DEPARTMENT OF PATHOLOGY AND LABORATORY MEDICINE

WEEK 5

ASSIGNMENT, OBJECTIVES, AND CASE STUDY

TOPIC OF THE WEEK: DEVELOPMENTAL PATHOLOGY/PERINATAL AND PEDIATRIC PATHOLOGY

REQUIRED READING:

Cotran, Kumar, Robbins: PATHOLOGIC BASIS OF DISEASE, 6th Edition,
Diseases of Infancy and Childhood (Chapter 11, pp. 459-489)
Female Genital Tract; Section on “Gestational and Placental Disorders,”
(Chapter 24, pp. 1079-1089)
Supplemental Material (Attached): Developmental Anomalies

REQUIRED STUDY FOR SMALL GROUPS

CASE BASED STUDY Small Group Sessions

ASSIGNMENTS:
- Laboratory Medicine Case Book Chapter 27 OR
- Laboratory Medicine Case Set CD ROM Chapter 37
- Printed Case 1 (attached); with the photograph exhibit in the Media Library.

OBJECTIVES:

1. Case Book, Chapter 27 OR Case Set Chapter 37
- Complications of premature rupture of the membranes in pregnancy
- Chorioamnionitis - pathogenesis, clinical course, and treatment; histopathology
- Serum human chorionic gonadotropin (hCG) as a test (understanding, interpretation, diagnostic use): Ravel: Clinical Laboratory Medicine, pp. 543-546
  Raskova, Shea, Skvara, and Mikhail: Laboratory Medicine Case Book, p. 291
- Serum alkaline phosphatase as a test (understanding, interpretation, diagnostic use):
  Ravel: Clinical Laboratory Medicine, pp. 312-314
  Raskova, Shea, Skvara, and Mikhail: Laboratory Medicine Case Book, p. 291
- Biochemical tests for congenital anomalies (understanding, interpretation, diagnostic use):
  Ravel: Clinical Laboratory Medicine, pp. 550-552
  Raskova, Shea, Skvara, and Mikhail: Laboratory Medicine Case Book, pp. 291-292
2. *Printed Case (Attached)*
- Pathogenesis of diagnosed problems
- Neo-natal anemia:
  
  Ravel: Clinical Laboratory Medicine, pp.135-139
- Histopathology of diagnosed problems
- Understanding of problems raised by questions for homework and discussion

**PATHTALK Small Group Sessions**

**ASSIGNMENTS:**
- *Projection slides* on carousels in the Media Library, labeled by weekly topic and subject
- Slide Manual (pp.25-29, Perinatal, Pediatrics)
- Journal Club Article (see your Course Book)

**OBJECTIVES:**
- Correlations of histopathology, gross pathology, and laboratory findings
- Review of pathophysiology

**ADDITIONAL MATERIAL (Optional, unless indicated otherwise)**

- SELF-STUDY MATERIAL, MATERIAL FOR SELF EVALUATION and VISUAL AND AUDIOVISUAL MATERIAL

See your Course Book (page 4) for a complete listing.
DEVELOPMENTAL DEFECTS (ANOMALIES)

Major anomalies differ from minor anomalies in that they produce significant functional or cosmetic impairment. The incidence of major anomalies is 3% of live births, and is higher in abortuses, stillborns, prematurity, and multiple gestation. Developmental defects are an important cause of pregnancy losses, neonatal mortality and morbidity, pediatric hospital admissions and long term disabilities. A minor developmental anomaly by itself may have no serious medical consequences to the patient, however, it indicates a flaw in development and can be a clue for internal major anomalies or a specific syndrome.

PATHOGENETIC MECHANISMS

From the stand point of developmental pathogenesis, a structural defect can be assigned into one of three categories: malformation, deformation and disruption. Whereas malformations occur early during embryonic organogenesis, deformations and disruptions occur at variable periods throughout gestation. The clinical importance of this distinction relates to prognosis and recurrence risk counseling. If a child's anomaly can be determined as disruptive in nature, parents can be given a negligible recurrence risk. If a child's anomaly can be determined to represent a late gestational deformation defect, an excellent prognosis can be given for spontaneous or postural correction.

MALFORMATION: a morphologic defect of an organ, part of an organ, or larger region of the body resulting from an intrinsically abnormal developmental process.

Examples: Absent primordium: agenesis
Incomplete closure: cleft lip and palate, neural tube defects
Incomplete separation: syndactyly
Incomplete septation: tracheoesophageal fistula, ventricular septal defect, truncus arteriosus
Persistence of early forms: Meckel's diverticulum
DEFORMATION: an abnormal form, shape, or position of a part of the body caused by mechanical forces.

Examples: Club feet, Hip dislocation, Scoliosis, Arthrogryposis, Hypoplastic lungs

Causes of deformation: Oligohydramnios, Twins, Uterine leiomyomas, Bicornuate uterus

DISRUPTION: a morphologic defect of an organ, part of an organ, or a larger region of the body resulting from the extrinsic breakdown of, or an interference with, an originally normal developmental process.

Examples: Small bowel atresia, Gastrochisis

Congenital amputation

DYSPLASIA: an abnormal organization of cells into tissue and its morphologic result.

(dyshistogenesis)

Examples: Hemangioma, Hamartoma, Renal dysplasia

CLASSIFICATION OF MULTIPLE DEFECTS

In an individual with multiple anomalies, the approach toward making a morphologic diagnosis consists of 4 stages.

1. to determine the pathogenetic mechanism for each anomaly.
2. to decide which is the earliest defect in morphogenesis.
3. to analyze relationship between defects.
4. to classify the multiple anomalies into the following:

SEQUENCE: a pattern of multiple anomalies derived from a single anomaly or pathogenetic mechanism.

Examples: Deformation: Oligohydramnios

Disruption: Amniotic bands sequence

Malformation: Micrognathia sequence

SYNDROME: a pattern of multiple anomalies that are pathogenetically related and not known to represent a single sequence.

Examples: Malformation: Down syndrome

Dysmetabolic: Hurler syndrome

Meckel syndrome

Fetal hydantoin syndrome

ASSOCIATION: a nonrandom occurrence in two or more individuals of multiple anomalies not known to be a sequence or syndrome.

Examples: VATER association

CHARGE association
INTERRELATIONSHIPS BETWEEN MALFORMATION, DEFORMATION AND DISRUPTION

The distinction between the three mechanisms of anomalies is useful for clinical purposes, however, they are interrelated and may overlap during embryonic and fetal development. In multiple anomalies, it is important to classify individual anomalies and analyse their interrelationships, so that a sequence could be developed to explain some, if not all of the anomalies.

Amniotic Band Disruption Complex (Sequence) is an example in which all three mechanisms may interact depending on the stage of embryonic/fetal development.

1. Bands cause disruptions by tearing and strangulation:
   - Amputation of limbs and fingers (pseudosyndactyly)
   - Constriction bands
   - Facial cleft
   - Encephalocele, and anencephaly

2. Bands cause deformations by tethering and crowding:
   - Club feet
   - Scoliosis

3. Bands cause malformations by interrupting morphogenesis:
   - Omphalocele
   - Cleft lip and palate
   - Choanal atresia

TERATOGENESIS AND MODIFYING FACTORS

Teratogens are chemical, physical and biological agents that cause developmental defects. However, exposure to a known teratogen does not invariably result in a defect, the factors that determine the expression of a developmental defect (teratogenesis) are:

1. Fetal and maternal genotypes.
2. Timing, in relation to developmental stage.
4. Dose of teratogen.
5. Interactions and secondary effects.

CAUSES OF DEVELOPMENTAL DEFECTS

See pages 437 - 440 in Robbins Pathologic Basis of Disease (5th edition)
Clinical Summary: An 24 year-old female presents to the ER in labor. She reports that this is her 3rd pregnancy, and that all her pregnancies have received very sketchy medical care. Upon fetal monitoring, the fetus has a rapid heart rate and other signs of fetal distress. After delivery the neonate is noted to be pale, with wide-spread subcutaneous edema and rapid heart-rate and breathing. A markedly enlarged spleen and liver can be palpated. After about 12 hours the infant’s pallor changes to a deep yellow.

Relevant Laboratory Data:

WBC 27,000 
Hgb 7.5 g/dl 
Retic rate: 10% 
Peripheral blood smear shows numerous nucleated red blood cells. 
Serum indirect bilirubin: 25 mg/dl 
ABG pH = 7.2 
Direct Coombs test of cord blood is +.

Questions:
1. What is the differential diagnosis for an infant with jaundice, anemia, and nucleated red blood cells in the peripheral blood? Which of the lab values above points toward the correct choice? Which additional test(s) might clinch the diagnosis?

2. What are the physiologic mechanisms behind the anemia, jaundice, and edema? Why did the infant’s skin color go from pallor to yellow?

3. What are the different forms of bilirubin found in the blood? How is bilirubin metabolized? What is “kernicterus”?

4. If the mother had been receiving adequate medical care during this and previous pregnancies, what measures should have been taken to prevent the neonate’s disease? Divide your answer into tests and therapeutic interventions, both for the mother and the 3 children

5. How does the ABO antigen system interact with the patient’s disease? How do you know that this antigen system is not the direct cause of the disease? Is there a related neo-natal condition in which the ABO antigens are directly involved?
6. The WBC, retic rate, and blood pH—do you think these are causes or effects of the patient’s condition? What are their significances?