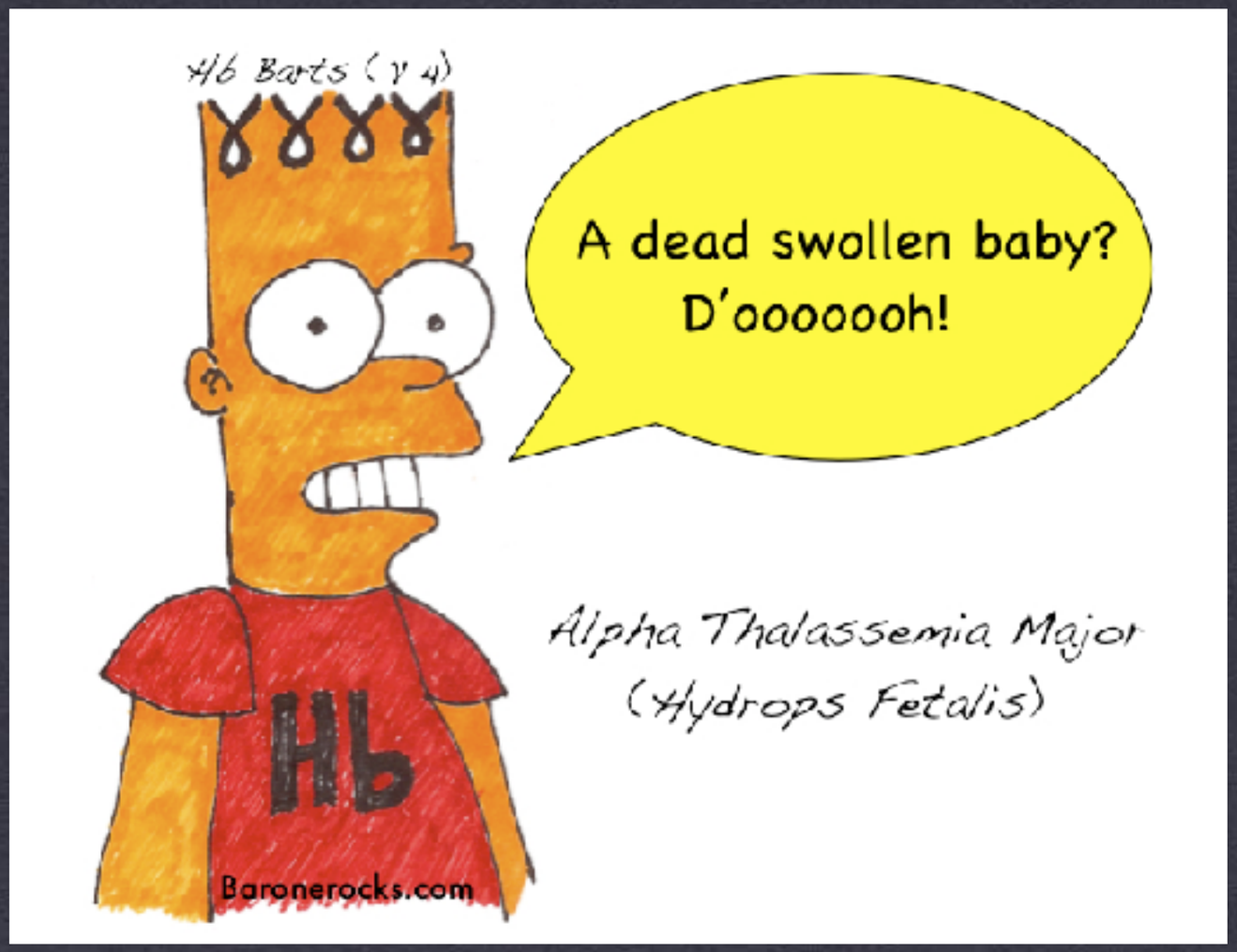
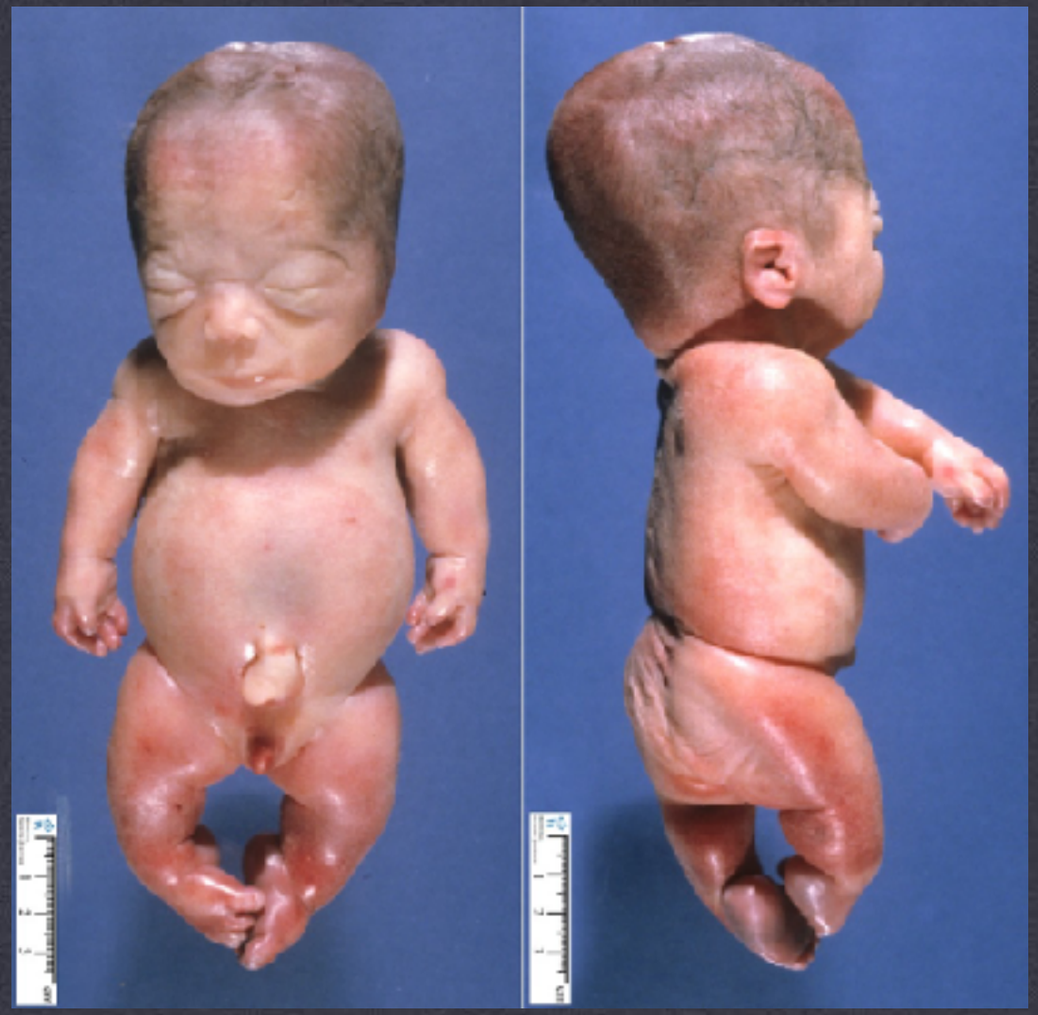




HYDROPS FETALIS SYNDROME

APICHAT PHOTI-A, MD.

PHRAMONGKUTKLAO HOSPITAL

Outlines

Part I

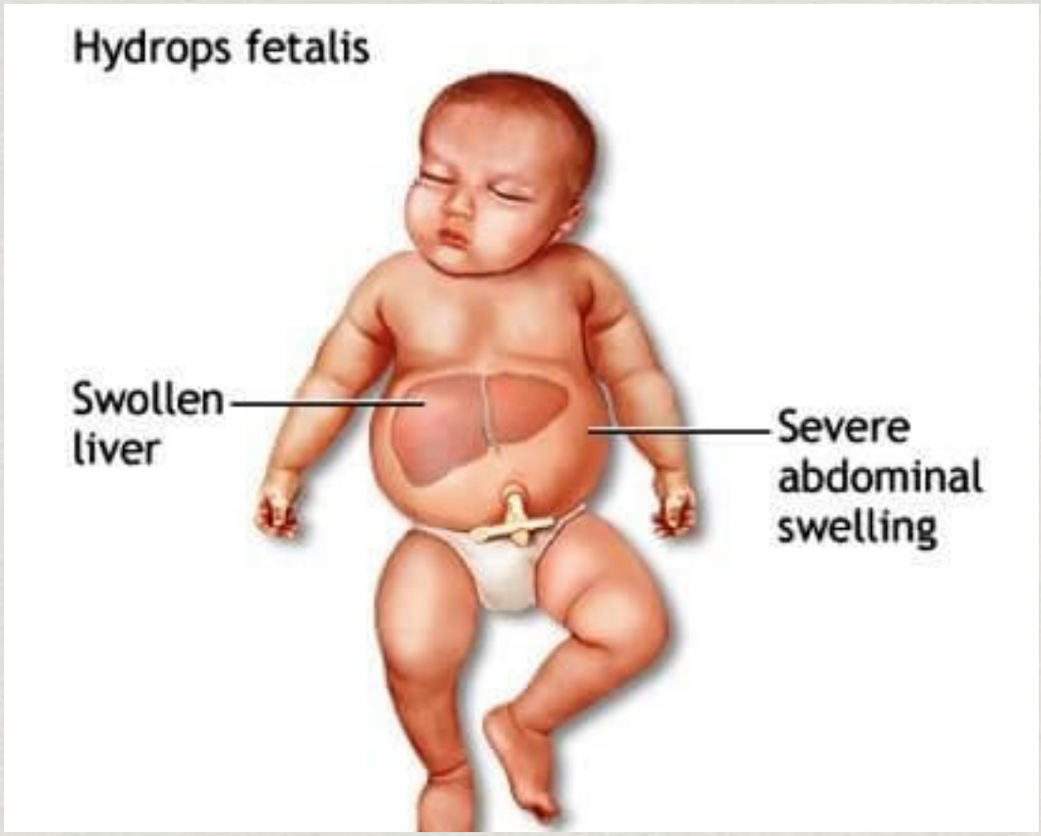
- Basic background of hydrops fetalis
- Pathophysiology

Part II

- An international registry of survivors with Hb Bart's hydrops fetalis syndrome

Hydrops Fetalis

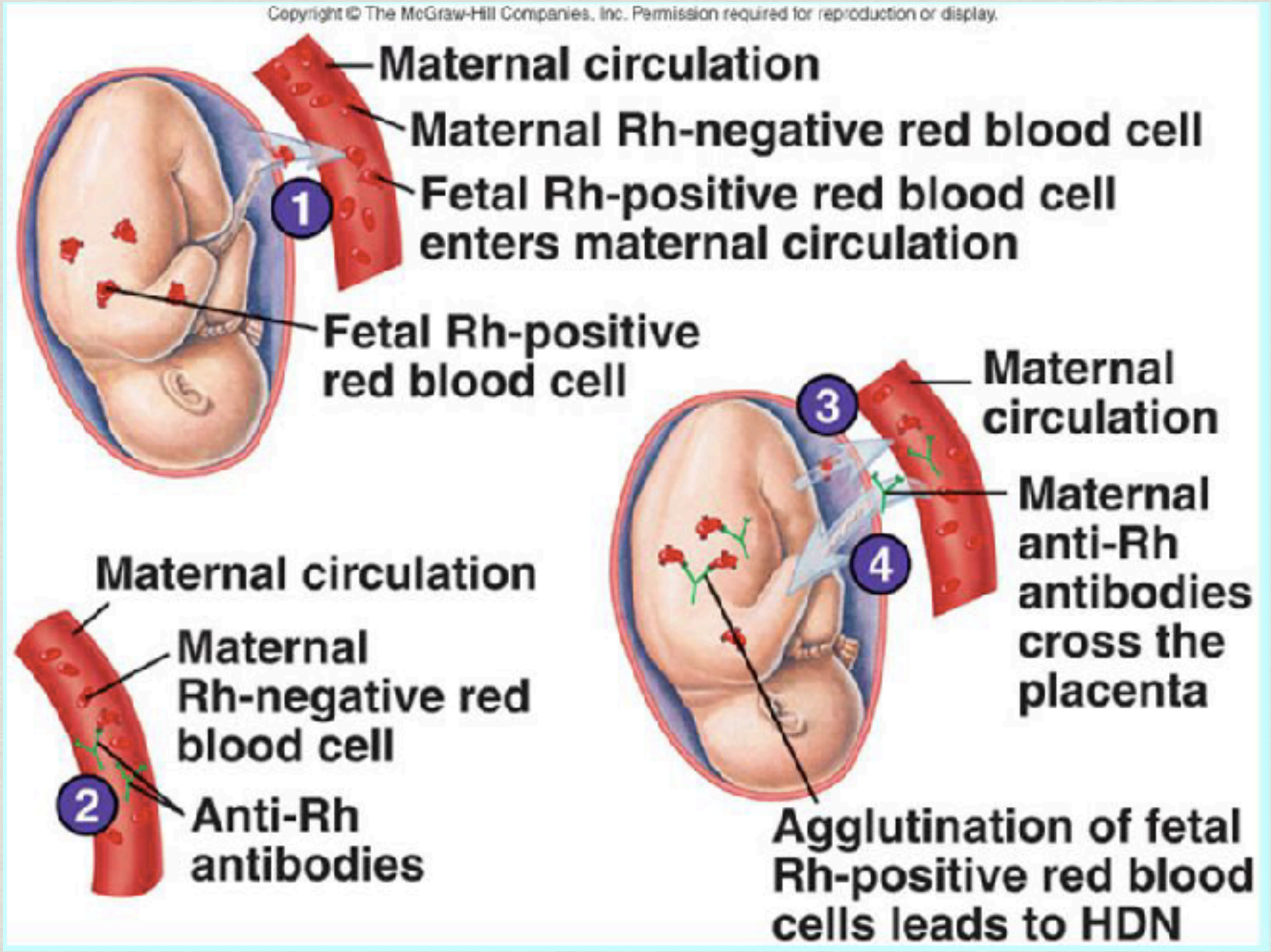
- First described in 1892
- Latin for ***"edema of the fetus"***
- found in about 1 per 2,000 births
- Characterized by an abnormal collection of fluid with at ***least two of the following***:
  - Edema
    (fluid more than 5 mm)
  - Ascites
  - Pleural effusion
  - Pericardial effusion



Etiology

Immune Hydrops	Nonimmune Hydrops
Anemia from red cell alloimmunization	No evidence of red cell alloimmunization
10-20% of cases	80-90% of cases

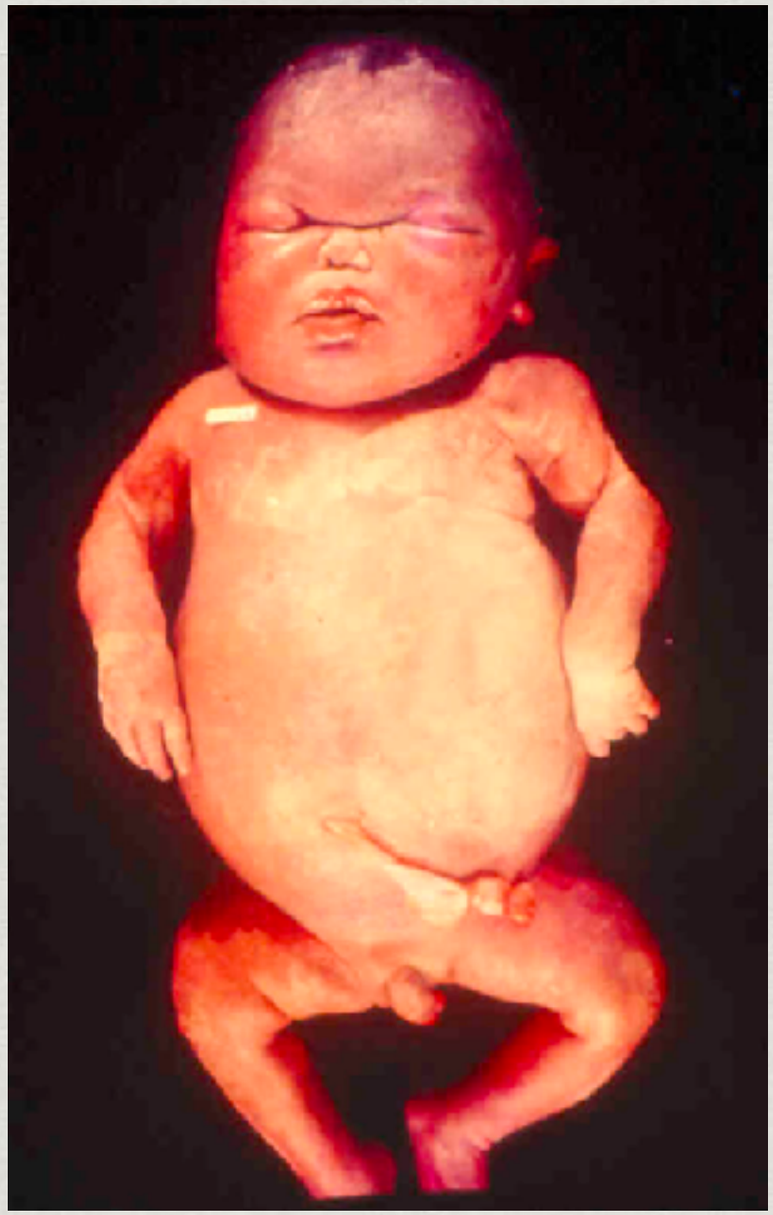
Immune Hydrops



Ref : www.Google.com/image/The McGraw-Hill companies

Nonimmune Hydrops

- Causes can be grouped in 6 broad categories
  - Cardiovascular
  - Genetic abnormalities
  - Intrathoracic malformations
  - Hematological disorders
  - Infectious conditions
  - Idiopathic forms



Ref : www.pregmed.org/hydrops-fetalis.htm

Etiology

Current Pediatric Reviews, 2005, *1*, 63-72

Aetiology, Diagnosis and Treatment of Hydrops Foetalis

Timo R. de Haan[1], Dick Oepkes[2], Matthias F.C. Beersma[3] and Frans J. Walther*,[1]

[1]*Division of Neonatology, Department of Paediatrics,* [2]*Department of Obstetrics,* [3]*Department of Medical Microbiology, Leiden University Medical Centre, Leiden, The Netherlands.*

Ref : Timo R. et al.,Current Ped Reviews, 2005

Etiology

Anemic Hydrops	Nonanemic Hydrops
Hematological	Metabolic
Infection	Cardiac
Feto-Maternal hemorrhage	Endocrine
	Genetic
	Thoracic disease
	Intestinal disease

Ref : Timo R. et al.,Current Ped Reviews, 2005

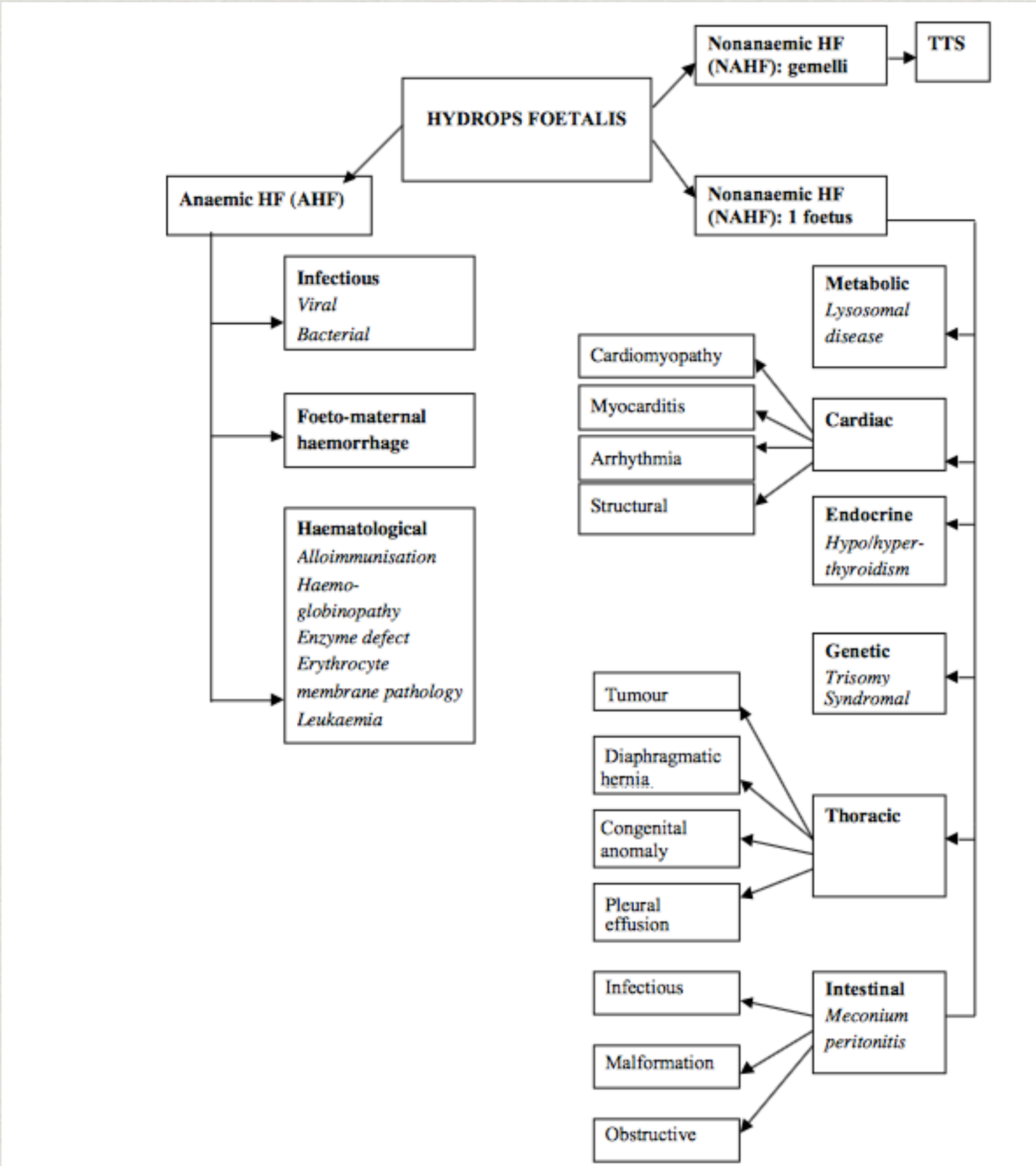


Fig. (1). Flow sheet for prenatal diagnosis of hydrops foetalis.

Ref : Timo R. et al.,Current Ped Reviews, 2005

Pathophysiology

- The precise pathophysiology of hydrops remains ***unknown***
- Theories includes
  - ***Heart failure*** form profound anemia and hypoxia
  - ***Portal hypertension*** due to hepatic parenchymal disruption caused by extramedullary hemopoiesis
  - ***Decreased colloid oncotic pressure*** resulting from liver dysfunction and hypopreteinemia

Pathophysiology

- ***The degree and duration of anemia*** is the major factor causing and influencing the severity of ascites
- Secondary factors include ***hypoproteinemia*** caused by liver dysfunction and ***capillary endothelial leakage*** resulting from tissue hypoxia
- Both of these lead to ***protein loss and decreased colloid oncotic pressure***

Pathophysiology

Severe anemia	**Congestive heart failure**	**Severe tissue hypoxia**
Hepatic extramedullary hematopoeisis & Decreased production of plasma proteins	**Increased central venous pressure**	**Endothelial cell damage**
Decreased plasma COP	**Increased capillary hydrostatic pressure**	**Capillary leak of fluid & protein**

Pathophysiology

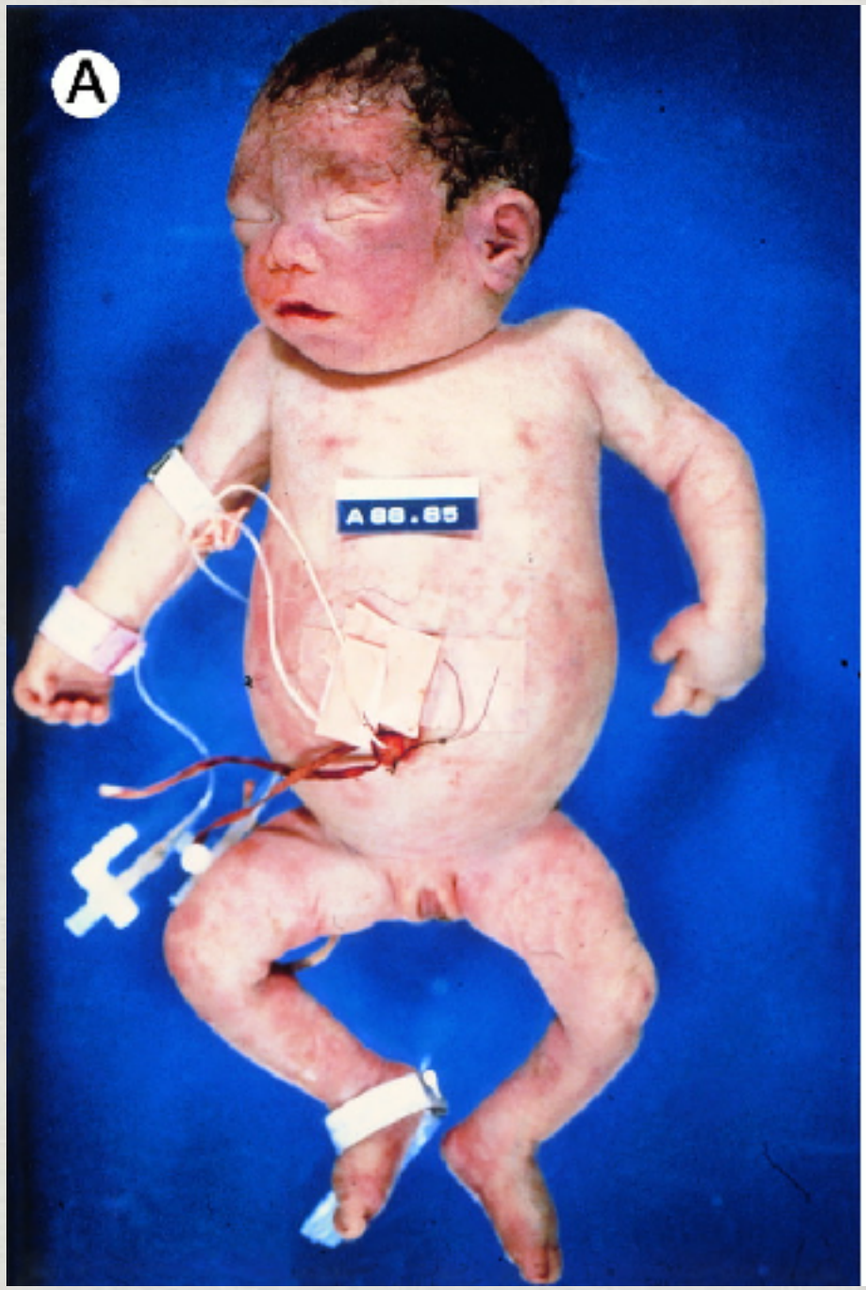
Decreased plasma COP

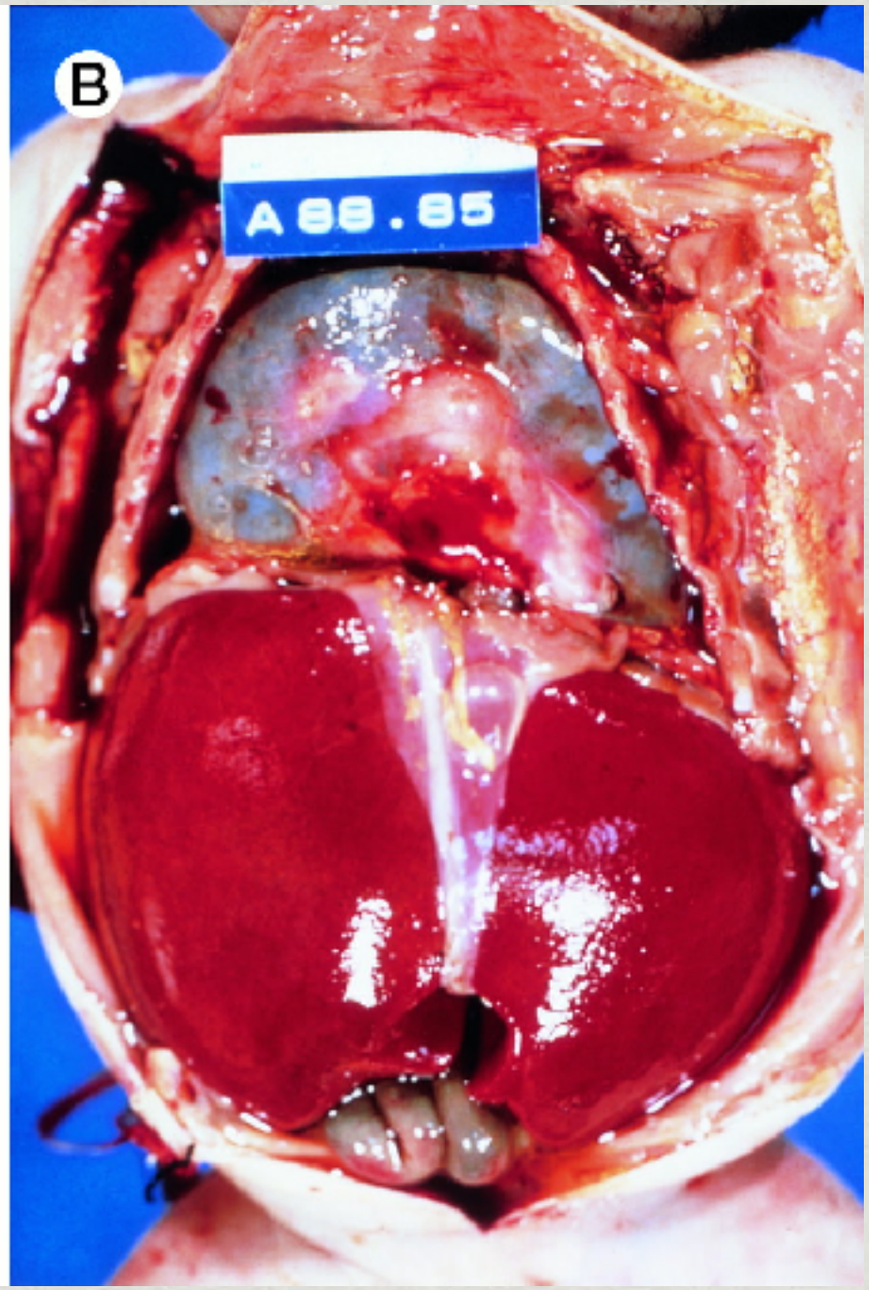
Increased capillary hydrostatic pressure

Capillary leak of fluid & protein

Increased fluid efflux from intravascular space

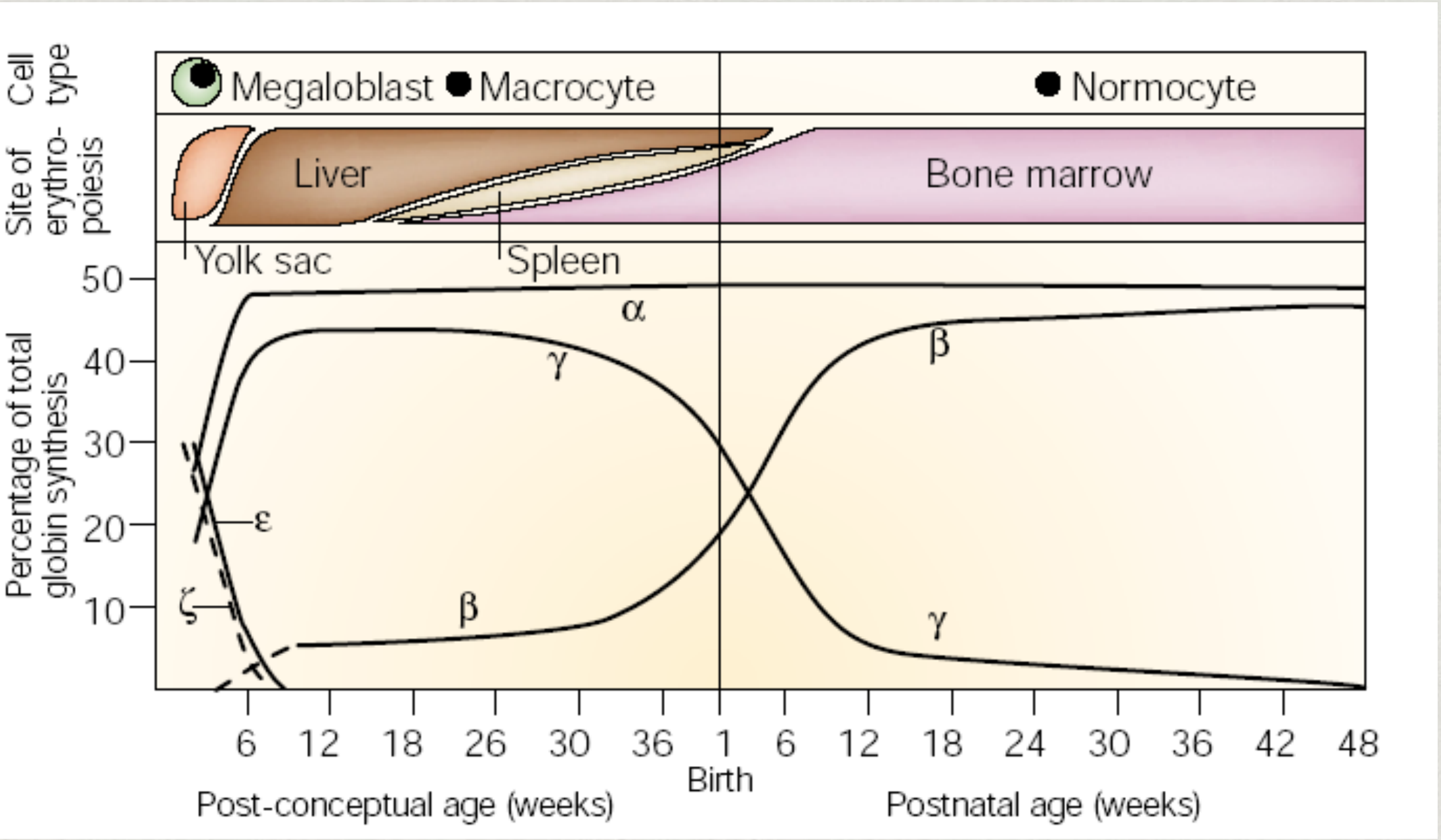
Hb Bart's Hydrop Fetalis Syndrome (BHFS)



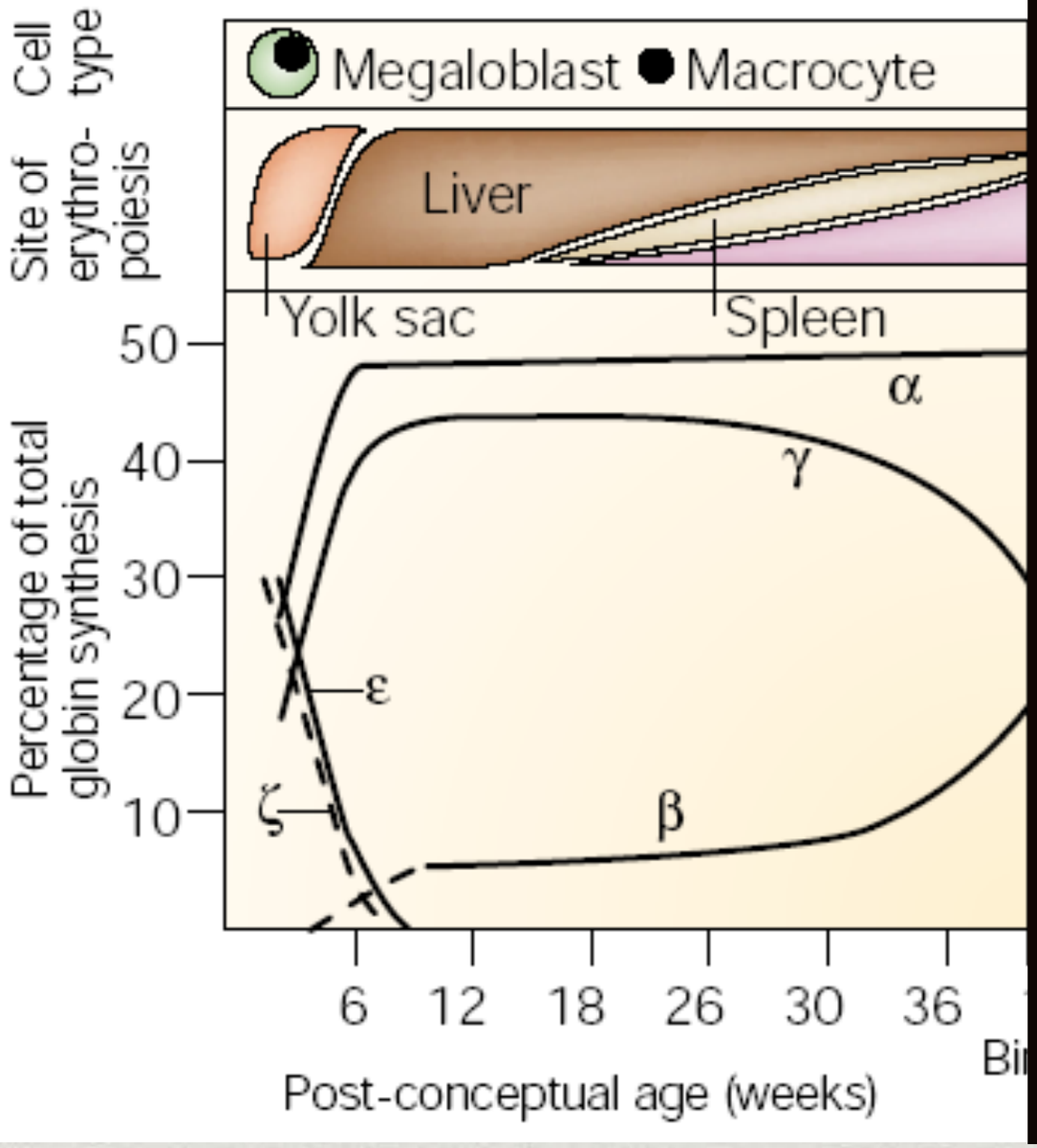


Ref : Chui, D. H. et.al., Hydrops Fetalis Caused by α-Thalassemia, ***Blood****, 91(7), 2213-2222.*

Globin gene synthesis



Globin gene synthesis



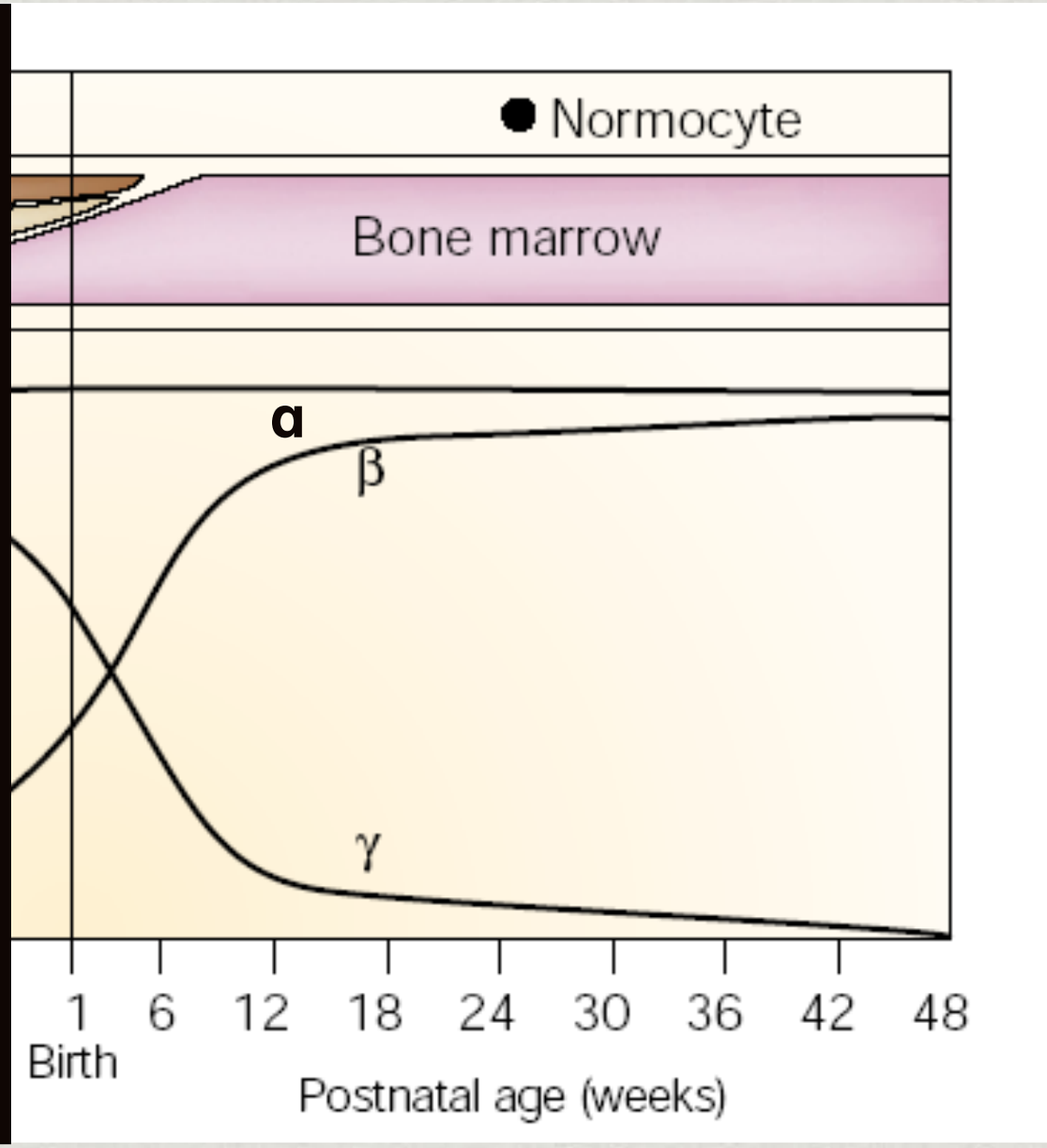
Embryonic Hemoglobin

- ***Hb Gower I*** : ζ2 ε2
- ***Hb Gower II*** : α2 ε2
- ***Hb Portland*** : ζ2 ɣ2

Globin gene synthesis

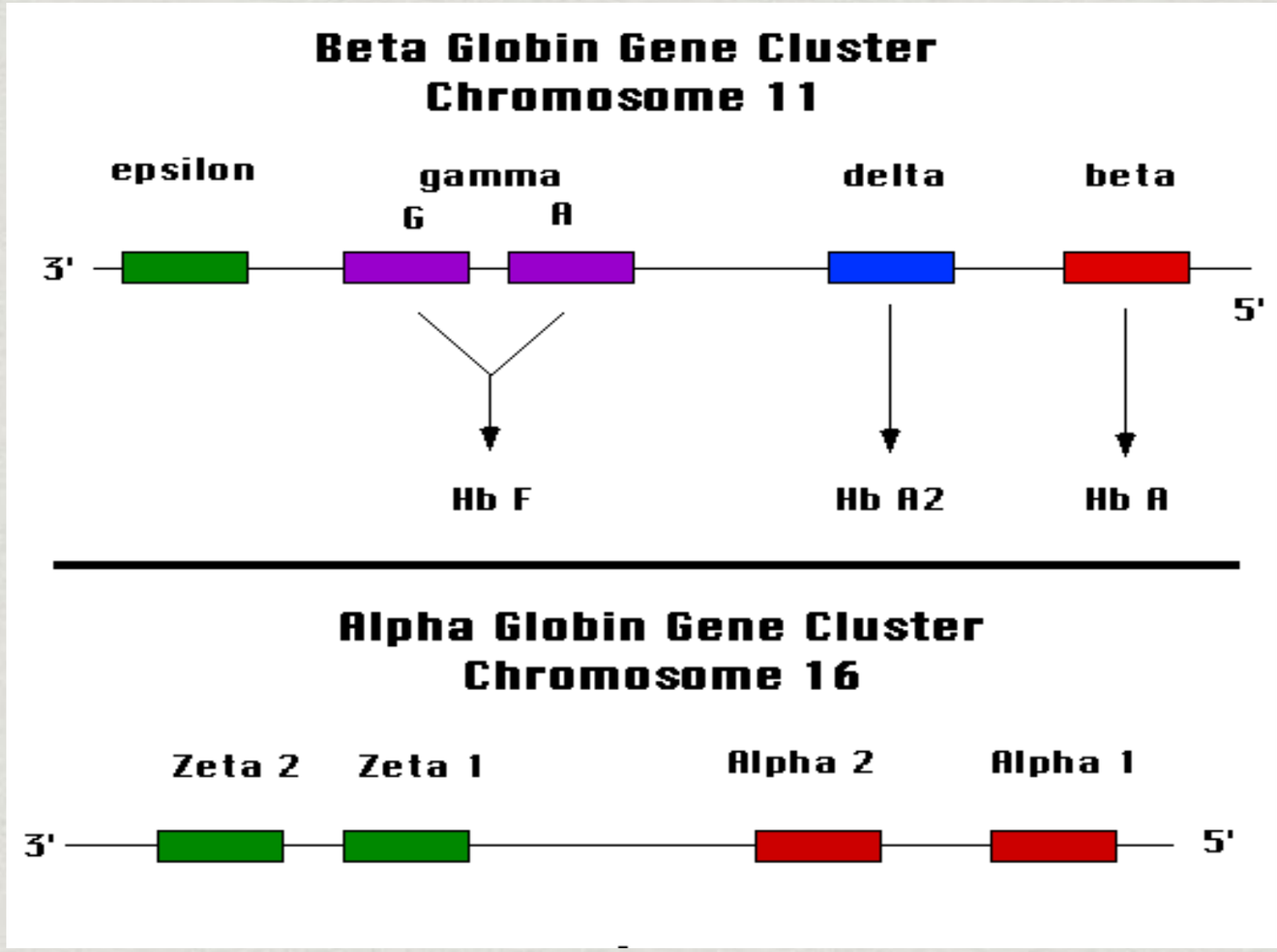
Fetal Hemoglobin

- ***Hb F*** : **α**2 **ɣ**2
- ***Hb A*** : **α**2 **β**2
- ***Hb A2*** : **α2 δ2**



Pathophysiology

Globin genes



Globin Proteins

β(Beta)

γ(Gamma)

δ(Delta)

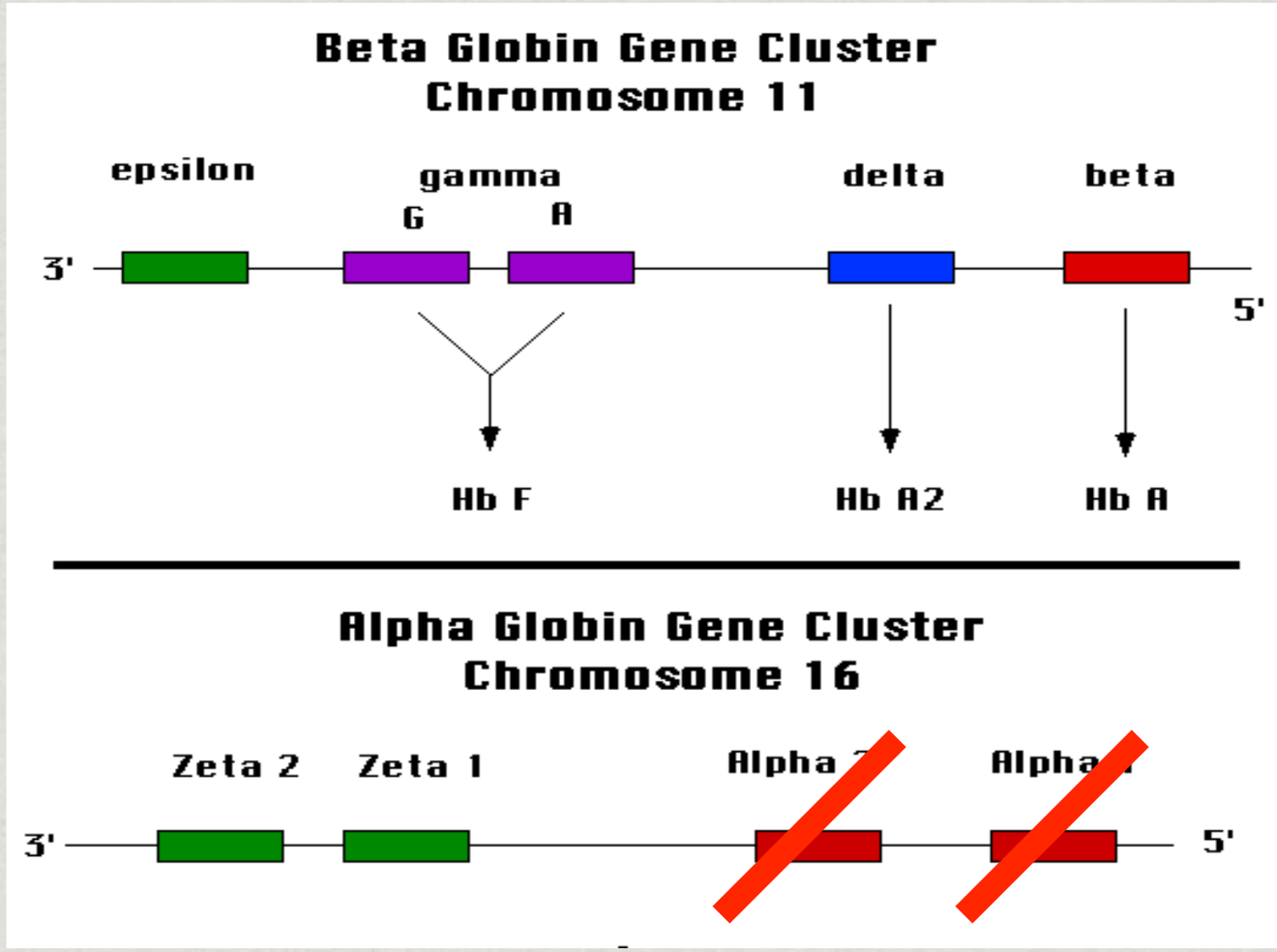
ε(Epsilon)

α(Alpha)

ζ(Zeta)

Pathophysiology

Globin genes



Globin Proteins

β(Beta)

γ(Gamma)

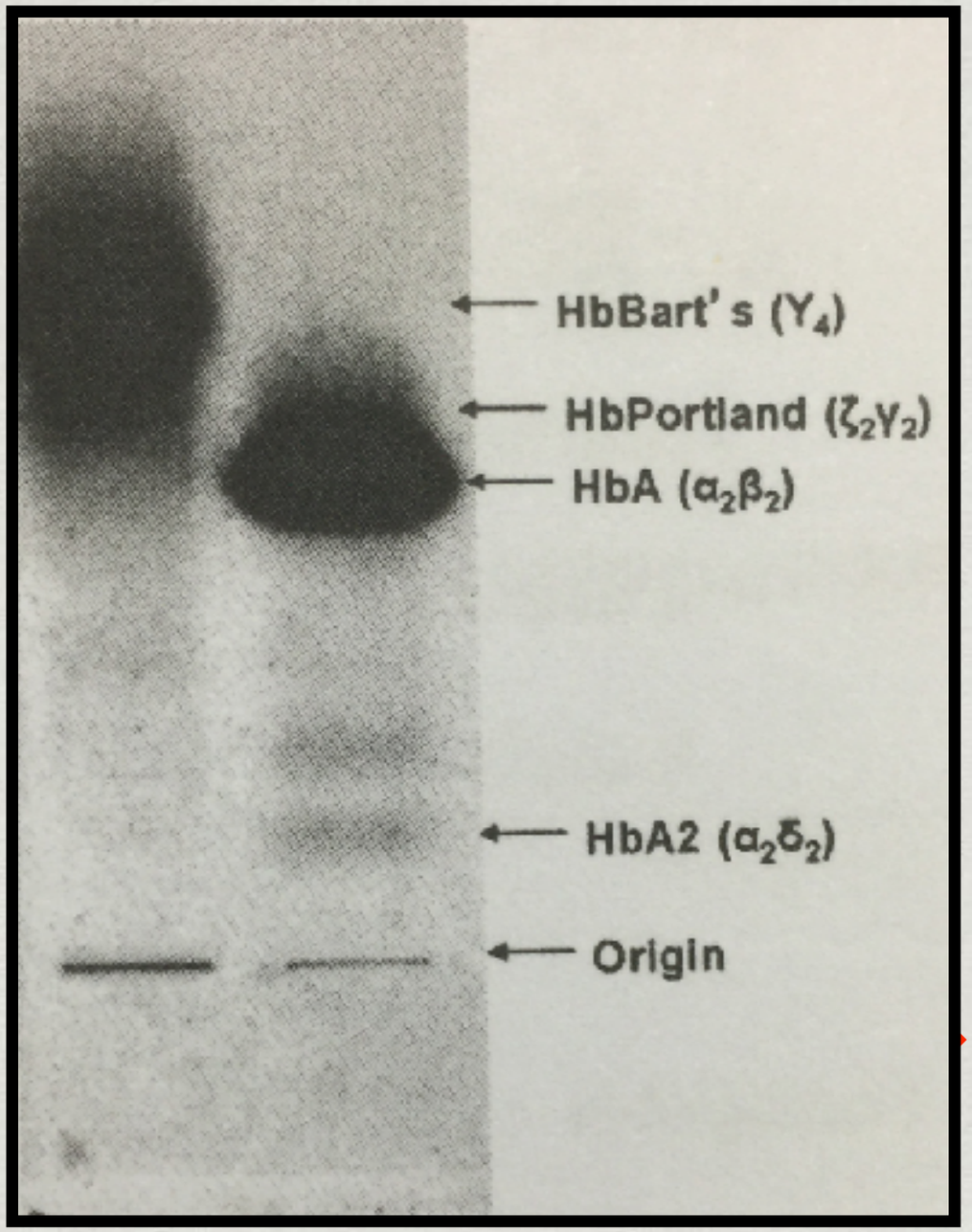
δ(Delta)

ε(Epsilon)

~~α(Alpha)~~

ζ(Zeta)

Pathophysiology



Globin Proteins

β(Beta)
γ(Gamma)
δ(Delta)
ε(Epsilon)

~~**α(Alpha)**~~
ζ(Zeta)

Review literature

An international registry of survivors with Hb Bart's hydrops fetalis syndrome

Duantida Songdej,[1,2] Christian Babbs,[1] and Douglas R. Higgs,[1] in collaboration with the BHFS International Consortium

[1]Medical Research Council Molecular Haematology Unit, Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom; and [2]Division of Hematology/Oncology, Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Table 1. Hb types present during development

Developmental stages	Normal	BHFS
Embryonic	Hb Gower I ($\zeta_2\varepsilon_2$)	Hb Gower I ($\zeta_2\varepsilon_2$)
	Hb Gower II ($\alpha_2\varepsilon_2$)	Hb Portland I ($\zeta_2\gamma_2$)
	Hb Portland I ($\zeta_2\gamma_2$)	
Fetal	Hb F ($\alpha_2\gamma_2$)	Hb Bart's (γ_4)
		Hb Portland I ($\zeta_2\gamma_2$)
Postnatal/adult	Hb A ($\alpha_2\beta_2$)	Hb H (β_4)
	Hb A_2 ($\alpha_2\delta_2$)	Hb Portland II ($\zeta_2\beta_2$)

Ref : SONGDEJ et al., An international registry of survivors with Hb Bart's hydrops fetalis syndrome, **Blood**, 2017; 129: 1251-1259

Hb Gower I : $\zeta_2\varepsilon_2$

Hb Portland I : $\zeta_2\gamma_2$

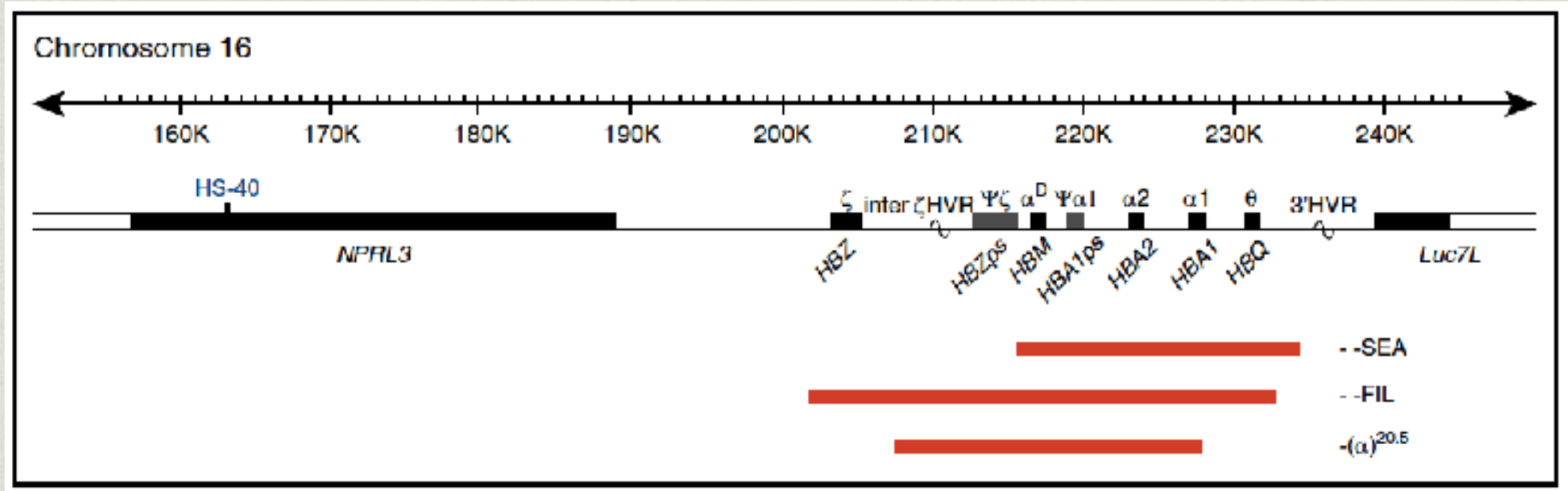
Hb Bart's : γ_4

Hb Portland I : $\zeta_2\gamma_2$

Hb H : β_4

Hb Portland II : $\zeta_2\beta_2$

Geographic distribution



69 cases		*Genotype*
50 cases	Homozygous SEA deletion	$(--^{SEA}/--^{SEA})$
2 cases	Heterozygous SEA and Filipino deletion	$(--^{SEA}/--^{FIL})$
1 cases	Homozygous $\alpha^{20.5}$ deletion	$(-\alpha^{20.5}/-\alpha^{20.5})$
14 cases	Deletion of all 4 α-globin genes	$(--/--)$
2 cases	Hb Bart's as the major globin present	

Prenatal diagnosis and intrauterine management

1990

4 cases
survived naturally

2000

17/29 cases (59%)
Intrauterine Rx

33/41 cases (80%)
Intrauterine RBC transfusion

2010

13/24 cases (54%)
Intrauterine Rx

6/41 cases (15%)
Intrauterine exchange transfusion

11/11 cases (100%)
Intrauterine Rx

2/41 cases (5%)
Intrauterine HSC transplantation

remain transfusion dependent !!!

Maternal complications

- Most common :
  Preterm delivery (47/66 : 71%)
- Antenatal period, the majority of problems arise in the ***3rd trimester*** with the median GA at detection being ***29 weeks (range 22-34 wks)***

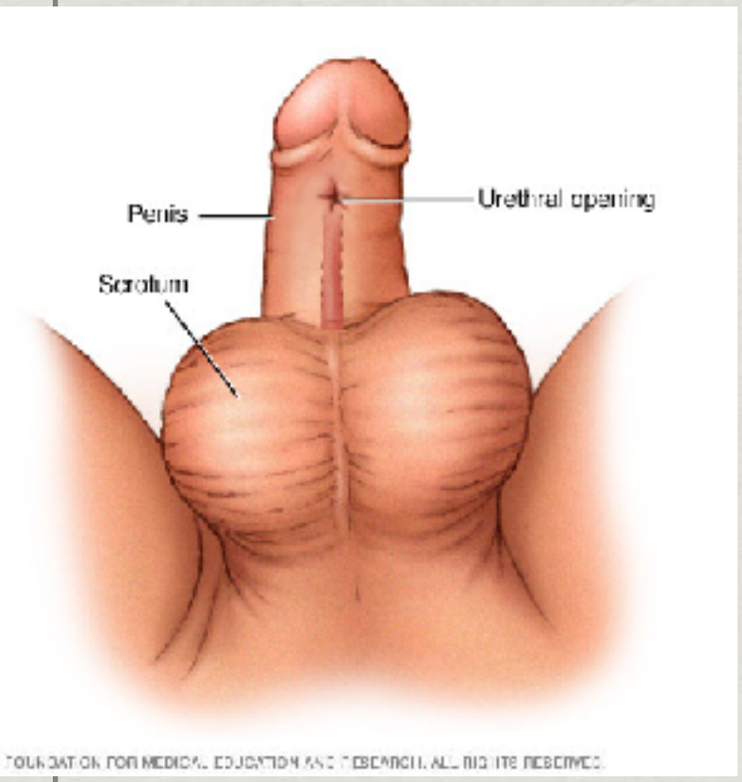
Table 4. Maternal complications

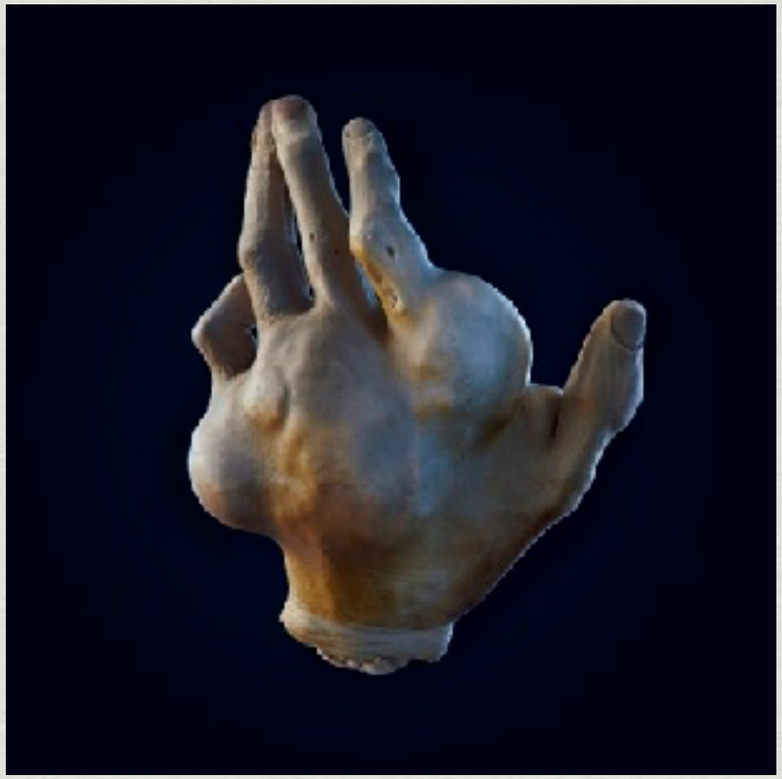
	BHFS survivor cases (%)	Non hydropic, %*
Previous pregnancies (n = 35)		
Abortion†	6 (17)	
Still birth/neonatal death	14 (40)	
Antepartum (n = 41)		
Polyhydramnios	6 (15)	<1
Oligohydramnios	3 (7)	
Intrauterine infection	2‡ (5)	
Preeclampsia	5 (12)	7
Abruptio placenta	1 (2)	
Delivery		
Preterm delivery (n = 66)	47 (71)	5-10
GA <30 wk	9 (14)	
GA ≥30-36+ wk	38 (57)	
Birth presentation (n = 41)		
Malpresentation	4 (10)	<5
Mode of delivery (n = 54)		
Assisted vaginal delivery	2 (4)	5
Caesarean section	31 (57)	2-3
Postpartum (n = 41)		
Postpartum hemorrhage	2 (5)	5

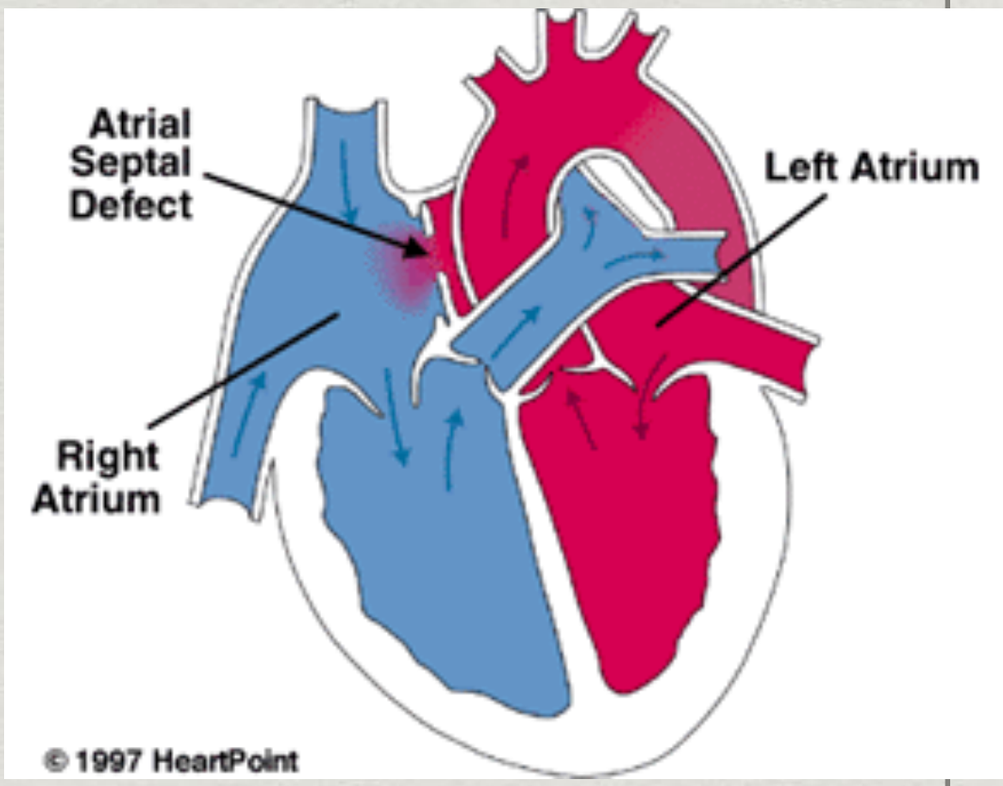
Neonatal course

- BHFS was diagnosed by ***Hb electrophoresis***, showing ***Hb Bart's (γ_4)*** to be the major Hb at birth
- Benefits of intrauterine treatment
  - less neonatal course
  - Improve APGAR score at 1,5 mins
  - Decrease fetal distress
  - Better response to initial resuscitation
  - less chance of severe birth asphyxia
  - Decrease duration of requirement of neonatal ventilation support

Congenital abnormalities





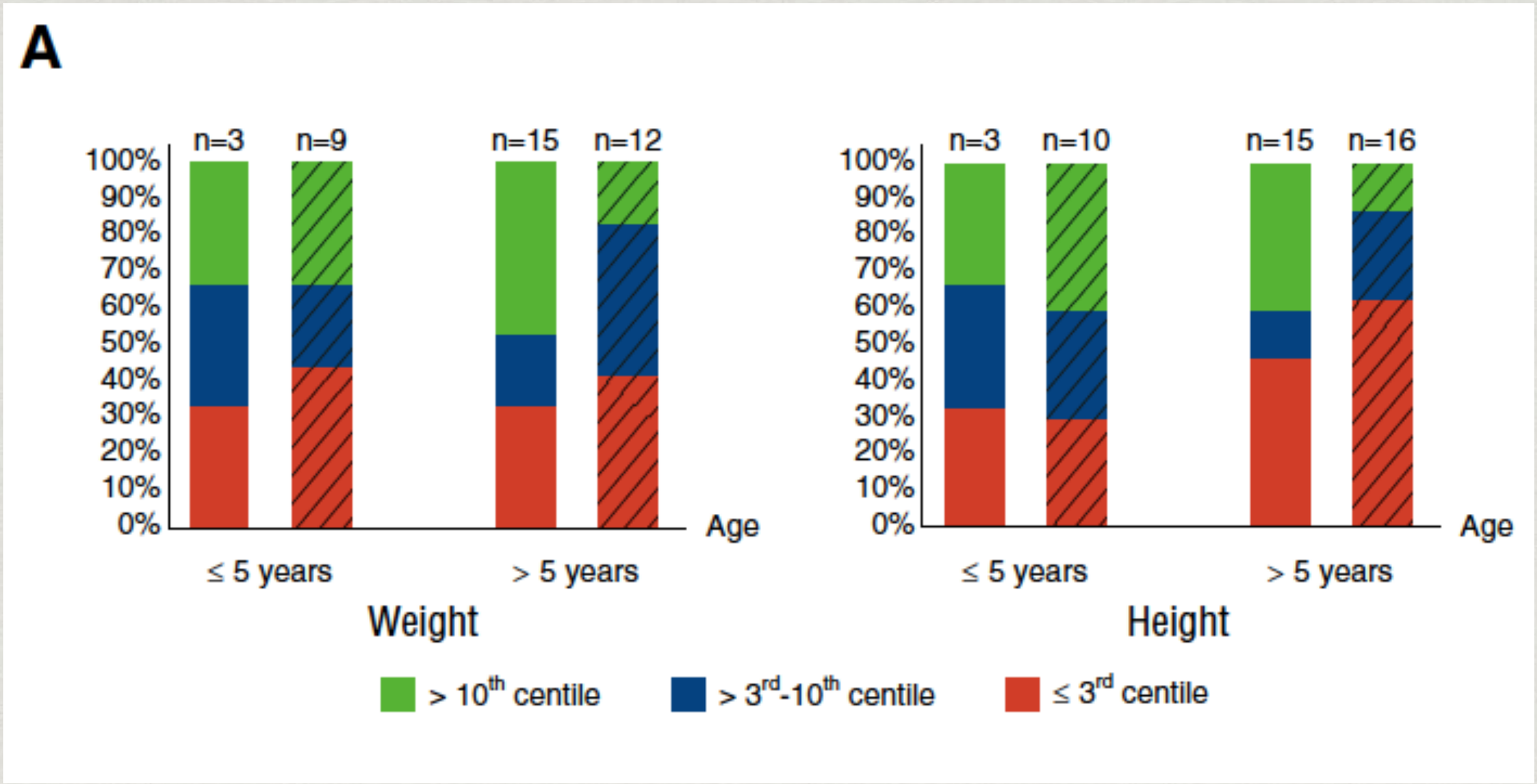


Hypospadia
21/37 males (57%)

Limb deformities
9/58 (16%)

Atrial septal defect
6/58 (10%)

Growth outcome



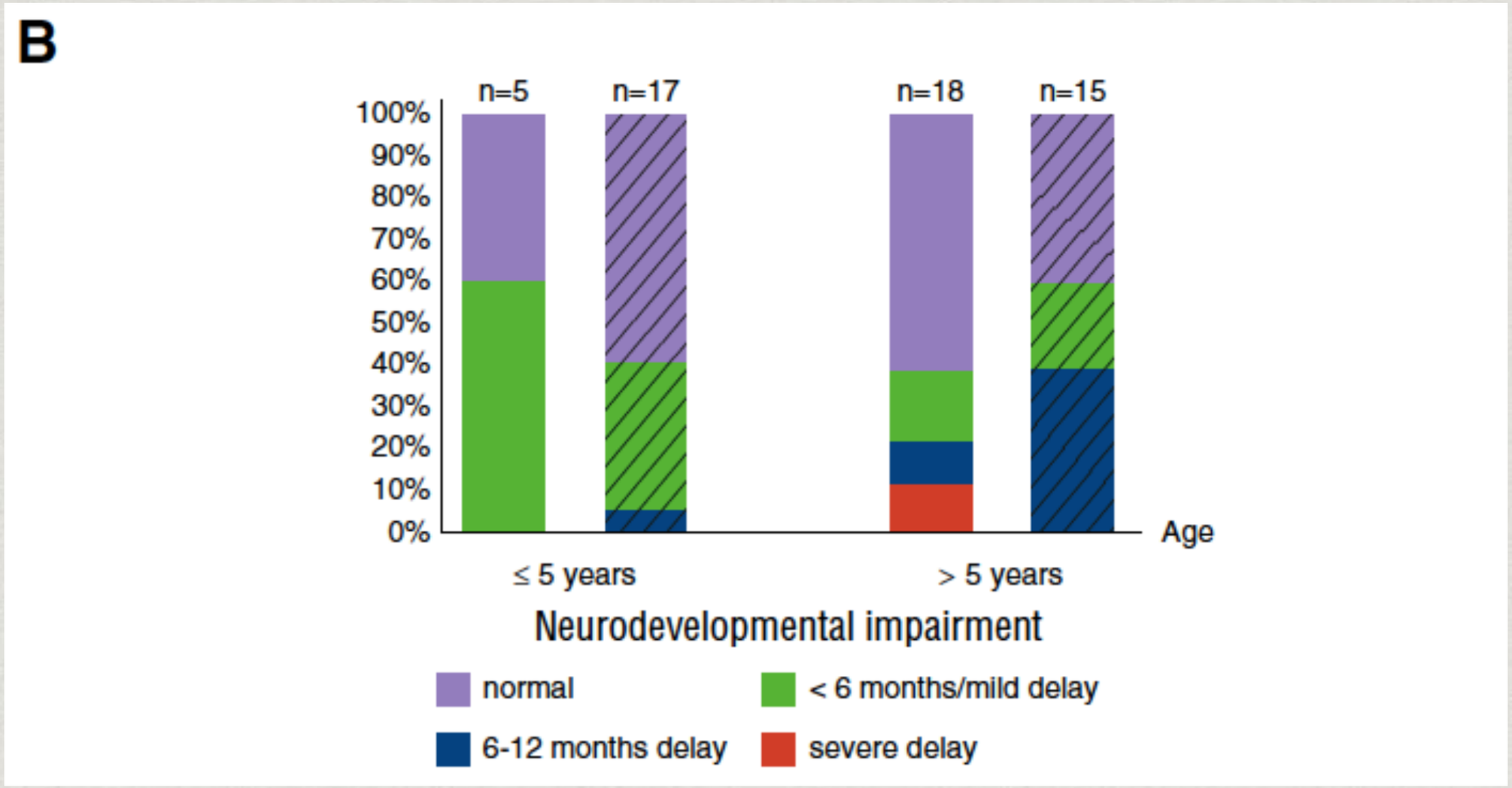
Growth outcome

- Patients who survived naturally until birth and who have long-term weight and height of **>**3rd percentile (n**=**10), in any given age group, were born ***more prematurely (median GA at birth 29 weeks)***

- ***In Thailand,*** The patients kept pretransfusional “functional” Hb (HbA, HbF) ***levels of 10 g/dL*** for ***at least 6 yrs*** at the time of last report.

- Of the 4 patients treated in this way, 3 have ***long-term normal growth*** and 1 has continuously ***improving growth***.

Neurodevelopmental outcome



Neurodevelopmental outcome

- Delay neurodevelopmental outcomes may had a ***difficult neonatal course***
- Significant neurodevelopmental delay remains in 3 of 10 patients "***transplanted"*** at **<** 5 yrs of age who are ***transfusion independent***
- Three of the 4 patients hypertransfused for at least 6 years have ***normal neurodevelopment***
- Appropriate transfusion regimen ***- favorable*** longterm neurodevelopmental outcomes

Current treatment

HSCT

- 18/69 (26%) - Post natal HSCT
  - 14/18 - Transfusion Independent
  - 4/18 - Unsuccessful
    - 1 case - Death
    - 3 cases - Graft rejection

Regular transfusion

- Start regular blood transfusion, every 2-5 wks
- Keep pretransfusion Hb 7-10 g/dL
- ***Functional Hb level***

  Total Hb x (1- HbH/100)

  - if > 10 g/dL -> subsequent transfusion + exchange transfusion (remove HbH)
- Complication : ***Iron overload***

Application and adaptation

- Largest study describing the ***natural history and long-term outcomes*** of individuals with BHFS

- ***Molecular diagnosis for DNA analysis*** obtains from CVS + less invasive procedure; ultrasound should perform in 1st trimester

- High carrier rate of α^{o}-thalassemia deletions were found in ***Hongkong, Thailand and China —"Public health policy"***

Application and adaptation

- Intrauterine intervention leads to ***prolonged gestation***, ***improved APGAR scores*** and ***shortened*** require of ***neonatal mechanical ventilation***

- Intrauterine transfusion - ***less neonatal course*** but ***may not*** provide additional benefit in long-term growth and neurodevelopment

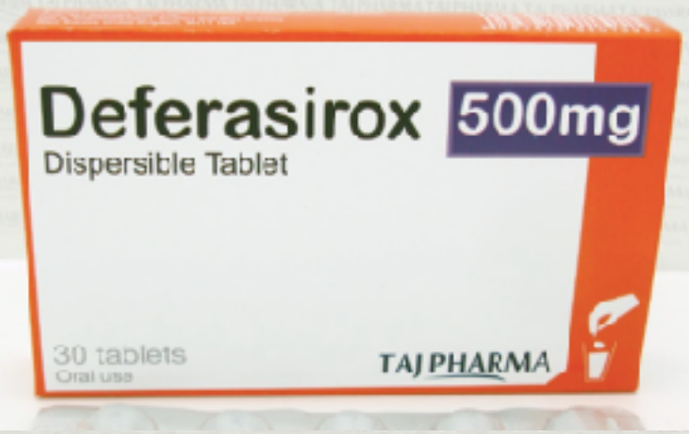
- Intrauterine HSC transplantation - ***still challenge !!!***

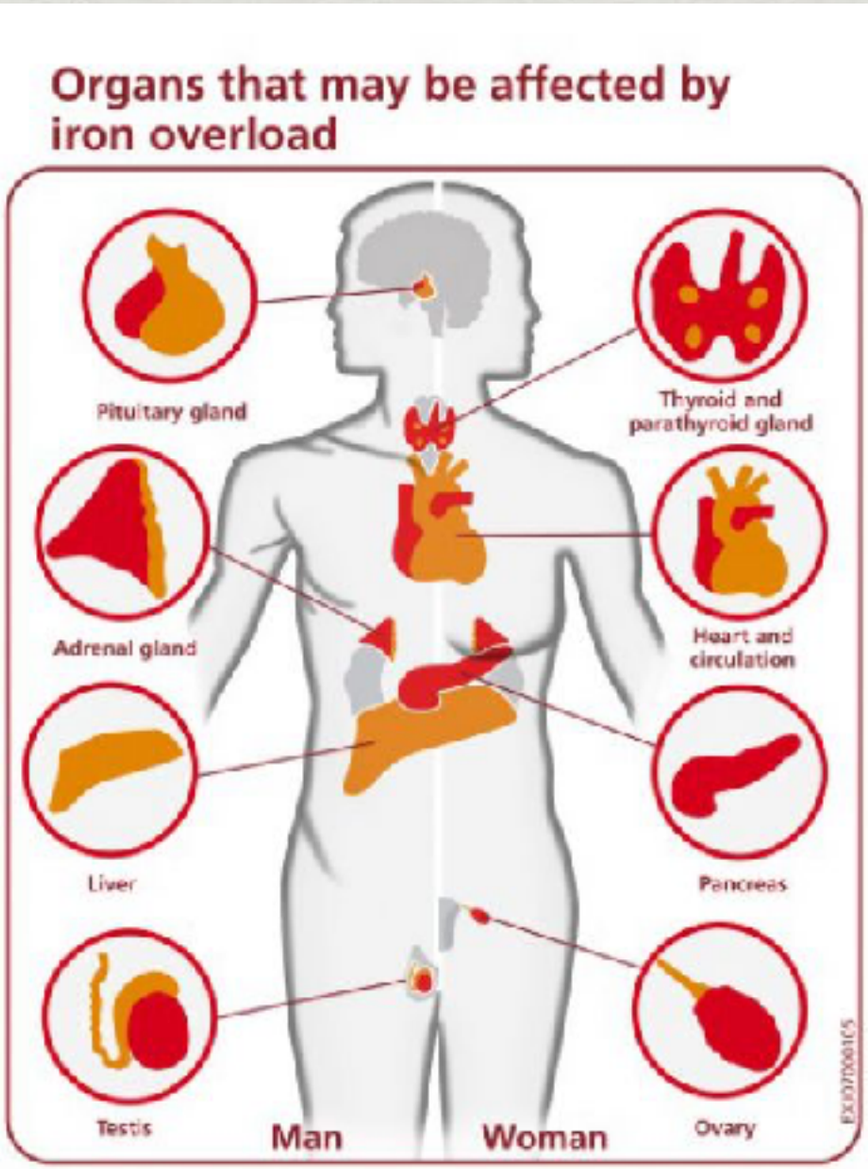
Application and adaptation

- 45% of untransfused in utero were born ***without hydropic features***
- Infants with no hydropic features ***have persistent expression of ζ(Zeta) globin*** *(required further study)*
- M/C cong. anomalies ; ***Urogenital defects and limb deformities***, ***prenatal u/s*** can early detect this abnormalities
- Mother of hydropic fetus - increase risk of OB complications

Application and adaptation

Transfusion-related complications





Toxic iron builds up across the body and can cause serious damage to vital organs, including the heart and liver.

Literature review - abstract only

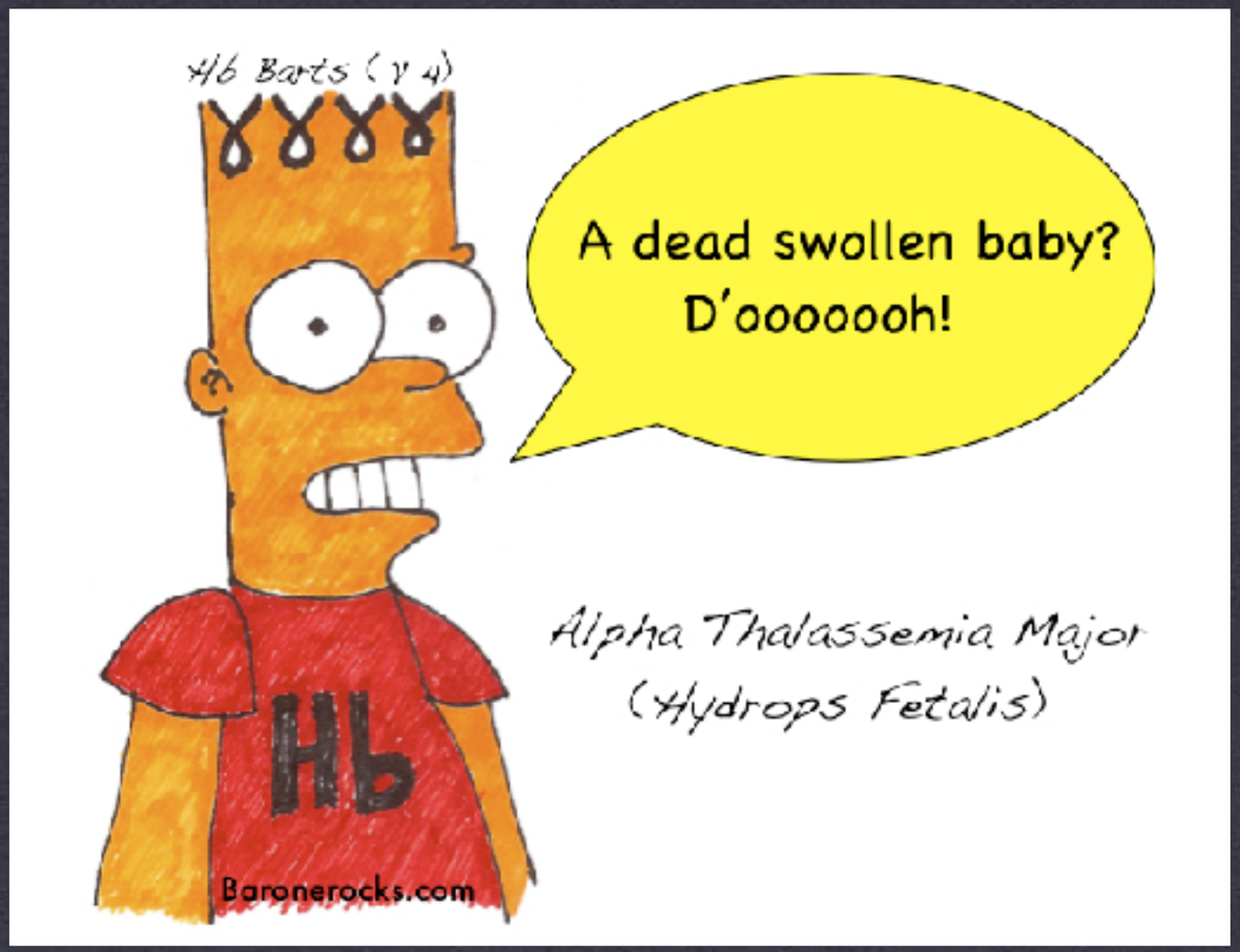
Management and Outcomes of Fetal Hydrops in a Tertiary Care Centre in Singapore

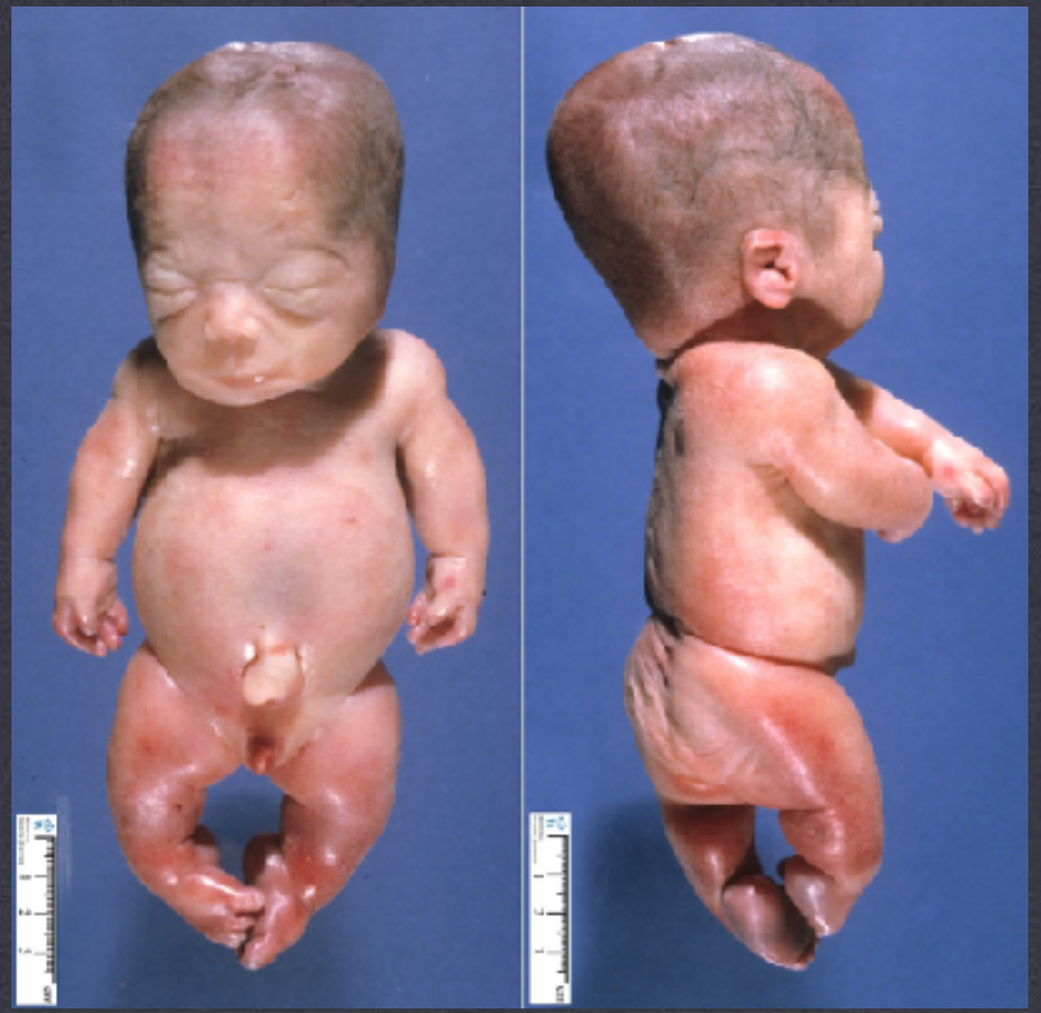
Xin Yi Thong, [1,2]*MBBS (S'pore)*, Le Ye Lee, [1,3]*MMed (Paeds), MRCPCH (UK)*, Dawn AK Chia, [4]*DCR(UK), DMU(UK)*, Yee Chee Wong,[4]*MBBS (S'pore), MMED (O&G, S'pore), FRCOG (UK)*, Arijit Biswas, [4]*MD, FRCOG, FAMS*

- *Ann Acad Med Singapore 2017;46:4-10*
- Materials and Methods: A retrospective review of all cases of fetal hydrops diagnosed from 2006 to 2013
- Results: Out of the 30 cases of fetal hydrops diagnosed antenatally, 17 were cases of Bart's hydrops which were all terminated in-utero. Of the remaining 13 cases, ***11 cases consisted of non-immune causes of hydrops.***
- ***92%, of the cases survived*** the perinatal period following a variable length of hospital stay ranging from a week to 3 months.

Take home message

- Bart's hydrops fetalis is fatal disease that requires early diagnosis and early treatment
- Couple of risks should perform prenatal diagnosis especially in ***Hongkong, Thailand and China***
- Regular transfusion to keep ***pretransfusion Hb 7-10 g/dL*** had benefit in improvement in long-term outcomes
- International registry should continue to ***develop guidelines for intrauterine intervention and postnatal transfusion***





ANY SUGGESTIONS ?