
6-14岁	< 120g/L

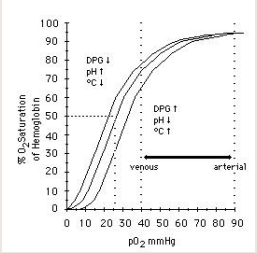
Table 4. The degree of Anemia

	Mild	Moderate	Severe	Extremely
children	-90g/L	-60g/L	-30g/L	<30g/L
neonate	144-120g/L	-90g/L	-60g/L	<60g/L

Pathophysiology of Anemia

- Pathophysiology
  - increased cardiac output
  - increased oxygen extraction
  - blood flow toward vital organs and tissues.
  - In addition, the concentration of 2,3-DPG increases within the RBC.

Fig5:The oxygen dissociation cur



Manifestation of Anemia

- Acute onset
  - elevated pulse, hemic flow murmur, poor exercise tolerance, headache, excessive sleeping, poor feeding, and syncope may occur.
- Slow onset
  - weakness, tachypnea , shortness of breath on exertion, tachycardia, cardiac dilatation, and congestive heart failure

Manifestation of Anemia

- 一般表现
  - 皮肤黏膜苍白
- 造血器官
  - 肝脏、脾脏、淋巴结肿大
  - 外周血有核红细胞、幼稚粒细胞
- 系统表现
  - 循环呼吸：呼吸心率加快、心脏扩大、收缩期杂音
  - 消化系统：食欲减低、恶心、腹胀、便秘
  - 神经系统：嗜睡烦躁、注意力不集中、头晕、耳鸣；智力减退、神经精神发育障碍

Classification of Anemia

形态学分类 morphology

病因学分类 etiology

Classification-morphology

Table 5	MCV (fl)	MCH (pg)	MCHC (%)
Normal ranges	80-94	28-32	32-38
Macrocytic	>94	>32	32-38
Normocromic /Normocytic	80-94	28-32	32-38
Microcytic	<80	<28	32-28
Hypochromic /Microcytic	<80	<28	< 32

Classification- Etiology

Reduced capacity to produce red blood cells
红细胞生成减少

Hemolysis
红细胞破坏—溶血性贫血

Blood Loss
失血性贫血

Classification- etiology

- Reduced capacity to produce red blood cells
  - Aplastic anemia 再生障碍性贫血
    - Fanconi's anemia
    - Acquired aplastic anemia
  - Pure red cell aplasia 纯红细胞再生障碍性贫血
    - congenital hypoplastic anemia (Diamond-Blackfan)
    - Acquired hypoplastic anemia

Classification- etiology

- Aplastic anemia 再生障碍性贫血
  - 原发性或获得性
  - 贫血、感染、出血的表现
  - 脾脏不肿大
  - 外周血三系减低，网织红细胞减低
  - 骨髓病理帮助确诊
  - 免疫抑制剂治疗+造血干细胞移植

Classification- etiology

- Aplastic anemia
  - 重庆儿童医院血液中心近年移植结果
    - 双胞胎骨髓移植2例
    - 兄妹骨髓移植11例
    - 无关供者3例

Classification- etiology

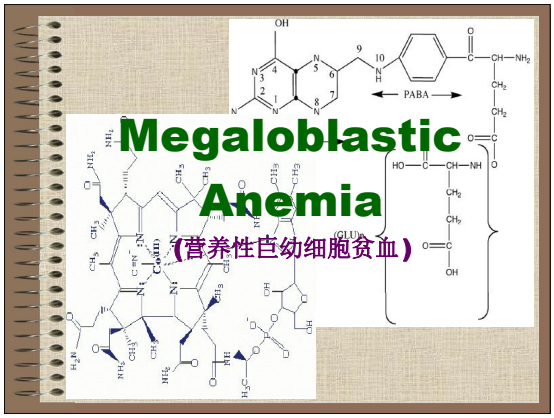
- Reduced capacity to produce red blood cells
  - Marrow Infiltration 骨髓浸润
    - Leukemia 白血病
    - Lymphoma 淋巴瘤
    - Neuroblastom 神经母细胞瘤
    - LCH 朗格罕细胞组织细胞增生症

Classification- etiology

- Acute leukemia 白血病
  - 造血系统的恶性增生性疾病
  - 发热、贫血、出血
  - 肝脾淋巴结肿大等浸润
  - 外周血各系血细胞异常，可以出现原始幼稚细胞
  - 骨髓原始幼稚细胞比例≥30%
  - 化疗为主的综合治疗

Classification- etiology

- Reduced capacity to produce red blood cells
  - Deficiency Syndrome
    - Iron
    - Folate
    - Vitamin B_{12}
    - Vitamin E
    - Vitamin B_6



INTRODUCTION

- Definition: A kind of anemia with larger RBC, caused by the deficiency of folic acid and/or vitamin B12
- Clinical features:
  - macrocytic anemia,
  - neuropsychiatric changes,
  - megaloblastic RBC in the bone marrow,
  - response to vitamin B12 and folic acid well.
- The incidence: changing from common to rare

ETIOLOGY

- Inadequate intake
- Decreased absorption
- Drug induced abnormalities
- Congenital abnormalities

ETIOLOGY

- **Inadequate intake**
  - All we need of B12 and folate is from food; The requirement:
    - ✓ for B12: 1ug/d;
    - ✓ for folate: 60-100ug/d (WHO)
  - Under clinical conditions where there are increased vitamin requirements (pregnancy, growth in infancy, chronic hemolysis).

ETIOLOGY

- **Inadequate intake**
  - Folates
    - abundant in many foods including green vegetables, fruits, and animal organs (liver, kidney).
    - Human breast milk, pasteurized cow's milk. and infant formulas provide adequate amounts of folic acid.
    - Goat's milk is deficient; folic acid supplementation must be given when it is the main food.
    - Unless supplemented, powdered milk may also be a poor source of folic acid.

ETIOLOGY

- **Inadequate intake**
  - Vitamin B12
    - Vitamin B12 (cobalamin) is present in many foods, mostly in animal foods,
    - Vitamin B12 deficiency may occur in the cases of extreme dietary restriction (strict vegetarians or vegans)
      - occurs in breast-fed infants whose mothers are vegans or themselves have pernicious anemia

ETIOLOGY

- **Decreased absorption**
  - Chronic diarrhea
  - Inflammatory diseases
  - Neonatal necrotizing enterocolitis
  - Surgery in interestine /terminal ileum

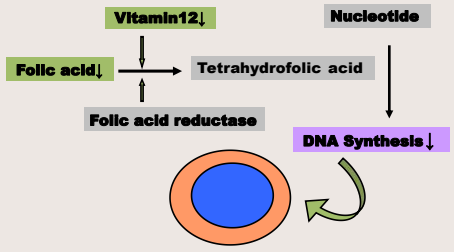
ETIOLOGY

- **Drug induced abnormalities**
  - Certain anticonvulsant drugs (e.g., phenytoin, primidone, phenobarbital) can impair absorption of folic acid
  - A number of drugs have anti-folic acid activity: Methotrexate

ETIOLOGY

- **Congenital abnormalities**
  - Ccongenital dihydrofolate reductase deficiency
  - Lack of intrinsic factor - *Congenital pernicious anemia*
  - Transcobalamin II (TC-II) deficiency

PATHOGENESIS



PATHOGENESIS

- Influence on hematopoiesis (造血)
  - Megaloblastic RBC
    - Decreased DNA synthesis delays the maturation of the nucleus of erythrocytes
  - Neutrophil and Megakaryocyte
    - hypersegmented neutrophils (many neutrophils with more than four to five lobes).
  - Ineffective erythropoiesis (无效造血)
    - that describes active erythropoiesis with premature death of cells, a decreased output of RBC from the marrow, and, consequently, anemia.

PATHOGENESIS

- Influence on neurological system
  - Vitamin B12 plays important role in keeping the **intact of the nerve fibers containing myelin sheath**
  - The deficient result in **neuropsychiatric** changes

CLINICAL MANIFESTATION

- General一般情况
  - 6～18mo
  - Weaknes s, fatigue, or irritability, failure to thrive,
  - glossitis, vomiting, diarrhea
  - Hair: less and yellowish.
- Anemia 血液系统:
  - Pale and puffy
  - icterus; Petechia
  - Hepatomegaly / splenomeagly

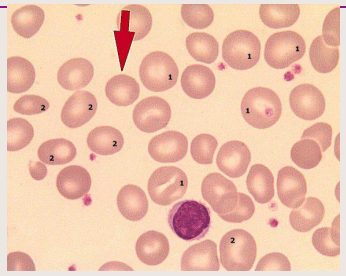
CLINICAL MANIFESTATION

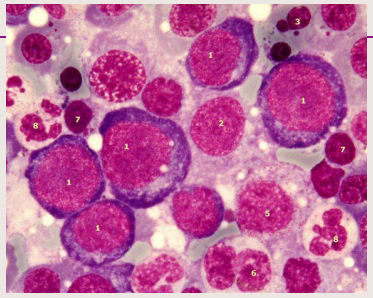
- Neurological involvement (神经系统)
  - developmental delay, developmental regression
  - Trembles, seizures
  - paresthesias, sensory deficits, hypotonia
  - neuropsychiatric changes.

Neurologic problems from vitamin B12 deficiency can occur in the absence of any hematologic abnormalities

LAB FINDINGS

- Macrocytic normochromic anemia
- Neutrophils may be large and hypersegmented, Neutropenia with/ thrombocytopenia
- Marrow film: megaloblastic forms of nucleated RBC
- Serum Vit B12 and /or folic acid

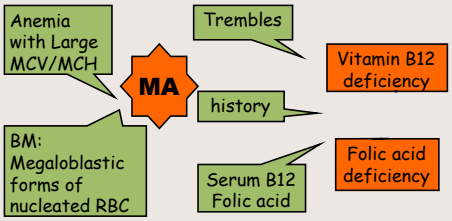




DIAGNOSIS

- Clinical manifestation: anemia
- Peripheral blood
  - macrocytic anemia, fragmented neutrophils ,
- Bone marrow
  - megaloblastic forms of nucleted RBC
- Serum B12 level and Folic acid concentration

DIAGNOSIS



TREATMENT

- General care
- Drug therapy
  - Vitamin B12
    - 25-100ug/次，2-3 times/w，weeks or to Hb normal；
    - One high dose：500ug im
  - Folic acid：5mg, tid, 2-3w，
  - Other drug：Vitamin C；B6：iron in recovery
- Transfusion

PREVENTION

- Good nutrition for mother
- Avoid strict diet restriction
- Provide solid food for infants
- Treat the GI disorders
- the drug induced MA

Classification- etiology

- **Hemolysis**
  - **Intrinsic RBC abnormalities**
    - Hemoglobinopathies
    - Enzymopathies
    - Membrane disorders
  - **extrinsic RBC abnormalities**
    - Immunologic: AIHA
    - others

Classification- etiology

- **Hemolysis: intrinsic RBC abnormalities**
  - Intrinsic membrane defects
    - Hereditary Spherocytosis:
      （遗传性球形红细胞增多症）
  - Hemoglobinopathy
    - Thalassemia （地中海贫血）
  - RBC enzyme defects
    - G6PD deficiency
      （红细胞葡萄糖-6-磷酸脱氢酶缺乏症）

Classification- etiology

- **遗传性球形红细胞增多症**

Hereditary Spherocytosis **(HS)**

- 先天性红细胞膜骨架蛋白异常所致的遗传性溶血性贫血

—贫血、黄疸、脾脏肿大

—外周血球形红细胞增多

—红细胞渗透脆性增加osmotic fragility test

—Splenectomy 脾脏切除治疗有效

Classification- etiology

- **Hemolysis: extrinsic RBC abnormalities**
  - Immunologic hemolysis
    - Isoimmune (Rh, ABO in neonate)
    - Autoimmune Hemolytic Anemia (AIHA)
      （自身免疫性溶血性贫血）

Classification- etiology

- **自身免疫性溶血性贫血 (AIHA)**
  - 原发或继发
  - 温抗体（IgG)和冷抗体型(IgM)
  - 贫血、黄疸、尿色加深
  - 脾脏肿大
  - 抗人球蛋白试验 Coombs test(+)

Classification- etiology

- **Blood Loss**
  - Gastrointestinal bleeding
    - Ucler 消化道溃疡
    - Ankylostomiasis （钩虫病）
  - Menstrual （月经）
  - Trauma （外伤）

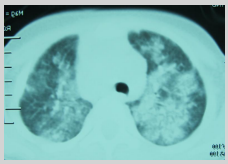



Table. Diagnosis Approach for Anemia

HYPOCHROMIC MICROCYTIC	NORMOCHROMIC NORMOCYTIC	MACROCYTIC	RETICULOCYTE COUNT
Iron deficiency -Chronic blood loss -Poor dietary intake -Cow's milk protein intolerance **Thalassemia** **Chronic inflammatory disease** **Lead intoxication** **Copper deficiency**	**Chronic inflammatory disease** **Malignancy marrow infitrition** **Recent blood loss** **Uremia** **Aplasia/ hypoplasi**	**VitaminB12 deficiency** **Folate deficiency** **Chronic liver disease** **Marrow failure** -Fanconi anemia -Aplastic anemia -Myelodysplasia **Drugs** - Axidothymidine	**HEMOLYSIS** Hemoglobinopathy -thalassemia Enzymopathy -G6PD deficiency Membranopathy -HS Acquired - AIHA/ DIC,HUS **BLOOD LOSS**

Summary and Homework

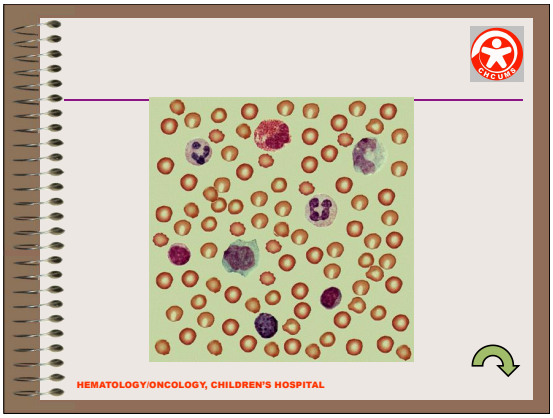
- Hematopoiesis
  - Fetal hematopoiesis
  - Bone marrow hematopoiesis
    - Red marrow/fatty marrow
    - Extramedullary hematopoiesis
- Blood cell
  - Counts in different ages
  - Physiologic anemia
  - Fetal Hb and normal Hb pattern
  - WBC and differential ratio
- Anemian
  - The definition of anemia
  - The classification of anemia

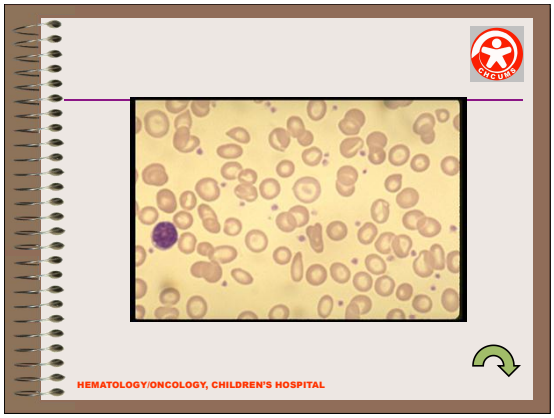
Hematopoiesis Related Terms

- CFU-GM
  - colony -forming units granulocyte-macrophages
- CFU-Meg
  - colony-forming unite-megakaryocyte
- CFU-E
  - colony-forming units-erythroid
- BFU-E
  - burst-forming units-erythroid
- G-CSF
  - colony-stimulating factor 粒细胞集落刺激因子
- TPO
  - thrombopoietin 血小板生成素
- EPO
  - Erythropoietin 红细胞生成素

RBC Index

- **MCV**
  - Mean corpuscular volume
- **MCH**
  - Mean corpuscular hemoglobin
- **MCHC**
  - Mean corpuscular concertration


HEMATOLOGY/ONCOLOGY, CHILDREN'S HOSPITAL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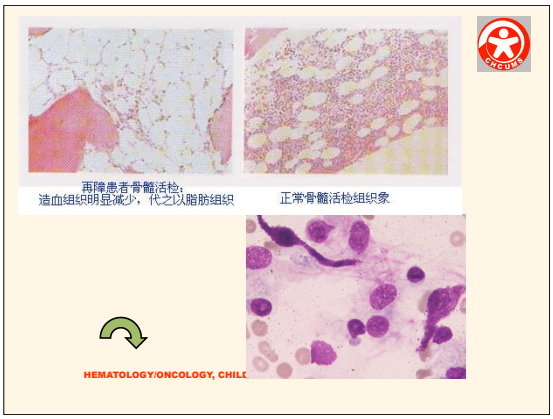
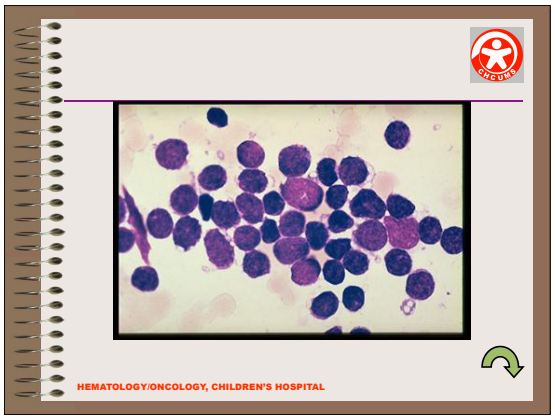

再障患者骨髓活检，
造血组织明显减少，代之以脂肪组织
正常骨髓活检组织象
HEMATOLOGY/ONCOLOGY, CHILD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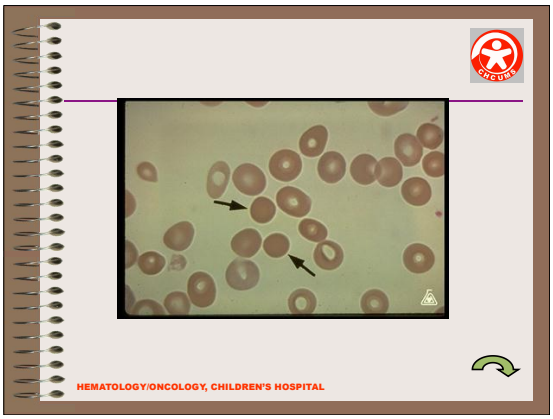
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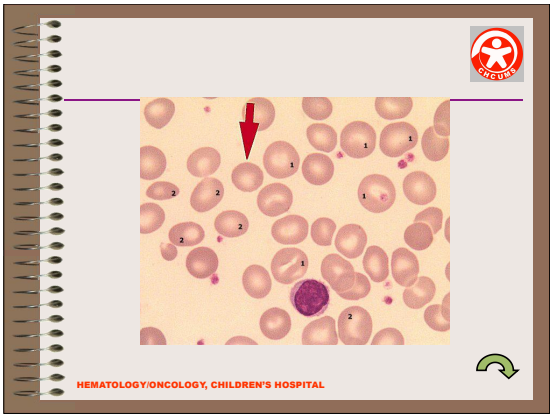
HEMATOLOGY/ONCOLOGY, CHILDREN'S HOSPITAL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