Fetal & Neonatal Pathology

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Self-Directed Reading Topics

- Intra-uterine growth retardation
  - Definition, causes, diagnosis & complications.
- APGAR SCORE
- Tumor & tumor like lesions in the newborn (e.g. haemangioma)
- Immaturity of organ systems in the pre-term neonate: Lungs, kidneys, brain & liver
- Perinatal infections
  - Transcervival (ascending)
  - Transplacental (haematological)
- Common birth injuries
  - Find out the common types of birth injuries at PMGH labor ward

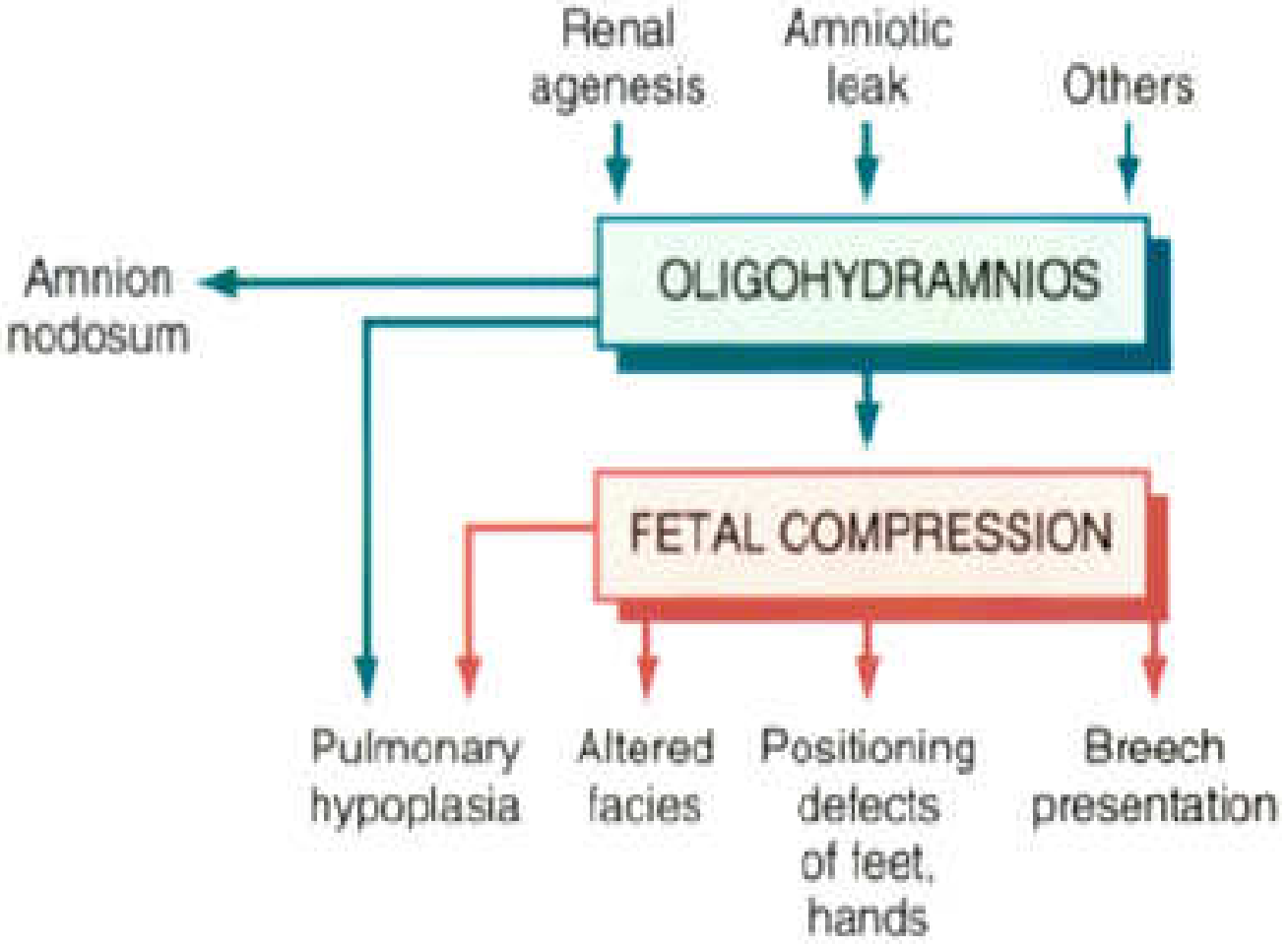
Overview

- Congenital malformations
- Neonatal respiratory syndromes
- Congenital heart diseases
- Erythroblastosis fetalis – haemolytic diseases of the new born
- Inborn errors of metabolism
  - Phenylketoneuria
  - Galactosemia
  - Cystic fibrosis (mucoviscidosis)

Congenital Malformations

- Definitions: Define the following terms.
  - **Malformations** – intrinsic abnormalities occurring during development. Can affect single organ systems or multiple organs.
  - **Deformations** – arise later in fetal life. Represent alterations in form or structure from mechanical factors. Abnormalities in shape, form or position of body. Much less risk of transmission. Uterine constraint common cause, oligohydramnions, multiple fetus.
  - **Disruptions** – secondary destruction or interference with organ or body. Amniotic bands common cause.
  - **A sequence** – pattern of cascade of anomalies.
  - **Syndrome** – constellation of congenital anomalies pathologically related that cannot be explained on a basis of a single, localised initiating event.
  - Agenesis, atresia, aplasia, hypoplasia, hyperplasia, hypertrophy or hypotrophy and dysplasia – self directed reading.

Figure 10-3 Schematic diagram of the pathogenesis of the oligohydramnios sequence.



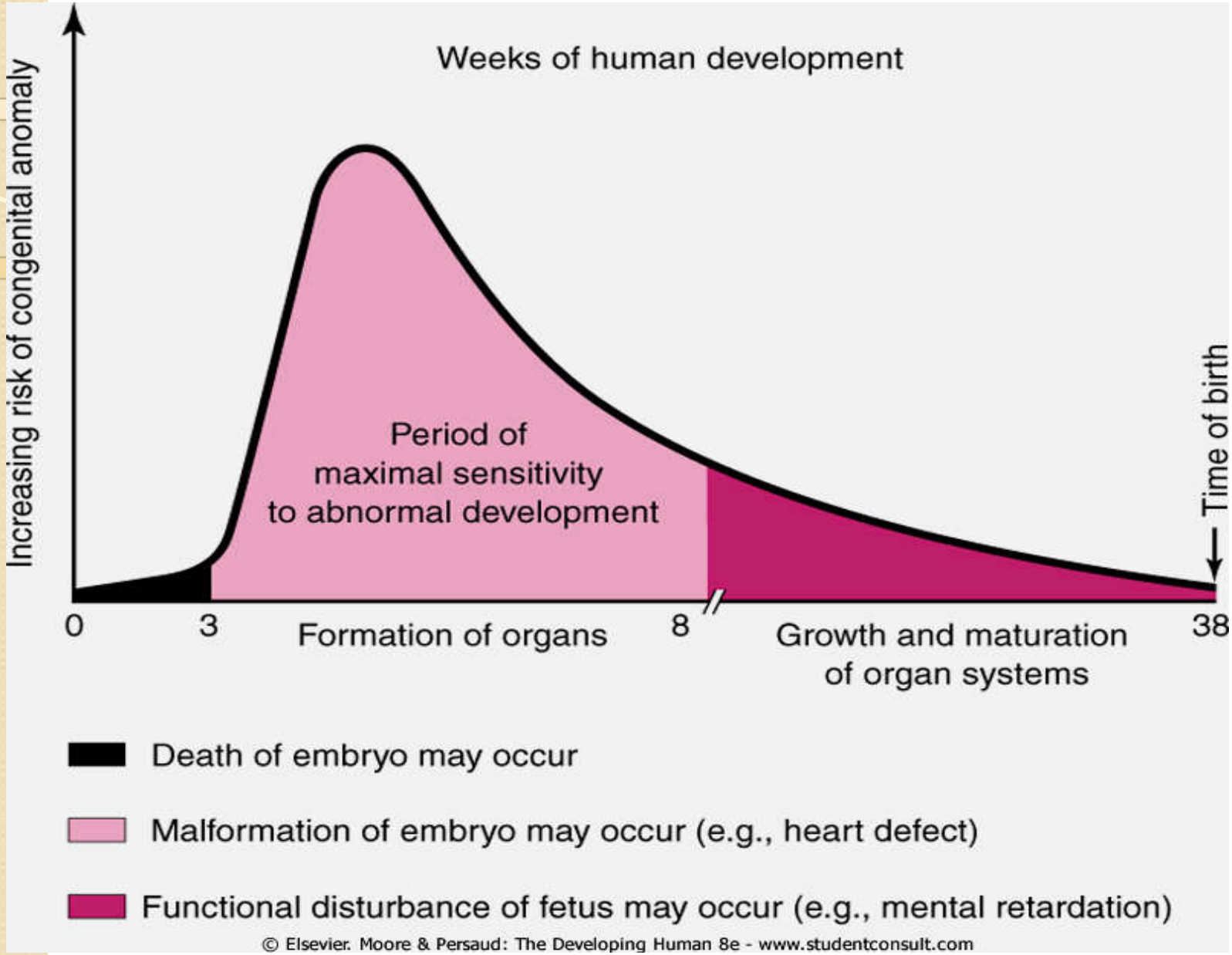
Ref: Robins Pathological Basis of Diseases, 7th Ed.

Study Guide – Mechanisms of malformations

- Complex and poorly understood. Timing of prenatal teratogenic insult is important factor.

- Teratogens and genetic factors act at different levels affecting:
  - Proper cell migration
  - Cell proliferation
  - Cellular interactions
  - Cell-matrix interactions
  - Programmed cell death (apoptosis)
  - Hormonal influences
  - Mechanical forces

- Describe the pathogenesis of congenital malformations – self study.



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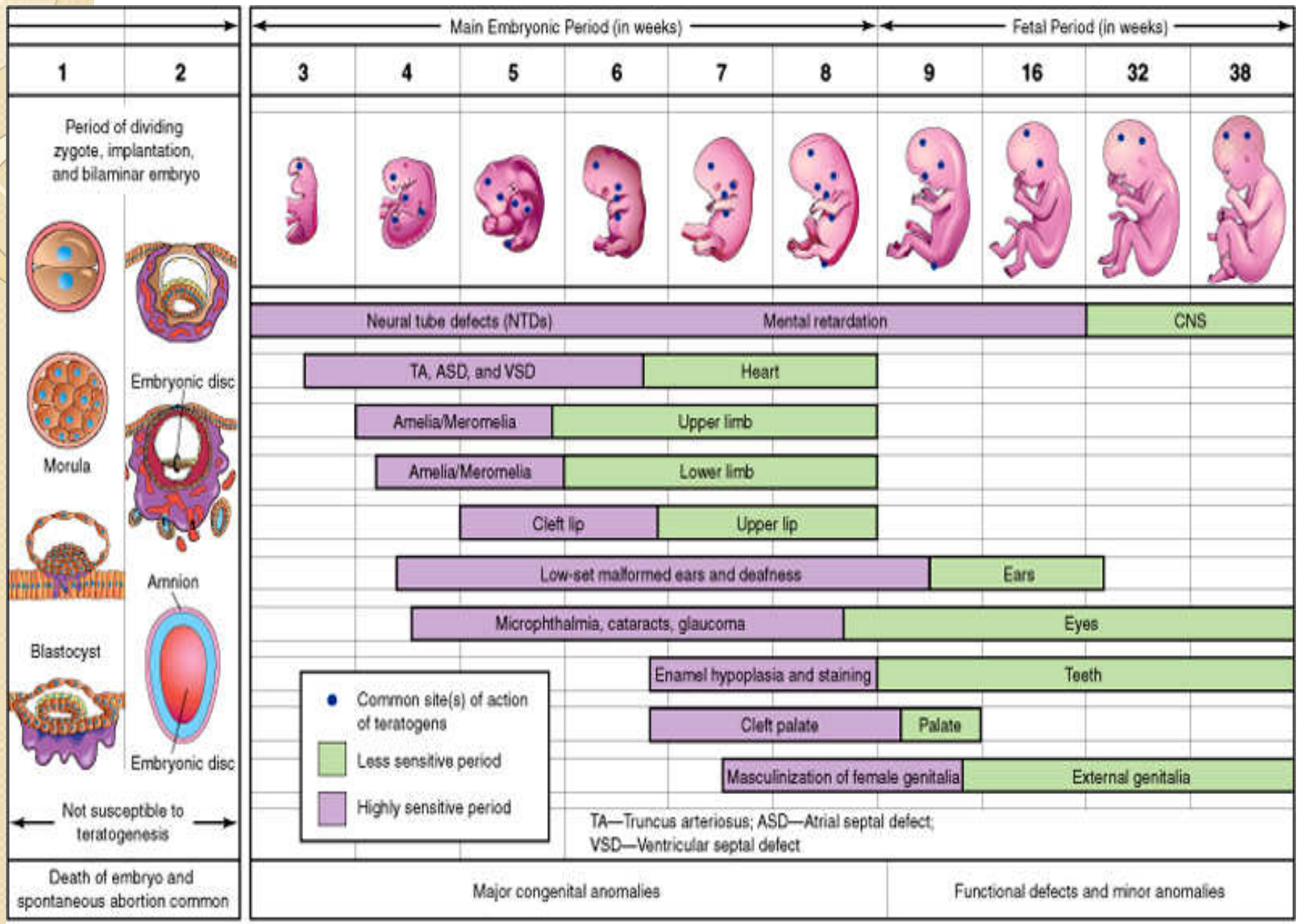

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Frequency of common malformations

Table 11–4. APPROXIMATE FREQUENCY OF THE MORE COMMON CONGENITAL MALFORMATIONS IN THE UNITED STATES

Malformation	Frequency Per 10,000 Total Births
Clubfoot without central nervous system anomalies	25.7
Patent ductus arteriosus	16.9
Ventricular septal defect	10.9
Cleft lip with or without cleft palate	9.1
Spina bifida without anencephalus	5.5
Congenital hydrocephalus without anencephalus	4.8
Anencephalus	3.9
Reduction deformity (musculoskeletal)	3.5
Rectal and intestinal atresia	3.4

Ref: Robins Pathological Basis of Diseases, 7th Ed

PNG Picture - Frequency

TABLE 1:
Birth defects recorded at Port Moresby General Hospital, January 85 to May arranged into categories

Total babies: 10,000

Babies with defects recognised at birth: 116

LIMBS	Number	Alive	Stillborn
talipes	20	19	1
polydactyly	7	7	0
shortened, deformed limbs	6	5	1
arthrogryposis	4	3	1
dislocated hip	4	3	1
club hands	3	2	1
missing digits	3	3	0
hyperextended knees	2	2	0
Totals	**49**	**44**	**5**

CENTRAL NERVOUS SYSTEM, HEAD and NECK	Number	Alive	Stillborn
Neural tube defects			
hydrocephalus	8	1	7
microcephalus	8	8	0
anencephalus	3	0	3
spina bifida/lumbosacral swelling	4	3	1
Totals	**23**	**12**	**11**
ear defects	10	10	0
cleft lip	7	6	1
cleft palate	7	6	1
facial defects	6	4	2
craniostenosis	2	0	2
cystic hygroma	2	1	1
laryngeal stenosis	2	2	0
micrognathia (Robin syndrome)	1	1	0
microphthalmia	1	1	0
Totals	**38**	**31**	**7**

Ref: Birth Defects in PNG

Contd..

TABLE 1: continued

ABDOMEN	Number	Alive	Stillborn
Perineal defects			
ambiguous genitalia	7	6	1
hypospadias	3	3	0
hydrocele	2	2	0
imperforate anus	1	1	0
Totals	**13**	**12**	**1**
Abdominal defects			
bowel obstruction	7	7	0
exomphalos, umbilical hernia	2	2	0
distended abdomen	1	1	0
renal agenesis	1	0	1
urachal fistula	1	1	0
ileal atresia	1	1	0
oesophageal atresia	1	1	0
Totals	**14**	**13**	**1**

THORAX	Number	Alive	Stillborn
congenital heart disease	9	9	0
diaphragmatic defect	7	7	0
hypoplastic lungs	1	1	0
small thorax (asphyxiating dwarfism)	1	1	0
Totals	**18**	**18**	**0**

GENETIC FAULTS	Number	Alive	Stillborn
cri-du-chat syndrome	1	1	0
trisomy 21 (Down syndrome)	4	3	1
trisomy 18 (Edward syndrome)	2	2	0
Turner syndrome	1	1	0
Totals	**8**	**7**	**1**

SKIN DEFECTS	Number	Alive	Stillborn
extensive haemangioma	2	2	0
Totals	**2**	**2**	**0**

Causes of Malformations

Table 11–3. CAUSES OF CONGENITAL MALFORMATIONS IN HUMANS

Cause	Malformed Live Births (%)
Genetic	
Chromosomal aberrations	10–15
Mendelian inheritance	2–10
Environmental	
Maternal/placental infections	2–3
Rubella	
Toxoplasmosis	
Syphilis	
Cytomegalovirus	
Human immunodeficiency virus (HIV)	
Maternal disease states	6–8
Diabetes	
Phenylketonuria	
Endocrinopathies	
Drugs and chemicals	1
Alcohol	
Folic acid antagonists	
Androgens	
Phenytoin	
Thalidomide	
Warfarin	
13-*cis*-retinoic acid	
Others	
Irradiation	1
Multifactorial (Multiple Genes ± Environment)	20–25
Unknown	40–60

REF: Robins Pathological Basis of Diseases, 6th Ed.

Neonatal Respiratory Distress Syndrome

- Common cause of RDS in the newborn is *hyaline membrane disease*.
- Underlying pathology – lung immaturity. Common in pre-term neonates.
- Deficiency of pulmonary surfactant is the defect.
- There is alternating atelactasis and dilation of the alveoli causing hypoxemia & CO2 retention.

Pathophysiology of RDS

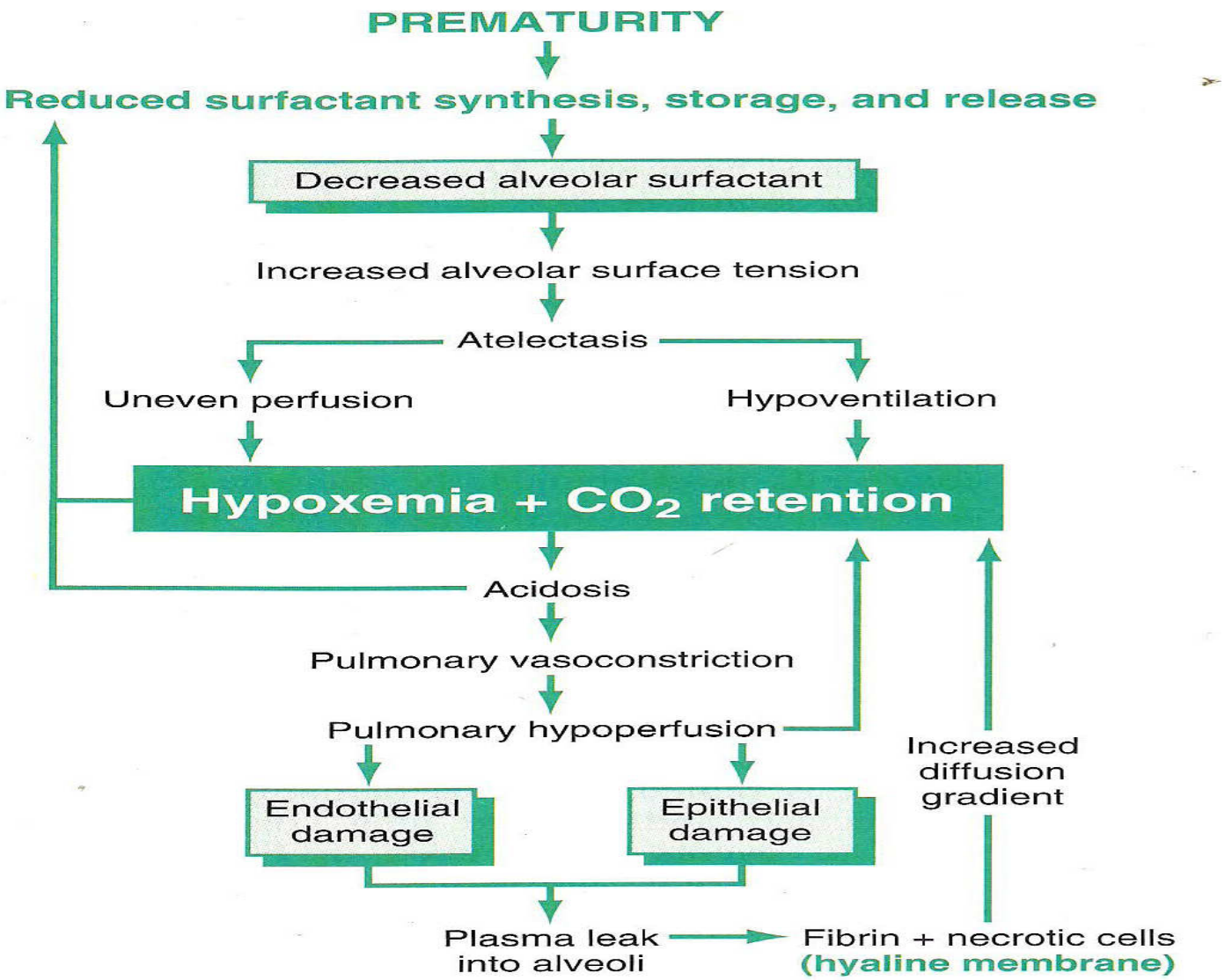


Figure 11–10

Ref: Robins Pathological Basis of Diseases, 6th Ed.

Transient Tachypnea of the Newborn (TTN)

Also known as Type II RDS or Retained Lung Fluid

Etiology & Predisposing Factors

- C-section
  - These infants do not have the fluid expelled from their airways as occurs in vaginal delivery
- Maternal Diabetes
  - Increased chance of C-section
- Cord Compression
- Anesthesia

TTN Pathophysiology

Primary problem = retained lung fluid

- Fluid not expelled from airways because of C-section
- Poor absorption of remaining fluid by pulmonary capillaries and lymphatics
- If retained fluid is in interstitial spaces, compliance decreased
- If retained fluid is in airways, airway resistance increased
- *TTN can be restrictive , obstructive, or both!*
- Fluid usually clears by itself after 24-48 hours after birth

Persistent Pulmonary Hypertension -PPHN-

Also known as Persistent Fetal Circulation

-PFC-

Failure to make the transition from fetal to neonatal circulation or a reversion back to the condition where pulmonary artery pressure exceeds aortic pressure

Results in R-L shunting across the D.A. and the Foramen Ovale

CONGENITAL HEART DISEASES

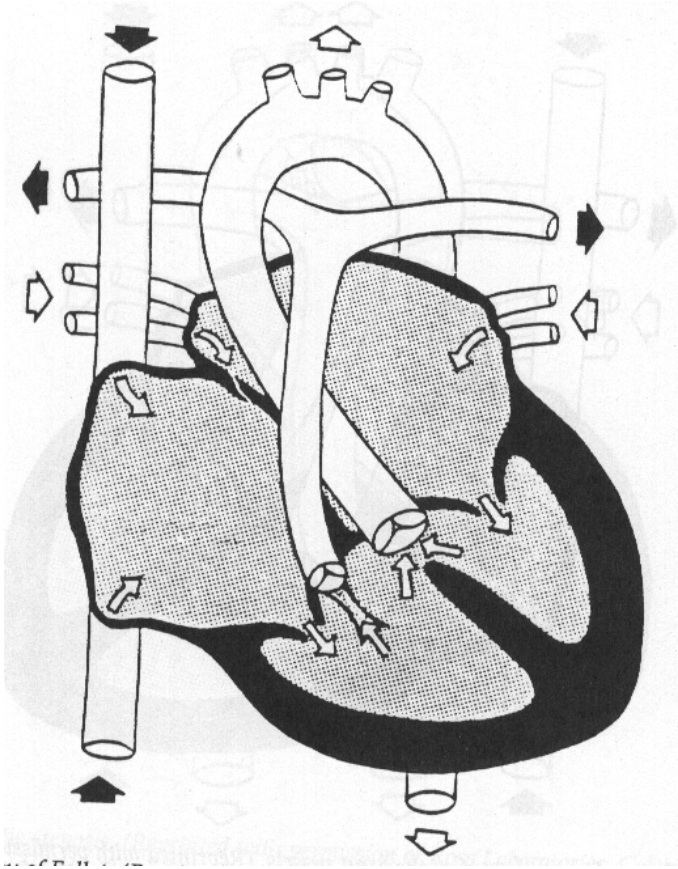
Relative Frequency of Lesions

Ventricular septal defect	25-30
Atrial septal defect (secundum)	6-8
Patent ductus arteriosus	6-8
Coarctation of aorta	5-7
Tetralogy of Fallot	5-7
Pulmonary valve stenosis	5-7
Aortic valve stenosis	4-7
Transposition of great arteries	3-5
Hypoplastic left ventricle	1-3
Hypoplastic right ventricle	1-3
Truncus arteriosus	1-2
Total anomalous pulm venous return	1-2
Tricuspid atresia	1-2
Double-outlet right ventricle	1-2
Others	5-10

Tetralogy of Fallot

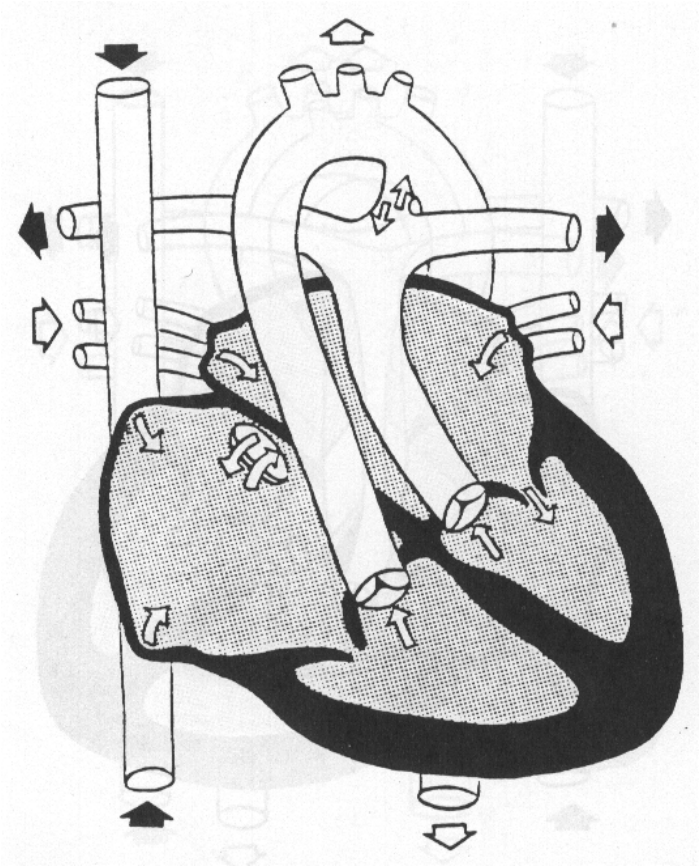
- “Cyanosis, especially in the adult, is the result of a small number of cardiac malformations well determined…. One…is much more frequent than the others…. This malformation consists of a true anatomopathologic type represented by the following tetralogy: (1) Stenosis of the pulmonary artery; (2) Interventricular communication; (3) Deviation of the origin of the aorta to the right; and (4) Hypertrophy, almost always concentric in type, of the right ventricle. Failure of obliteration of the foramen ovale may occasionally be added in a wholly accessory manner.”
  - Fallot, Ètienne-Louis-Arthur. Contribution to the pathologic anatomy of morbus caeruleus (cardiac cyanosis). *Marseilles Med*. 1888; 25:418-20.

Tetralogy of Fallot



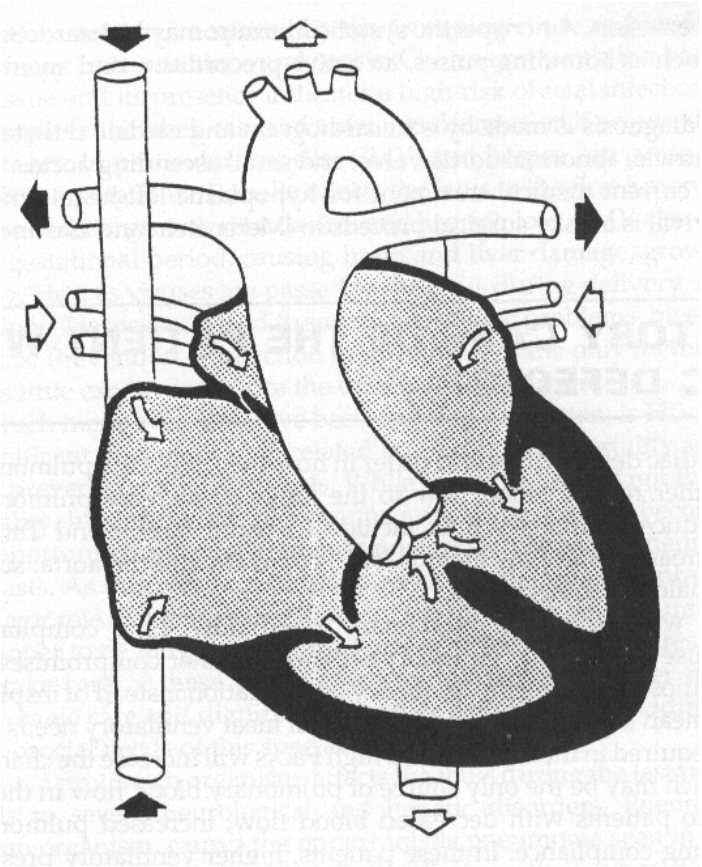
- VSD
- Over-riding aorta
- Pulmonary valve stenosis
- Right ventricular hypertrophy
- Significant cyanosis because of R-L shunt

Complete Transposition of the Great Vessels



- Pulmonary artery arises from left ventricle and Aorta arises from right ventricle
- R-L shunt through PDA, ASD, or VSD needs to be present for infant to survive until corrective surgery
  - Balloon septostomy during cardiac catheterization

Truncus Arteriosus



- Aorta and pulmonary artery are the same vessel
- Large VSD
- Requires MAJOR surgical repair
- Mortality is 40-50%

Patent Ductus Arteriosus

*-PDA_*

Failure of the D.A. to close at birth or a re-opening of the D.A. after birth. Allows shunting between the pulmonary artery and the aorta

Occurrence

- 1 per 2000 term babies
- 30-50% of RDS babies

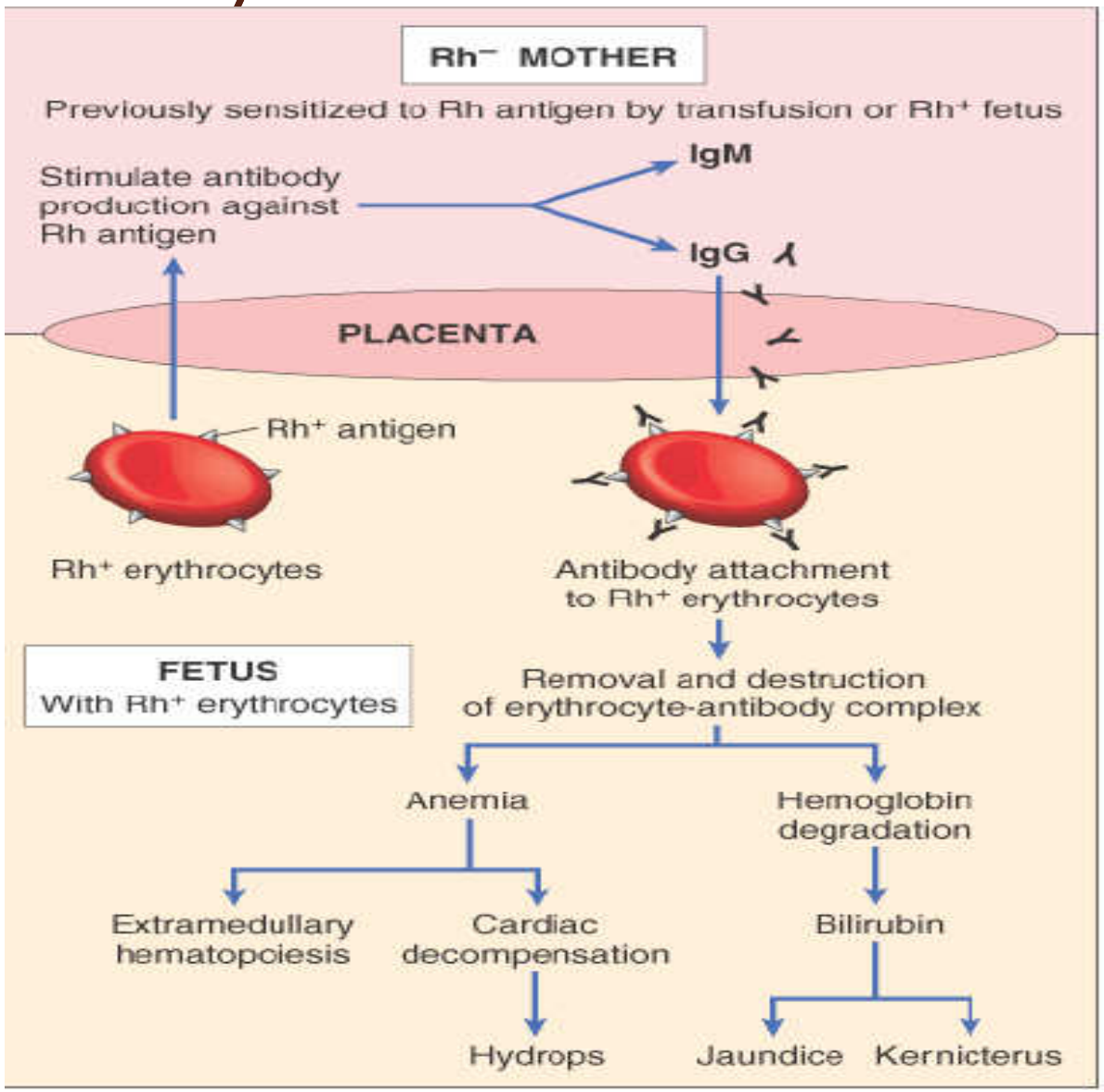
Etiology & Predisposing Factors

- Prematurity
  - D.A. not as sensitive to increasing PaO2
- Hypoxia
  - Decreasing PaO2 allows it to re-open for up to three weeks after birth
- Thus, a PDA can occur in a premature infant who is NOT hypoxic or in a term baby who is hypoxic
  - *Worst case is a premature infant who is hypoxic!*

Erythroblastosis Fetalis (Hemolytic Disease of the Newborn)

- Definition: haemolytic disease in the newborn caused by blood-group incompatibility between mother & child. (ABO and Rh)
- However, there are also non-immune causes.
- Sensitisation occurs in last trimester of pregnancy or during birth (absence of synciotrophoblast)
- Occurs in subsequent pregnancies. Not the first.

Pathogenesis of erythroblastosis



Ref: Robins Pathological Basis of Diseases, 7th Ed.

Non-Immune Causes

Table 11–5. GENERAL CAUSES OF NONIMMUNE HYDROPS FETALIS*

General Cause	Estimated %
Cardiovascular	17–35
Malformations	
Tachyarrhythmia	
High-output failure	
Chromosomal	13.5–15.7
45,X	
Trisomy 21	
Hematologic	4.2–12
Pulmonary	3–6
Cystic adenomatoid malformation	
Diaphragmatic hernia	
Multiple malformation syndrome	3–15
Twin-twin transfusion	3–10.3
Infection	1.5–5.3
Cytomegalovirus	
Bacteria	
Toxoplasmosis	
Skeletal dysplasia	3–4
Gastrointestinal	2–3.7
Urogenital	2.2–3
Tumors	2.5–3
Metabolic disorders	1
Idiopathic	15.5–40

Ref: Robins Pathological Basis of Diseases, 6th Ed.

Inborn Errors of Metabolism

- Phenylketonuria
- Galactosemia
- Cystic fibrosis (Mucoviscidosis)

Clinical Symptomatology of Inborn Errors of Metabolism (IEM) in the Neonate or Infant

Symptoms indicating *possibility* of an IEM (one or all)

- Infant becomes acutely ill after period of normal behavior and feeding; this may occur within hours or weeks
- Neonate or infant with seizures and/or hypotonia, especially if seizures are intractable
- Neonate or infant with an unusual odor

Symptoms indicating *strong possibility* of an IEM, particularly when coupled with the above symptoms

- Persistent or recurrent vomiting
- Failure to thrive (failure to gain weight or weight loss)
- Apnea or respiratory distress (tachypnea)
- Jaundice or hepatomegaly
- Lethargy
- Coma (particularly intermittent)
- Unexplained hemorrhage
- Family history of neonatal deaths, or of similar illness, especially in siblings
- Parental consanguinity
- Sepsis (particularly *Escherichia coli)*

Inborn Errors of Metabolism of Acute Onset: Nonacidotic, Nonhyperammonemic Features

Neurologic Features Predominant (Seizures, Hypotonia, Optic Abnormality)

- Glycine encephalopathy (nonketotic hyperglycinemia)
- Pyridoxine-responsive seizures
- Sulfite oxidase/santhine oxidase deficiency
- Peroxisomal disorders (Zellweger syndrome, neonatal adrenoleuko-dystrophy, infantile refsum disease)

Jaundice Prominent

- Galactosemia
- Hereditary fructose intolerance
- Menkes kinky hair syndrome
- α_1-antitrypsin deficiency

Hypoglycemia (Nonketotic): Fatty acid oxidation defects (MCAD, LCAD, carnitine palmityl transferase, infantile form)

Cardiomegaly

- Glycogen storage disease (type II phosphorylase kinase b deficiency[18])
- Fatty acid oxidation defects (LCAD)

Hepatomegaly (Fatty): Fatty acid oxidation defects (MCAD, LCAD)

Skeletal Muscle Weakness: Fatty acid oxidation defects (LCAD, SCAD, multiple acyl-CoA dehydrogenase

Phenylketonuria

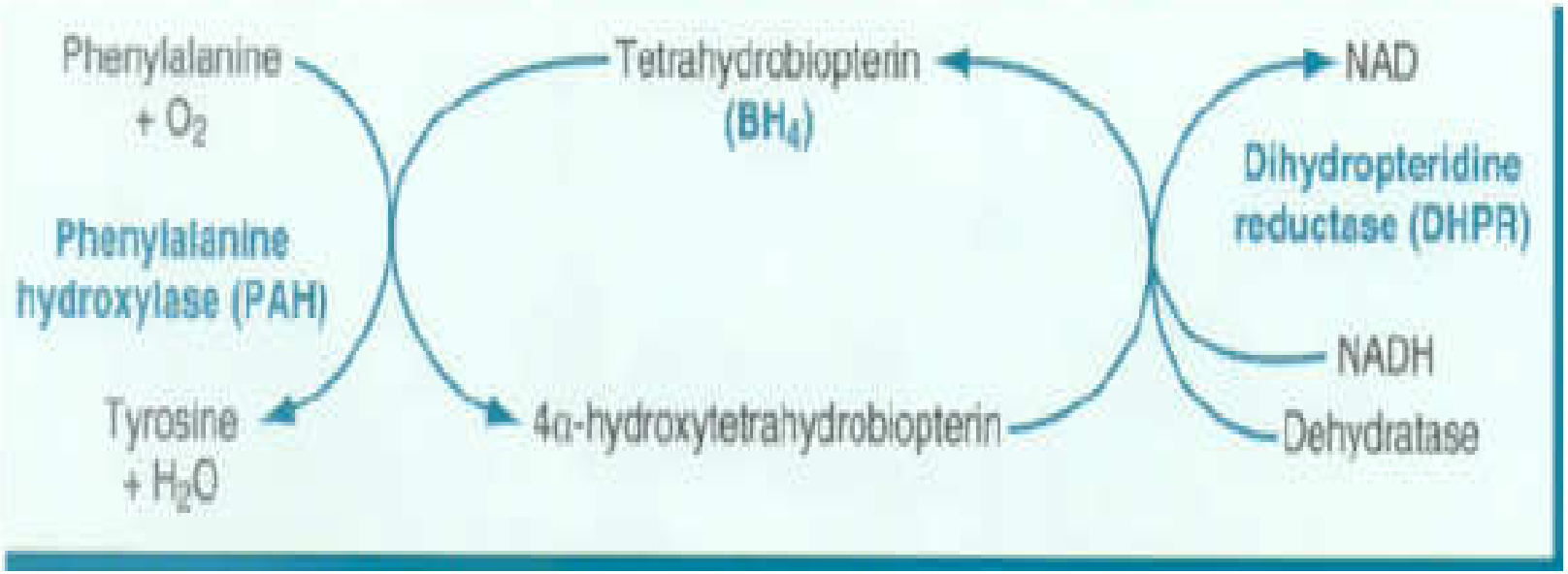
- Autosomal recessive disorder (must have 2 pair of the gene to express phenotypically i.e. homozygous)
- Molecular basis: severe lack of phenylalanine hydroxylase leading to increased levels of phenylalanine in the blood and PKU. Rising plasma levels of phenylalanine impair brain development. Phenylalanine hydroxylase converts phenylalanine to tyrosine.

Molecular Basis

- Deficiency of liver enzyme phenylalanine hydroxylase.
- Phenylalanine hydroxylase converts phenylalanine to tyrosine.
- Lack of enzyme results in increased level of phenylalanine.
- Phenylalanine – essential amino acides cannot by synthesised by body. Therefore obtained in protein rich foods.
- Phenylalanine builds up to toxic levels manifested in clinical picture, esp. mental retardation.

Molecular basis

Figure 10-17 The phenylalanine hydroxylase system.

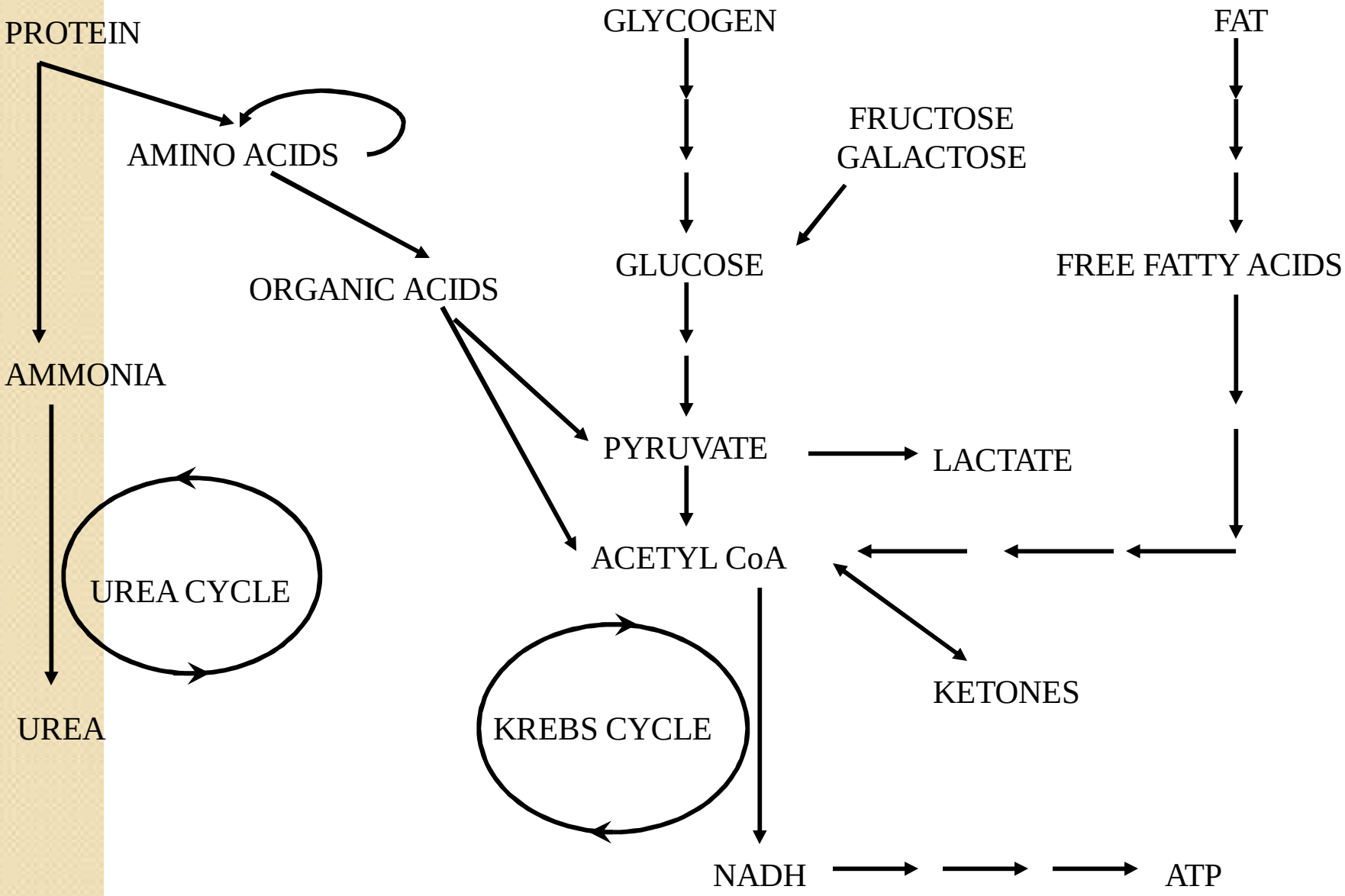


Ref: Robins Pathological Basis of Diseases, 7th Ed.

Galactosemia

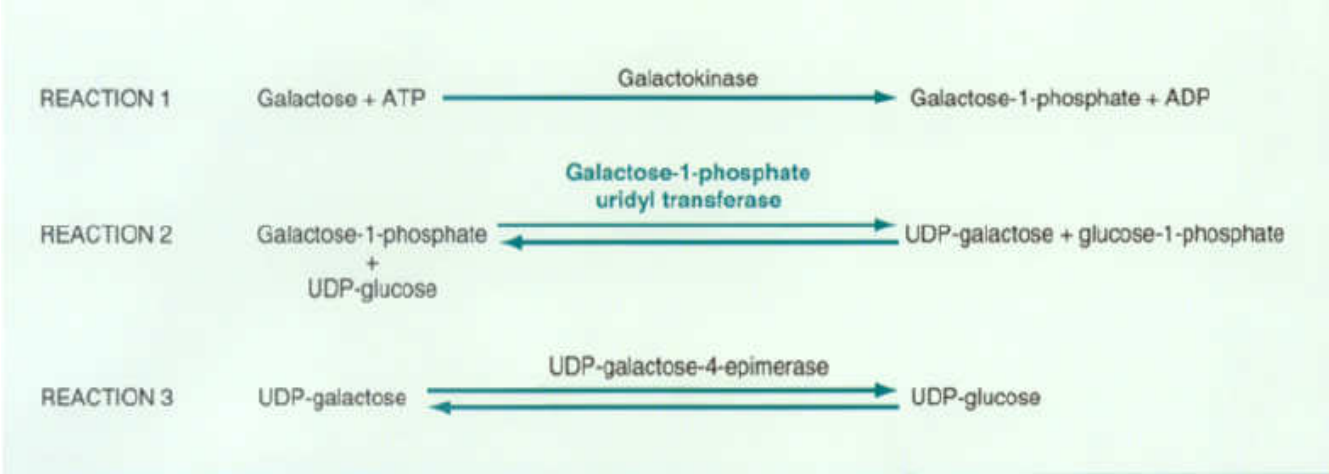
- Autosomal recessive disorder
- Impaired galactose metabolism
- Many variants but common one is absent of a transferase enzyme in step 2 in galactose metabolism
- Lactose is major cabohydrate in breast milk.
- Lactose split into galactose & glucose.
- Glucose enters Krebs cycle.

Galactose undergoes 3 step reaction before entering Krebs cycle.



An integrated view of the metabolic pathways

Molecular basis



lactose

- Major carbohydrate in mammalian milk

Splint into glucose & galactose

- Glucose enters Krebs cycle
- Galactose coverted to glucose in 3 reaction steps before entering Krebs cycle

Galacatose converted to glucose in 3 steps

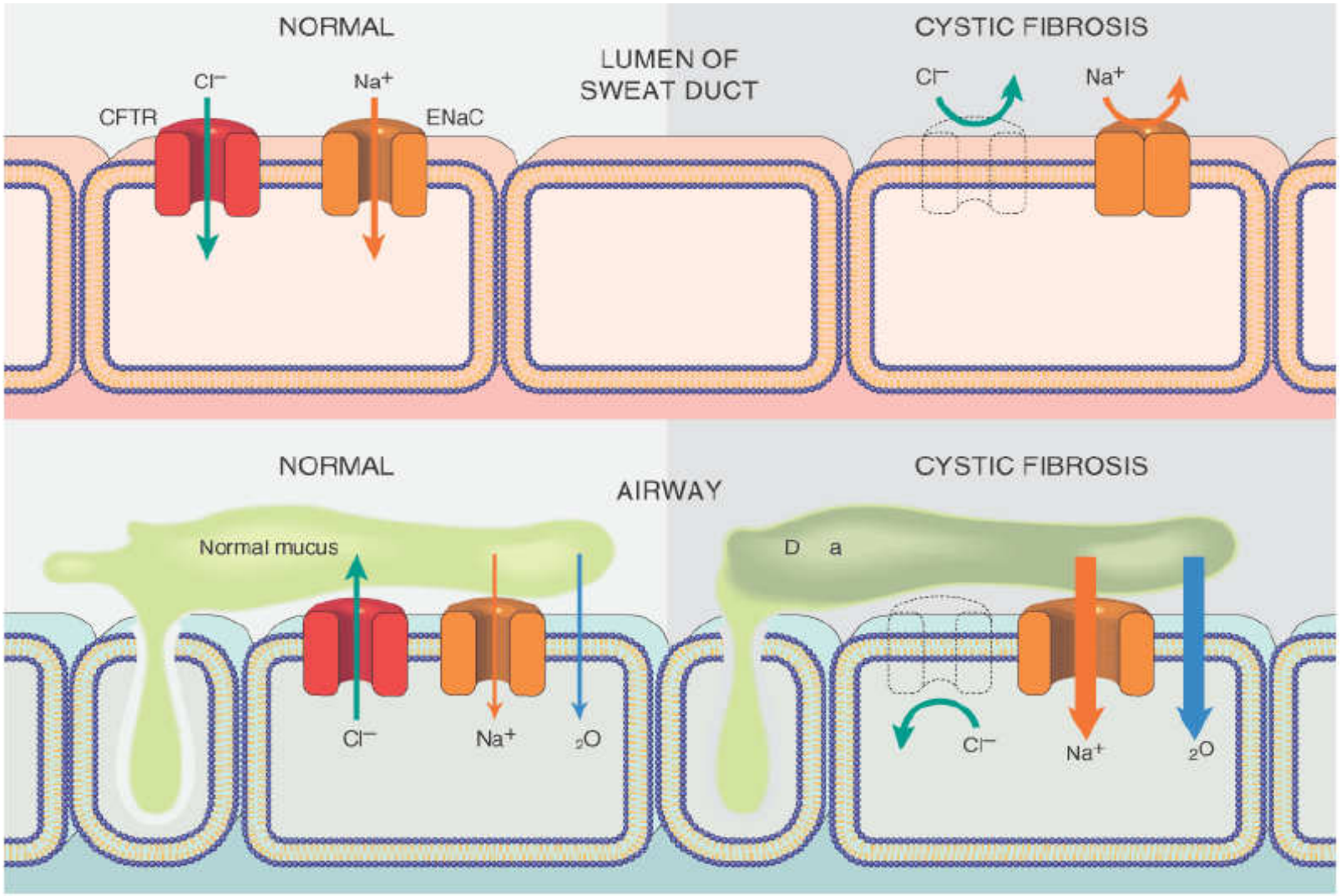
- Enzyme (galactose-1phosphate uridly transferase) in reaction 2 absent.
- Common variant

As a result of transferase lack ,galacatose-1-phosphate accumulates and deposited in various sites leading to clinical manifestations observed.

Cystic Fibrosis

- Primary defect is in the regulation of epithelial chloride transport by a chloride channel protein (CFTR) encoded by the cystic fibrosis gene.
- Various mutations & variants.
- Autosomal recessive disorder (must have 2 pairs of defective gene to express symptoms). Homozygous express symptoms.
- 2-4% of may be heterozygous.

Molecular basis



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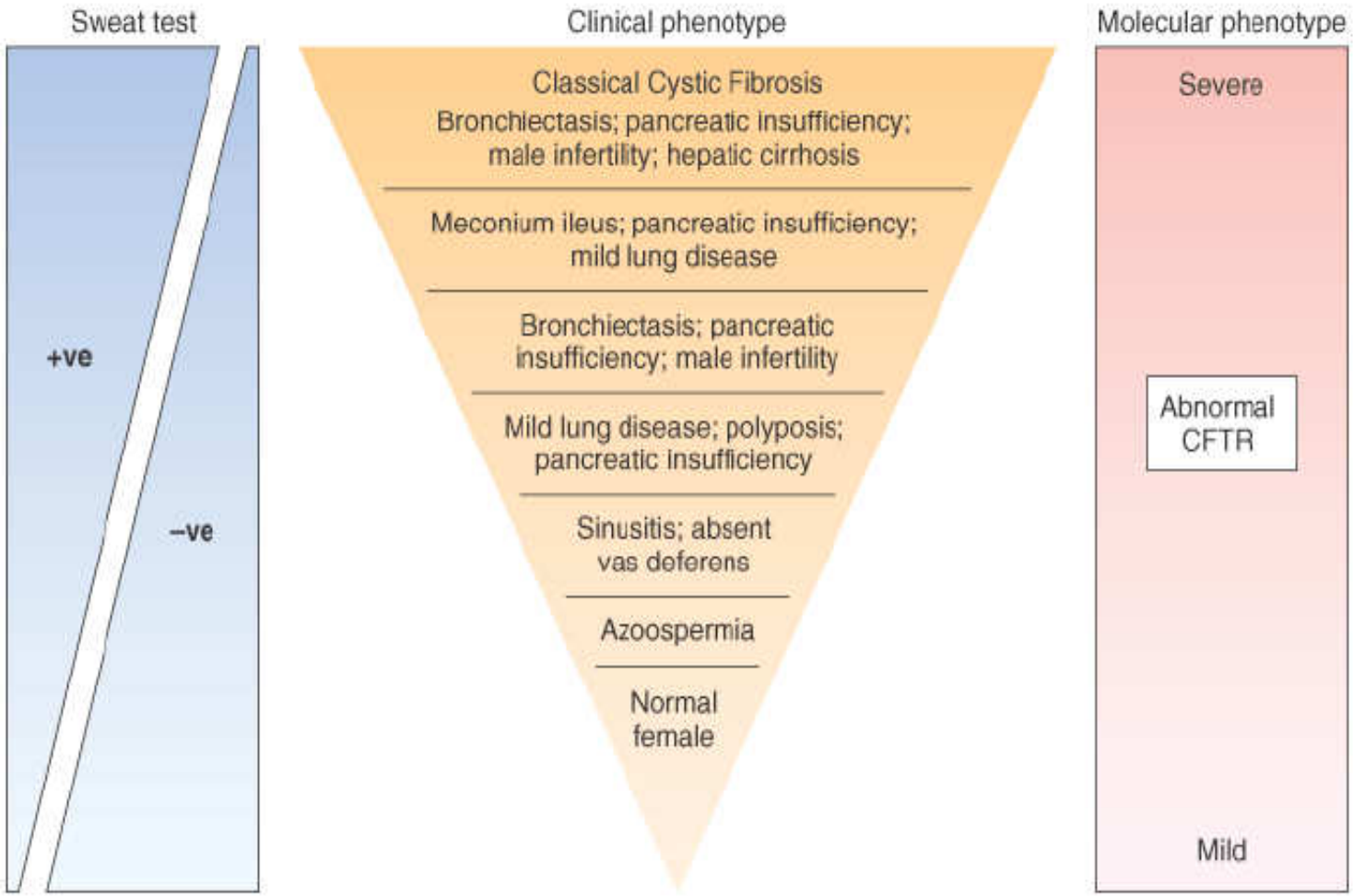

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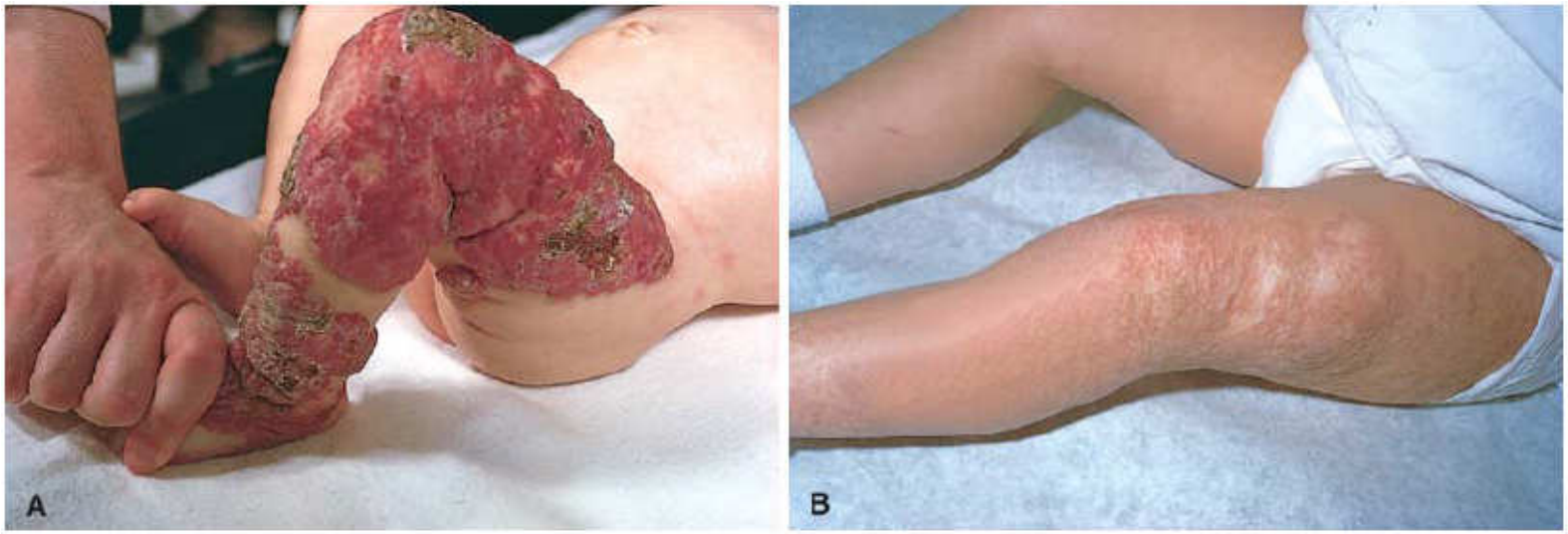
Tumor Like Lesions



Ref: Robins Pathological Basis of Diseases, 7th Ed.

Malignant Tumors

Only 2% of malignant tumors occur in infancy & childhood.

0 to 4 Years
Leukemia
Retinoblastoma
Neuroblastoma
Wilms tumor
Hepatoblastoma
Soft tissue sarcoma (especially rhabdomyosarcoma)
Teratomas
Central nervous system tumors

Ref: Robins Pathological Basis of Diseases, 7th Ed.

Genetic Markers of childhood tumors

Tumor Type	Genetic Markers	Other Diagnostically Useful Features
Neuroblastoma	17q gain,* 1p deletion*	Clinical elevation in level of urinary catecholamines
	N-*myc* amplification*	Neurosecretory granules by electron microscopy
	DNA hyperdiploidy, near triploidy†	Neuron-specific enolase expression
	t(11;22),‡ t(21;22), t(7;22)	*MIC2* (CD99) gene expression
	EWS-FLI1 or *EWS-ERG* fusion transcript	
Rhabdomyosarcoma	t(2;13),‡* t(1;13)—alveolar rhabdomyosarcoma (ARMS)	Myogenin and Myo D1 expression (all subtypes)
	11p15.5 deletion—embryonal rhabdomyosarcoma (ERMS)	Alternating thick and thin filaments by electron microscopy
	PAX3-FKHR and *PAX7-FKHR* fusion transcript (ARMS)	
Burkitt lymphoma	t(8;14),‡ t(2;8), t (8;22)	B-cell phenotype expressing CD19, CD20, CD10, IgM
		Epstein-Barr virus latent infection (endemic cases)
Lymphoblastic lymphoma/ acute lymphoblastic leukemia	Hyperdiploidy (>50),† Hypodiploidy(<46)*	Terminal deoxynucleotidyl transferase (TdT)+
	B-lineage: various translocations, including t(12;21) (*TEL-AML1*),‡,† t (9;22) (*BCR-ABL*, Philadelphia chromosome),* t(4;11) (AF4-MLL)*, t (1;19) (*PBX-E2A*) T-lineage: 1p32 abnormalities (*TAL1* gene)	Various B- and T-lineage antigens
Wilms tumor	11p13 (*WT1*) deletion/mutation	
	11p15.5 abnormalities of imprinting (e.g., *IGF2*, *H19*, $p57^{KIP2}$)	
	16q,* 1p,* 7p deletion	
Retinoblastoma	13q14 (*RB*) deletion/mutation	Retinal S antigen expression
Medulloblastoma	17p deletion	Evidence of neuronal differentiation (synaptophysin expression) or glial differentiation (glial fibrillary acid protein [GFAP] expression)
	Isochromosome 17q	

PNET, peripheral neuroectodermal tumor.

*Generally associated with a poorer prognosis.

†Generally associated with a better prognosis.

Laboratory Diagnosis

- Prenatal screening for genetic defects
- Ultra-sound scan
- Screening tests in newborns
- Specific genetic markers for tumors
- UEC
- LFT

Laboratory Assessment of Neonates Suspected of Having an Inborn Error of Metabolism

Routine Studies	Special Studies
Blood lactate and pyruvate	
Complete blood count and differential	Plasma amino acids
Plasma ammonia	Plasma carnitine
Plasma glucose	Urine amino acids
Plasma electrolytes and blood pH	Urine organic acids
Urine ketones	
Urine-reducing substances	

Study Guide

- How is prenatal screening for genetic defects done? What is the appropriate sample to obtain to send to laboratory?
- What are the current neonatal screening tests available for screening inborn errors of metabolism?
- What complications can be expected in a newborn of a diabetic mother? What is the pathogenesis of these complications?
- How is diagnosis of cystic fibrosis confirmed?
- What is genetic counseling?

END

Reference: Robins Pathological Basis of Diseases, 6th & 7th Ed.

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