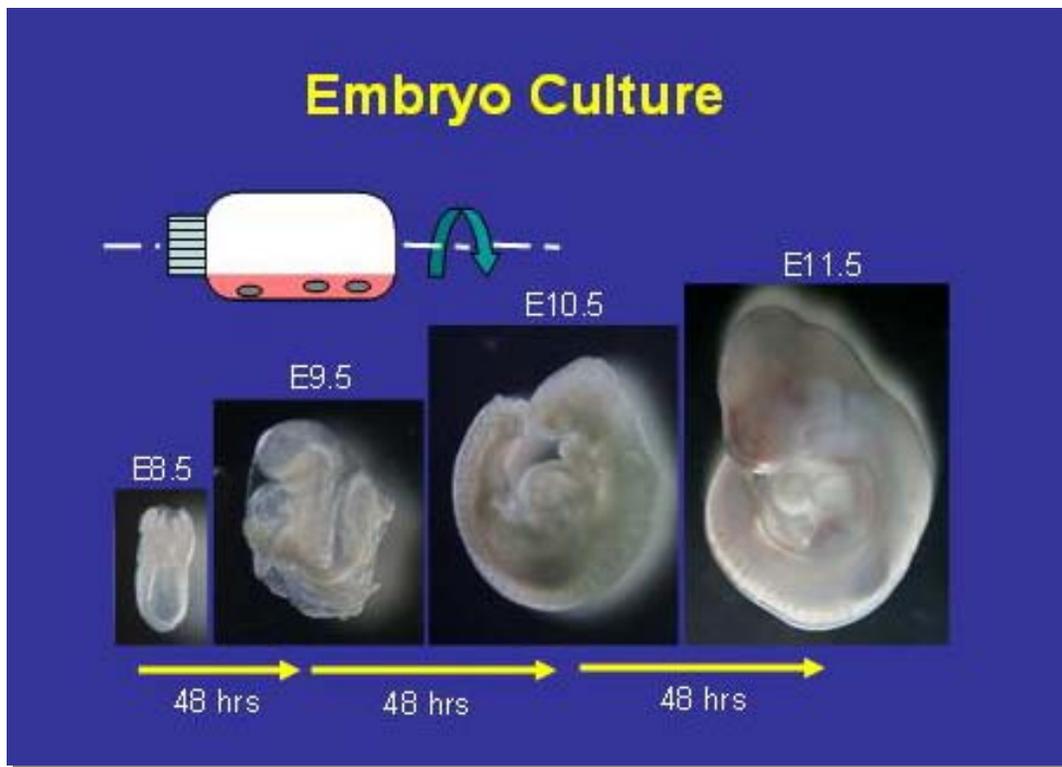


# Human EMBRYOLOGY Study Guide 2005



*Photo of rat embryo cultures courtesy of E. Albert Reece, M.D., Ph.D., M.B.A.  
Vice-Chancellor, UAMS; Dean, College of Medicine*

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## Introduction to Human Embryology

This study guide is designed to help you as you learn embryology in both Medical Microanatomy and Gross Anatomy. For the first time, we have created a flow of topics that focuses you initially in early embryology and then presents the topics timed with the organ systems being studied in Gross Anatomy.

The first weeks of development will be taught in the Microanatomy course and a separate examination will be given over this topic during the third week of the course. This gives you time to concentrate on this material and the self-scheduled exam will run over the third week. The early embryology topics will be taught by Drs. Cindy Kane and Bruce Newton, both of whom are developmental neurobiologists. Dr. Kane works on the effects of fetal alcohol syndrome on glial cells and Dr. Newton's research is focused on the gonadal steroid control of spinal cord development.

In addition, for the first time, we are pleased to include a lecture on Neural Axis Malformations by Dean E. Albert Reece, M.D., Ph.D., M.B.A, who has an active research program that focuses on diabetes and neural tube malformations. Dean Reece is an Obstetrician-Gynecologist who sets a wonderful example of a clinician who translates work with diabetic patients to the lab bench as he shows how high glucose causes neural tube malformations. The cover of this study guide illustrates his work with rat embryos.

After the third week in Microanatomy, the embryology topics are presented in the Gross Anatomy course. **Please note that all questions over these topics will be in the Gross Anatomy exams.** Both Gross Anatomy and Microanatomy lecturers will contribute to these topics. Many of the lectures are listed on the Microanatomy schedule. This study guide includes most of the objectives and guides for these lectures. In addition, it includes the objectives and guide for lectures on the embryology of the Ear, Eye and Head and Neck, to be presented in January-February 2006.

During the final week in Microanatomy, we will focus on studies of the male and female reproductive system and you will be able to see this translated in a clinical correlation lecture on Maternal-Fetal Interactions, by Dr. Helen Kaye, Chair, Department of Obstetrics and Gynecology. While this topic remains in the Microanatomy course (as a study of the histophysiology of the reproductive organs, the information is also relevant to your studies of early embryology.

We hope that this focused look at embryology is beneficial and that you enjoy your studies!

## Week 1 Schedule: Early embryology

Day	Date	Time	Event	Subject	Faculty	Text Assignments
M	Oct. 10	9:00	Intro	Introduction to course	Childs	
M	Oct. 10	10:00	Lecture 1	Nervous System I	Newton	B&C(Ch6); G&H- 183-198, 203-210, 215-217
M	Oct. 10	11:00	Lecture 2	Nervous System II	Newton	See above
T	Oct 11	9:00	Lab 1	Nervous system histology	Stanley, Newton, Childs, Kane	Histology Time CD Newton Neurocytology CD
T	Oct 11	11:00	Lecture 3	Fertilization and embryogenesis I	Kane	L Ch 1-2
W	Oct 12	10:00	Lecture 4	Embryogenesis II	Kane	L Ch 2-3
W	Oct 12	11:00	Lecture 5	Embryogenesis III	Kane	L Ch 3-4
Th	Oct 13	10:00	Lecture 6	Early Embryology IV	Kane	L Ch 4-6
Th	Oct. 13	11:00	Lecture 7	Embryology of the Peripheral and Autonomic NS- I	Newton	L 433-447, 474-478, 95
Th	Oct 13	4:15	Tutorial		Lecturers	
F	Oct. 14	9:00	Lecture 8	Embryology of the Peripheral and Autonomic NS- II	Newton	L 433-447, 474-478, 95
F	Oct 14	10:00	Lab review	Review of basic tissues	Cave, Childs, Stanley, Burns	G&H85-108; B&C 45-5379-90

Key (colored copies of schedule only): Blue= Microanatomy-Gross Anatomy correlates;  
Red=Embryology; Green=Tutorials B&C=Burns and Cave; G&H=Gartner and Hiatt;  
L=Langman

Tutorial: Ed III Conference room.

All Lectures, Clinical Lectures and Reviews: Held in Ed III Building, Room G219 (Pauly Auditorium).

All Laboratories: Self-Study using Downing "Histology Time" CD with faculty present in the 8<sup>th</sup> floor laboratories Ed II building.

### Self Scheduled Quiz 1 over basic tissues

Self scheduled Exam on Basic Tissues, 25 questions covering Epithelia (3), Connective tissue (4), Muscle (3), and Nerve-10 lecture, 5 lab. Available Thursday, Oct 13 and through Monday, Oct 17th. At midnight. Allow 1 h. Lecture 3: Embryology I: Fertilization and Week 1

# Lecture 3: Embryology I: Week 1

**Dr. Kane**

## ***Reading Assignment:***

Langman, Ch 1-2

## ***Learning Objectives:***

Without reference materials, the student should be able to:

1. Identify and define structural elements involved in this stage of human development from representational images. For each structural element, describe:
  - a. The precursors of each structure
  - b. Additional structures to be derived from each structure as development progresses
  - c. The functional significance of each structure
  - d. The functional and regulatory inter-relationships between structures at each stage of development as described in text and lecture

Key figures: 2.1, 2.5B, 2.6, 2.10, 2.12, 2.13

2. Construct a temporal sequence of significant events during this developmental period
3. Describe the purpose of the key developmental processes during this developmental period. In doing so,
  - a. Define the key tissues, cells and molecules
  - b. Distinguish the key regulators
  - c. Explain the purpose of the process
  - d. Compare and contrast normal and abnormal outcomes

Key developmental processes:

Follicular development  
Ovulation  
Fertilization  
Cleavage and morulation  
Blastocyst formation  
Implantation in endometrium

4. Extrapolate embryonic structures present during this developmental period into derivative adult structures
5. Distinguish the functional and/or morphological consequences of specific teratologic events during this developmental period as described in the text, lab and lecture

## ***Competencies:***

1. Apply knowledge of developmental processes to describe in detail the construction of an adult human from male and female gametes to

- a) the general public
  - b) professional peers
2. Communicate knowledge-based information to patients regarding risk of birth defects and prevention of birth defects
    - a) In relation to relevant causative mechanisms, both genetic and epigenetic
    - b) In relation to relevant cellular and molecular processes of development
    - c) In relation to temporal periods of prenatal development
  3. Given patients with either common or rare developmental anomalies, apply state-of-the-art knowledge of developmental processes to correctly diagnose and explain in detail the underlying cause of the structural and/or functional teratology

**Sample questions:**

1. Which of the following developmental anomalies would result in the birth of an individual which could be a genetic chimera?
  - A. Polygyny
  - B. Polyspermy
  - C. Immediate cleavage
  - D. A & B are correct
  - E. A, B & C are correct

Answer: C

2. Infertility is a major health problem, occurring in approximately 20% of couples who want to have children. A young couple has come to your office because they want children but have failed to conceive in the past 2 years. You counsel them that a major cause of female infertility is due to uterine tube scarring caused by pelvic inflammatory disease. However, your tests indicate patent uterine tubes in the woman. The focus of your tests in the male is based on your knowledge that the primary cause of male infertility is which of the following?
  - A. Low sperm count
  - B. Non-motile sperm
  - C. Abnormal sperm morphology
  - D. Failure to ejaculate
  - E. Reproductive system tumors

Answer: A

3. Arrange the following developmental events in proper sequence.
  - A. Oocyte Anaphase II
  - B. Ovulation
  - C. Oocyte Metaphase I
  - D. Sperm penetrates zona pellucida
  - E. Male pronucleus formation

Answer: C, B, D, A, E

4. A fetus is aborted in mid pregnancy. Chromosome analysis shows it to be triploid with an XYY sex chromosome constitution. Which single event could account for the abnormality?

- A. Polyspermy
- B. Polygyny
- C. Translocation
- D. Nondisjunction
- E. All of the above

Answer: A

5. Assuming the gamete amount of DNA in the human to be 1.5 picograms, how many picograms of DNA is there in the nucleus of an oocyte after ovulation but prior to fertilization?

- A. 0.75
- B. 1.5
- C. 3
- D. 4.5
- E. 6

Answer: C

6. In vitro fertilization produces numerous embryos. Why are least three are normally implanted in the woman's uterus? Why are the remaining embryos usually frozen and stored?

7. A 30-year old woman has survived endometrial cancer. Although her uterus has been surgically removed, her ovaries are intact and she desperately wants to have her own child. She and her husband are extremely wealthy and are fortunate to identify a woman who, for \$15,000, is willing to serve as a surrogate mother during the pregnancy. The couple has undergone *in vitro* fertilization and 6 viable embryos have been produced. Three embryos are implanted into the surrogate mother and the remaining embryos are frozen. Prior to birth of a single infant, the genetic parents are killed in an automobile accident. The surrogate mother claims that she has invested considerable time and emotions into the pregnancy and that she is now closely bonded to the unborn fetus; thus, she claims that she is the baby's rightful mother and that she should receive the large inheritance coming to the baby. However, the sister of the genetic father claims that she has a blood relationship to the unborn baby and that she should care for the child after birth and will oversee the large inheritance until the baby is of majority age. This issue goes to court, where the outcome of the remaining frozen embryos must also be decided. What are the legal and ethical issues involved in this case? Who should be the legal guardian of the child? What about the frozen embryos? How does the extremely large inheritance involved affect these issues?

### **Study Guide:**

Read and outline Sadler text Chpt 2, pp. 31-48 before lecture

Review by self-study the mitosis and meiosis content from Cell Biology course  
Note: the content of Sadler Chpt 1 will be covered in the context of female and male reproductive system development

Emphasize clinical correlates (pp. 33, 40-42, and 44-45)

Solve practice problems p. 48 (Answers p. 486)

### ***Helpful Hints:***

Many students find it helpful to prepare for Objective #1 by drawing from memory simple diagrams of figures in the textbook (refer to key figures above), label the structures with descriptors as in the text, and annotate details to each descriptor regarding:

- a. The precursors of each structure
- b. Additional structures to be derived from each structure (including adult derivatives)
- c. The functional significance of each structure
- d. The functional and regulatory inter-relationships between structures

In addition, these diagrams can serve as useful instruments for organizing study for the remaining objectives as well as the exam.

Temporally study events in “Weeks 1, 2 or 3”; it is not necessary to memorize events “day-by-day” (but keep in mind objective #2 above)

Note: Images included in the exam will be derived from any source and will be representational of the images presented in the text, lab and lecture

# Lecture 4: Embryology II: Week 2

Dr. Kane

## **Reading Assignment:**

Langman, Chapter 2-3

## **Learning Objectives:**

Without reference materials, the student should be able to:

1. Identify and define structural elements involved in this stage of human development from representational images. For each structural element, describe:
  - a) The precursors of each structure
  - b) Additional structures to be derived from each structure as development progresses
  - c) The functional significance of each structure
  - d) The functional and regulatory inter-relationships between structures at each stage of development as described in text and lecture

Key figures: 3.1, 3.3, 3.4, 3.6, 3.8

2. Construct a temporal sequence of significant events during this developmental period.
3. Describe the purpose of the key developmental processes during this developmental period (refer to key processes in helpful hints below). In doing so,
  - a) Define the key tissues, cells and molecules
  - b) Distinguish the key regulators
  - c) Explain the purpose of the process
  - d) Compare and contrast normal and abnormal outcomes

Key developmental processes:  
Formation of placenta and uteroplacental circulation  
Differentiation of embryoblast  
Formation of yolk sac, amniotic cavity, and chorionic cavity  
Extrapolate embryonic structures present during this developmental period into derivative adult structures

  - e) Distinguish the functional and/or morphological consequences of specific teratologic events during this developmental period as described in the text, lab and lecture

## **Competencies:**

1. Apply knowledge of developmental processes to describe in detail the construction of an adult human from male and female gametes to
  - a) the general public
  - b) professional peers

2. Communicate knowledge-based information to patients regarding risk of birth defects and prevention of birth defects
  - a) In relation to relevant causative mechanisms, both genetic and epigenetic
  - b) In relation to relevant cellular and molecular processes of development
  - c) In relation to temporal periods of prenatal development
3. Given patients with either common or rare developmental anomalies, apply state-of-the-art knowledge of developmental processes to correctly diagnose and explain in detail the underlying cause of the structural and/or functional teratology

**Sample question:**

The syncytiotrophoblast

- A. Has well defined plasma membrane boundaries between the cells
- B. Shows little invasive activity
- C. Arises from cytotrophoblast
- D. Is derived from inner cell mass tissue
- E. None of the above

Answer: C

**Study Guide:**

Read and outline Sadler text Chpt 3, pp. 51-62 before lecture

Emphasize clinical correlates (pp. 58-61)

Solve practice problems pp. 62 (Answers p. 487)

# Lecture 5: Embryology III: Week 3

Dr. Kane

## **Reading Assignment:**

Langman Ch 3-4

## **Learning Objectives:**

Without reference materials, the student should be able to:

4. Identify and define structural elements involved in this stage of human development from representational images. For each structural element, describe:
  - a) The precursors of each structure
  - b) Additional structures to be derived from each structure as development progresses
  - c) The functional significance of each structure
  - d) The functional and regulatory inter-relationships between structures at each stage of development as described in text and lecture

Key figures: 4.1, 4.3, 4.4, 4.5, 4.9, 4.11, 4.13, 4.14, 4.15, 4.16, 4.17
5. Construct a temporal sequence of significant events during this developmental period.
6. Describe the purpose of the key developmental processes during this developmental period (refer to key processes in helpful hints below). In doing so,
  - a) Define the key tissues, cells and molecules
  - b) Distinguish the key regulators
  - c) Explain the purpose of the process
  - d) Compare and contrast normal and abnormal outcomes

Key developmental processes:  
Gastrulation  
Notochord formation  
Axis specification  
Differentiation of placenta
7. Extrapolate embryonic structures present during this developmental period into derivative adult structures
8. Distinguish the functional and/or morphological consequences of specific teratologic events during this developmental period as described in the text, lab and lecture

## **Competencies:**

1. Apply knowledge of developmental processes to describe in detail the construction of an adult human from male and female gametes to
  - a. the general public
  - b. professional peers

2. Communicate knowledge-based information to patients regarding risk of birth defects and prevention of birth defects
  - a) In relation to relevant causative mechanisms, both genetic and epigenetic
  - b) In relation to relevant cellular and molecular processes of development
  - c) In relation to temporal periods of prenatal development
3. Given patients with either common or rare developmental anomalies, apply state-of-the-art knowledge of developmental processes to correctly diagnose and explain in detail the underlying cause of the structural and/or functional teratology

**Sample questions:**

1. An infant is born with a sacrococcygeal teratoma. Biopsy and histologic analysis reveal that it contains intestinal epithelia, cardiac muscle, cartilage, and integument tissue. You counsel the mother that the tumor is benign and recommend surgical removal. This tumor was caused by which developmental anomaly?
  - A. Failure of somite formation
  - B. Failure of primitive streak formation
  - C. Failure of primitive streak regression
  - D. Failure of notochord formation
  - E. Failure of notochord regression

Answer: C

2. Histologic analysis would reveal an endodermal tissue component in which of the following structures?
  - A. Cloacal plate
  - B. Prochordal plate
  - C. Allantois
  - D. All of the above
  - E. None of the above

Answer: D

3. The intraembryonic coelom (or chorionic cavity) is lined with which of the following?
  - A. Splanchnic and somatic mesoderm
  - B. Endoderm
  - C. Ectoderm
  - D. Chorionic membrane
  - E. Amniotic membrane

Answer: A

**Study Guide:**

Read and outline Sadler text Chpt 4 pp. 65-85 before lecture

Emphasize clinical correlates (pp. 79-80)

Solve practice problems p. 85 (Answers p. 487)

# Lecture 6 Embryology: Week 3 to Birth

Dr. Kane

## **Reading Assignment:**

Langman Chapters 4-6

## **Learning Objectives:**

Without reference materials, the student should be able to:

1. Identify and define structural elements involved in this stage of human development from representational images. For each structural element, describe:
  - a) The precursors of each structure
  - b) Additional structures to be derived from each structure as development progresses
  - c) The functional significance of each structure
  - d) The functional and regulatory inter-relationships between structures at each stage of development as described in text and lecture

Key figures: 5.1, 5.2, 5.3, 5.5, 5.8, 5.9, 5.11, 5.12, 5.13, 5.14, 5.16, 5.17, 5.18, 6.2

Key tables: 5.1, 5.4, 6.2
2. Construct a temporal sequence of significant events during this developmental period
3. Define the structures and processes involved in genesis and differentiation of each organ system
4. Describe the purpose of the key developmental processes during this developmental period. In doing so,
  - a. Define the key tissues, cells and molecules
  - b. Distinguish the key regulators
  - c. Explain the purpose of the process
  - d. Compare and contrast normal and abnormal outcomes

Key developmental processes:

  - Neural induction
  - Neurulation
  - Mesoderm differentiation
  - Endoderm differentiation
  - Neural crest differentiation
  - Lateral and cephalocaudal folding
  - Segmentation and patterning
  - Fetal development
5. Extrapolate embryonic structures present during this developmental period into derivative adult structures
6. Distinguish the functional and/or morphological consequences of specific teratologic events during this developmental period as described in the text, lab and lecture

### **Competencies:**

1. Apply knowledge of developmental processes to describe in detail the construction of an adult human from male and female gametes to
  - a. the general public
  - b. professional peers
2. Communicate knowledge-based information to patients regarding risk of birth defects and prevention of birth defects
  - a. In relation to relevant causative mechanisms, both genetic and epigenetic
  - b. In relation to relevant cellular and molecular processes of development
  - c. In relation to temporal periods of prenatal development
3. Given patients with either common or rare developmental anomalies, apply state-of-the-art knowledge of developmental processes to correctly diagnose and explain in detail the underlying cause of the structural and/or functional teratology

### **Sample questions:**

1. A piece of tissue from an area of an embryo, which will normally develop into CNS, is transplanted to an area which will normally develop into ventral body wall. The transplantation occurs prior to induction by the notochord. Into what structure will the transplanted tissue develop?
  - A. Ventral body wall
  - B. Notochord
  - C. CNS
  - D. Eye
  - E. Liver

Answer: A

2. Which structures are included in the umbilical cord?
  - A. Umbilical vein
  - B. Remnant of allantois
  - C. Remnant of yolk sac
  - D. A and B only
  - E. A, B and C

Answer: E

3. Identify the origin of the following structures with A, B or C.  
A = ectoderm      B = endoderm      C = mesoderm
  - \_\_\_ Secretory epithelial cell in cutaneous gland
  - \_\_\_ Neurons in central nervous system
  - \_\_\_ Neurons in spinal dorsal root ganglia
  - \_\_\_ Absorptive epithelial cell in small intestine
  - \_\_\_ Skeletal muscle cell

Answers, in order: A, A, A, B, C

4. Sclerotome differentiation from the somite is initiated by a major regulatory factor secreted by the notochord and floor plate of the neural tube. This factor is

- A. SHH
- B. WNT
- C. BMP-4
- D. NT-3
- E. PAX3

Answer: A

***Study Guide:***

Read and outline Sadler text Chpt 5, pp. 87-114 and Chpt 6, pp. 117-125 before lecture

Note: Placenta and twinning will be studied in the context of the female reproductive system. Content of Sadler Chpt 7 will be covered in the context of individual organ system development.

Emphasize clinical correlates (pp. 111-112 and 123-125)

Solve practice problems p. 114 and problem #1 on p. 147 (Answers p. 488)

# Lectures 7 and 8: Embryology of the Peripheral and Autonomic Nervous Systems

**Dr. Newton**

## ***Reading Assignment***

Guides to studying this unit

All of the relevant information for your study of Neuroembryology is available in Langman's Medical Embryology text. Pages for your reading assignment are: 95 (Table 5.1), 433-447 and 474-478.

Concentrate on understanding cell differentiation and migration from neuroepithelium, formation of alar and basal plates and their derivatives, neural tube defects (but not molecular regulation of development), contributions of neural crest.

## ***Learning Objectives***

At the end of this unit the student should be able to:

1. Describe the origins of neural tissue, included formation of neuroectoderm, the process of neurulation and neural crest formation.
2. Using spinal cord as a model describe the formation of mantle and marginal layers, alar and basal plates and list cell types found in each region.
3. List the cell types derived from neuroepithelium and describe their function in the CNS.
4. List the cell types derived from neural crest.
5. Describe the defects that can occur following incomplete closure of the neural tube.
6. Describe the origins of the sympathetic and parasympathetic components of the autonomic nervous system.

## ***Sample Questions***

(Answers are at the end of this Unit)

1. What would be the consequence of removing all neurons in the intermediate horn of the thoracic and lumbar spinal cord?

- A. Parasympathetic ganglion neurons would lose all of their afferent input
- B. Parasympathetic ganglion neurons would lose all of their efferent output
- C. Sympathetic ganglion neurons would lose all of their afferent input
- D. Sympathetic ganglion neurons would lose all of their efferent output

2. From your knowledge of neuroembryology why would disruption of neuroblast migration to the developing spinal cord alar plate lead to serious problems with sensory function?

- A. There would be no sensory ganglion neurons formed
- B. There would be no sensory neurons in the dorsal horn
- C. The trunk of the spinal nerve would not be formed
- D. There would be no sensory neurons in the ventral horn

Answers to questions: 1. C, 2. B

## Week 2: Musculoskeletal and Teratology (Monday)

Day	Date	Time	Modality	Topic	Faculty	Text assignment
M	Oct 17	8:00	Exam	Final seating for Quiz on tissues		
M	Oct 17	9:00	Lecture 9	Embryology: Musculoskeletal System	Kane	L Ch 8-9
M	Oct. 17	10:00	Lecture 10	Integument and Breast	Kane	G&H Ch 14 & 20
M	Oct. 17	11:00	Clinical	Neural Axis Malformations	E. Albert Reece	
T	Oct. 18	9:00	Lab	Integument and Breast	Kane, Stanley, Drew, Childs	
T	Oct 18	11:00	Lecture 11	Blood and lymph vessels	Drew	B&C 123-130 G&H-251-256, 259-267, 270-271
W	Oct. 19	9:00	Lab 3	Blood and lymph vessels	Stanley, Drew, Childs, Kane	
W	Oct. 19	11:00	Lecture 12	Bone and Cartilage	Stanley	B&C Ch 9; G & H Ch 7
Th	Oct 20	9:00	Lecture 13	Bone Development	Stanley	
	Oct 20	10:00	Lab 4	Bone, Cartilage and Bone Development	Childs, Stanley, Drew, Kane	
<b>Th</b>	<b>Oct 20</b>	<b>4:15</b>	<b>Tutorial</b>		<b>Lecturers</b>	
<b>F</b>	<b>Oct 21</b>	<b>10:00</b>	<b>Lab Rev</b>	<b>Catch-up in lab and review</b>	<b>All Lecturers</b>	

Key: (on colored copies of schedule) Blue= Microanatomy-Gross Anatomy correlates; Red=Embryology; Green=tutorials

B&C=Burns and Cave; G&H=Gartner and Hiatt; L=Langman

All Lectures, Clinical Lectures and Reviews: Held in Ed III Building, Room G219 (Pauly Auditorium).

All Laboratories: Self-Study using Downing "Histology Time" CD with faculty present in the 8<sup>th</sup> floor laboratories Ed II building.

**Exam I: Skin, Blood vessels, Lymph vessels, Bone, Cartilage (7 lectures, 3 labs)+ 5 review questions=40 points; Self schedule Thursday 4-midnight; Friday 4-6; Sat 10-6; Sunday noon-midnight; Monday 4—midnight; allow 2 h**

# Lecture 9: Embryology: Musculoskeletal System

Dr. Kane

## **Reading Assignment:**

Langman-Chapter 8-9

## **Learning Objectives:**

Without reference materials, the student should be able to:

1. Identify and define structural elements involved in this stage of human development from representational images. For each structural element, describe:
  - a) The precursors of each structure
  - b) Additional structures to be derived from each structure as development progresses
  - c) The functional significance of each structure
  - d) The functional and regulatory inter-relationships between structures at each stage of development as described in text and lecture  
Key figures: 8.1, 8.3, 8.7, 8.8, 8.13, 8.16, 8.18, 8.19, 8.21, 9.1, 9.2, 9.3, 9.4, 9.5  
Key tables: 8.1
2. Construct a temporal sequence of significant events during this developmental period
3. Define the structures and processes involved in genesis and differentiation of each organ system
  - a. Describe the purpose of the key developmental processes during this developmental period. In doing so,
  - b. Define the key tissues, cells and molecules
  - c. Distinguish the key regulators
  - d. Explain the purpose of the process
  - e. Compare and contrast normal and abnormal outcomesKey developmental processes:
  - Mesoderm differentiation
  - Formation of skull
  - Formation of limbs
  - Formation of vertebral column, ribs and sternum
  - Myotome differentiation and striated muscle patterning
  - Dermatome patterning
  - Cardiac and smooth muscle development
4. Extrapolate embryonic structures present during this developmental period into derivative adult structures
5. Distinguish the functional and/or morphological consequences of specific teratologic events during this developmental period as described in the text, lab and lecture

### **Competencies:**

1. Apply knowledge of developmental processes to describe in detail the construction of an adult human from male and female gametes to
  - a. the general public
  - b. professional peers
2. Communicate knowledge-based information to patients regarding risk of birth defects and prevention of birth defects
  - a. In relation to relevant causative mechanisms, both genetic and epigenetic
  - b. In relation to relevant cellular and molecular processes of development
  - c. In relation to temporal periods of prenatal development
3. Given patients with either common or rare developmental anomalies, apply state-of-the-art knowledge of developmental processes to correctly diagnose and explain in detail the underlying cause of the structural and/or functional teratology

### **Sample questions:**

1. Skeletal muscle is derived from the dermomyotome with differentiates from the somites. Dorsolateral cells differentiate and migrate to form the hypomere which gives rise to muscles of the limb and body wall. Which gene specifically controls differentiation into hypomere by acting as a transcription factor to regulate downstream genes?

- A. PAX 1
- B. PAX 3
- C. SHH
- D. MYF5
- E. MYO-D

Answer: E

2. Absence of digits is usually unilateral, while extra digits or fusion of digits is usually bilateral. Cleft hand and foot (lobster claw deformity) are caused by absence of the 3<sup>rd</sup> digit with frequent fusion of the thumb/index finger and the 4<sup>th</sup>/5<sup>th</sup> digits. Fusion of digits is usually restricted to the fingers or toes and is commonly accompanied by clubfoot in which the foot is adducted and plantar flexed. Which term identifies abnormal fusion of digits?

- A. Ectrodactyly
- B. Polydactyly
- C. Syndactyly
- D. Amelia
- E. Micromelia

Answer: C

3. Which of the following directly contribute tissue to the formation of the bone and cartilage of the skeletal system?

- A. Sclerotome
- B. Somatic mesoderm
- C. Neural crest

- D. A and B only
- E. A, B and C are correct

Answer: E

4. Although most smooth muscle and cardiac muscle is derived from splanchnic mesoderm, the smooth muscle of the pupil, sweat gland and mammary gland is derived from:

- A. Somites
- B. Somatic mesoderm
- C. Intermediate mesoderm
- D. Ectoderm
- E. Endoderm

Answer: D

5. The zone of polarizing activity (ZPA) controls anterioposterior patterning in the limb. The ZPA produces \_\_\_\_\_, which directly induces expression of the downstream gene sonic hedgehog (SHH).

- A. Homeobox proteins
- B. Retinoic acid
- C. Engrailed proteins
- D. Radical fringe proteins
- E. Vitamin D

Answer: B

### **Study Guide:**

Read and outline Sadler text Chpt 8, pp. 171-196 and Chpt 9, pp. 199-208 before lecture. Study musculoskeletal teratologies in Table 7.1, Fig. 7.2, and Clinical Correlation p. 160

Note: Details of Figs. 8.3, 8.5 and 8.6 and Table 9.1 will be covered in the context of head & neck development. Processes of membranous (Fig. 8.2) and endochondral (Fig. 8.15) ossification will be covered in the context of bone development

Emphasize clinical correlates (pp. 177-180, 189-193, 194 and 206)

Solve practice problems pp. 196 and 208 (Answers p. 490)

## Week 3 Schedule: Embryology Exam

<i>Day</i>	<i>Date</i>	<i>Time</i>	<i>Modality</i>	<i>Topic</i>	<i>Faculty</i>	<i>Text assignment</i>
<b>M</b>	<b>Oct 24</b>	<b>8:00</b>	<b>Exam</b>	<b>Last seating for Exam I</b>	<b>Childs/ Stanley</b>	
M	Oct. 24	10:00	Lecture 14	Blood	Drew	B&C Ch 12; G&H Ch 10
M	Oct. 24	11:00	Lecture 15	Blood /blood cell development/bone marrow	Drew	
T	Oct 25	9:00	Lab 5	Blood, Blood cell development/bone marrow	Drew, Stanley, Kielian, Burns	
T	Oct 25	11:00	Lecture 16	Defense I	Drew	G&H Ch 12; B & C Ch 13
W	Oct 26	8:00-11:00	GROSS ANATOMY			
Th	Oct 27	9:00	Lecture 17	Defense II	Drew	
Th	Oct 27	10:00	Lab 6	Defense II	Drew, Stanley, Kielian, Burns	
<b>*Th</b>	<b>Oct 27</b>	<b>4:15</b>	<b>Tutorial</b>		<b>Lecturers</b>	
F	Oct. 28			No Microanatomy class – Gross Anatomy exam		

### ***Self scheduled Early Embryology Exam:***

**8 lectures X 5 questions/lecture=40 questions. Allow 1 h and self scheduling all week, beginning Monday PM, October 24th.**

**PLEASE NOTE:**  
**All Topics after this Early Embryology section will be tested in the Gross Anatomy Course.**

## Week 4 Schedule: Respiratory, Ear, Eye, Endocrine System

Day	Date	Time	Modality	Topic	Faculty	Text assignment
M	Oct 31		<b>Exam</b>	<b>Last seating for Embryology exam</b>		
M	Oct 31	10:00	Lecture 18	Eye	Burns	G& H 512-524; B & C Ch 19-I
M	Oct 31	11:00	<i>Gross Anatomy</i>	<i>Embryology of body cavities/ respiratory/serous membranes</i>	<i>Tank</i>	
T	Nov. 1	9:00	Lecture 19	Ear	Burns	G524-534 (omit Fig. 22-19); B&C Ch 19-II
T	Nov 1	10:00	Lab 7	Eye and Ear	Childs, Burns Stanley,	
W	Nov 2	9:00	Lecture 20	Respiratory system	Kielian	B& C Ch 10; G& H 343-362
W	Nov 2	10:00	Lab 8	Respiratory system	Kielian, Stanley, Drew, Childs	
Th	Nov 3	10:00	Lecture 21	Endocrine I (incl embryology)	Childs	
		11:00	Lecture 22	Endocrine II (incl embryology)	Childs	
<b>Th</b>	<b>Nov 3</b>	<b>4:15</b>	<b>Tutorial</b>		<b>Lecturers</b>	
F	Nov 4	9:00	<b>Tutorial</b>	<b>Catch up in the lab/review</b>	<b>All Lecturers</b>	
F	Nov. 4	11:00				

Code: (on colored copies of schedule) Blue= Microanatomy-Gross Anatomy correlates; Red=Embryology; Green=tutorials

B&C=Burns and Cave; G&H=Gartner and Hiatt; L=Langman

### ***Exam II: Blood/blood cell dev.; Immune system/ Respiratory/Ear and Eye***

**Self schedule: Thurs 4—midnight; Friday 4-6; Saturday 10-6; Sunday noon—midnight; Monday 4—midnight; Wednesday 8—10 (final seating)**

**7 lectures and 4 labs=55 questions + 5 review questions=60 total questions. Allow two hours.**

## Week 5 Schedule: Cardiovascular and Endocrine systems

Day	Date	Time	Modality	Topic	Faculty	Text assignment
M	Nov 7	10:00	<i>Gross Anatomy</i>	<i>Embryology of GI tract</i>	<i>TBA: GA faculty</i>	
M	Nov 7	11:00	<i>GROSS/MICRO</i>	<b>Histology of Heart;</b> <i>Embryology: Dev of Heart I</i>	Burns	G:173-177, 267-270 B&C, Ch 11 & L 223-254 (omit molecular)
T	Nov 8	9:00	Lecture 23	Endocrine III: incl GI, cardiac	Childs	
T	Nov. 8	10:00	Lab 9	Endocrines	Burns, Stanley, Childs, TBA	
<b>W</b>	<b>Nov 9</b>	<b>8:00</b>	<b>Exam II</b>	<b>Last seating</b>		
	Nov 9	10:00	<i>Gross Anatomy</i>	<i>Embryology: Development of Heart II</i>	Burns	L 223-254 (omit molecular)
W	Nov 9	11:00	<i>Gross Anatomy</i>	<i>Embryology: Development of Great Vessels</i>	Burns	L 101-103,256-264 (omit "cardinal v."),267-273
Th	Nov 10	9:00	<b>Clin Lecture 3</b>	<b>Heart Defects</b>	<b>(Bornemeier – ACH)</b>	
	Nov 10	10:00	Lab 10	<i>Histology of Heart; Optional Models of Dev. Of Heart</i>	Burns, Stanley	
Th	Nov10	<b>4:15</b>	<b>Tutorial</b>	<b>Tutorial</b>	<b>Lecturers</b>	
F	Nov 11		Holiday	Veterans Day		

Key: Blue= Microanatomy-Gross Anatomy correlates; Red=Embryology; Green=tutorials  
B&C=Burns and Cave; G&H=Gartner and Hiatt; L=Langman

# Gross Anatomy Lectures: Embryology of the Heart: Normal and Abnormal

Dr. Burns

## Reading Assignment:

Langman (9<sup>th</sup>) 223-231 omit “molecular ---”; 232-254.

## Learning Objectives:

*Compare and contrast in writing and/or by constructing diagrams, i.e. describe:*

- A. *The normal developmental steps taken between the angiogenesis stage to the completion of the 4-chambered fetal heart.*
- B. *The blood flow route(s) taken by all blood entering and exiting the developing fetal heart as well as blood flow within the fetal heart, with special emphasis on the foramen ovale. Include blood flow in the fetal circulation (vessels) with particular attention to the % oxygen saturation of the blood in each different region of the fetal circulation.*
- C. *The structure-function and pathophysiological relationships between the normal situation and that found in the following cardiac anomalies:*
  1. *Atrial Septal Defects of both the primum and secundum type*
  2. *Premature closure of the foramen ovale*
  3. *Persistent atrio-ventricular canal*
  4. *Ventricular Septal Defects of both the membranous and muscular type*
  5. *Ectopia cordis*
  6. *Tricuspid atresia*
  7. *Tetralogy of Fallot*
  8. *Transposition of the great vessels*
  9. *Persistent truncus arteriosus*
- D. *The structures of the fetal heart and circulation which have adult remnants/derivatives*
- E. *The structure-function changes which occur between the fetal cardiovascular system and that of the newborn infant.*
- F. *The surgical interventions used to “correct” the anomalous situation, if that content is included in the lecture outline.*

*Include in your study the content contained in the outline whether it is included in the embryology text or not and omit all content contained in the textbook that is not contained in the outline, e.g. omit the development of the major contributors to the inferior vena cava.*

## Lecture Outline

- I. Positional changes

- A. Cardiogenic area (mesoderm) originally located rostral to the buccopharyngeal membrane in the early embryo.
  - B. Differential growth, mainly of brain (cephalic folding), causes 180° rotation of cardiogenic area to a position caudal to the buccopharyngeal membrane.
  - C. The left and right lateral body folds cause a lateral to medial movement of the two (right and left) endothelial “heart” tubes. (Note: the cephalic, caudal and left and right body folds, in effect, make the embryo rise up from its previous flat attachment to the yolk sac to a progressively narrowing foregut attachment to the yolk sac, finally ending in the umbilical cord arrangement).
    - 1. Further lateral to medial movement results in the fusion, in this region, of the two endothelial heart tubes; thus,
    - 2. A single endocardial tube forms by embryonic day 22, which is suspended, temporarily, by a dorsal mesocardium (a ventral mesocardium never forms). Consider that ovulation + fertilization occurred on day 14 of the average menstrual cycle and the single endocardial tube forms on embryonic day 22 – 14 + 22 = day 36 of a menstrual cycle (“My menstrual period now is 8 days late” – but the woman actually is 22 days pregnant and does not know this yet.
    - 3. The heart tube is suspended in intra-embryonic coelom, the future pericardial cavity.
    - 4. The endocardial tube is beating and transporting primitive blood throughout the 3 major circulatory routes: embryo proper, yolk sac, and placenta.
- II. Histogenesis
- A. Mesenchymal cells differentiate into angioblasts (primitive endothelium) or primitive blood cells (trapped in tubes of angioblasts). Angioblasts differentiate into endothelium of vessel.
  - B. Heart tube is lined by endothelium which is covered on its outside by a thick layer of splanchnic mesoderm more specifically known as the myoepicardial mantle, which is at first, separated from the endothelium by the cardiac jelly.
  - C. The myoepicardial mantle cells differentiate into:
    - 1. Myoblasts which form the thick myocardium (cardiac muscle).
    - 2. Mesothelial cells of the epicardium (visceral pericardium).
  - D. The adult histological pattern is thus established.
    - 1. Endocardium
    - 2. Myocardium
    - 3. Epicardium or visceral pericardium
- III. Formation of the Heart Loop
- A. Straight heart tube attached at both ends to limits of pericardial cavity.

- B. Straight heart now consists of, from venous to arterial end, some dilatations and constrictions. The dilatations are:
1. Sinus venosus
  2. Atrium
  3. Ventricle (separated from the atrium by a narrowing called the atrioventricular junction)
  4. Bulbus cordis which is continuous cranially with the aortic sac and the aortic arches
- C. Bulbus cordis and the single ventricle (bulboventricular portion) grow fast; heart bends to the right on itself fitting into pericardial cavity. The developing heart is genetically preprogrammed to bend to the right, i.e. it will do so even *in vitro*.
1. U-shaped bulboventricular loop is formed.
  2. A bulboventricular sulcus is now visible externally.
  3. Internally, the bulboventricular fold or flange forms on the inside edge of the bulboventricular sulcus which delineates the primary interventricular foramen and thus the future left and right ventricles.
  4. The atrium and the sinus venosus eventually come to lie posterior to the bulbus cordis and ventricle.
  5. The atrium and sinus venosus now expand rapidly and move superiorly so that the common or single atrium appears on either side of the bulbus cordis and is deeply grooved by it.
  6. The external appearance of the heart is now well established and strongly suggests its future four chambers.
- D. Bulbus cordis can now be divided into:
1. A proximal portion which will form the trabeculated part of the right ventricle; the trabeculated left ventricle being derived from the primitive ventricle.
  2. A mid-portion, the conus cordis, an outflow tract for both ventricles – the right part of which becomes the funnel-shaped, non-trabeculated conus arteriosus or infundibulum (outflow region of adult right ventricle). Remember from G.A. that the inflow and outflow tracts of the rt. ventricle are partially divided by a muscular crest, the crista supraventricularis.
  3. A distal portion, the truncus arteriosus, which will form proximal portions of the aorta and pulmonary trunk.

#### IV. Development of the Sinus Venosus

- A. Sinus venosus consists of:
1. A common transverse chamber
  2. Left and right sinus horns
- B. Each sinus horn receives blood from:
1. Umbilical vein (oxygenated blood returning from the placenta)

2. Cardinal vein system via a common cardinal vein (deoxygenated blood returning from the embryo proper via the anterior and posterior cardinal veins).
  3. Vitelline vein (deoxygenated blood returning from yolk sac)
- C. Sinu-atrial fold develops which separates the left sinus horn from the developing left atrium.
- D. Left sinus horn regresses except for:
1. Distal part remains in the adult as the oblique vein (of Marshall).
  2. Proximal part remains as the adult coronary sinus.
- E. Right sinus horn enlarges and becomes incorporated into the right atrium forming the smooth-walled portion of the adult atrium: the superior and inferior vena cava in this region are fashioned from the enlarged right sinus horn which is not incorporated into the wall of the right atrium.
1. Right and left valves of the sinus venosus, on the posterior aspect of the developing right atrium, guard the sinu-atrial orifice as it opens into the posterior aspect of the right atrium.
  2. Right and left valves are fused together, dorso-cranially, into a ridge called the septum spurium.
  3. Initially the valves are large, but when the right sinus horn is entirely incorporated into the atrium, the left venous valve regresses and fuses with the developing septum secundum. The superior portion of the right venous valve and the septum spurium together form the crista terminalis. (Note this is different than Langman; he thinks superior right venous valve disappears entirely but this is incorrect.) The inferior portion of the right venous valve is divided into two parts: 1) the valve of the inferior vena cava and 2) the valve of the coronary sinus. The valve of the inferior vena cava directs blood from the inferior vena cava toward the foramen ovale, a hole in the interatrial septum. The inferior edge of the septum secundum is termed the crista dividens. The crista dividens splits the stream of blood coming from the inferior vena cava so that 75% of the blood goes through the foramen ovale into the left atrium and 25% of the volume remains in the right atrium. With 75% of the volume of blood coming in from the inferior vena cava and crossing through the foramen ovale to the left atrium, the net effect is a right to left shunt. The foramen ovale and the ductus arteriosus permit a majority of the blood to by-pass the non-functioning, but developing lungs. The foramen ovale supplies the developing left atrium with blood to pump (very little blood is coming from the lungs to the left atrium) and thereby assures proper development of the left atrium, i.e., give the left atrium the volume of blood it needs to exercise with and thus develop normally.

## V. Septum Formation in the Atrium

- A. Septum primum, a thin crescent-shaped membrane, grows down from the postero-superior wall of the common atrium.
1. Septum primum grows toward the developing antero-superior (not Langman's superior) and postero-inferior (not inferior) endocardial cushions in the atrioventricular canal. The free edges of the two endocardial cushions are growing toward each other (left fist approaching right fist analogy).
  2. The opening between the advancing free edge of septum primum and the two endocardial cushions is the ostium primum.
  3. Ostium primum thus gets smaller and smaller as the septum primum gets larger and larger and approaches the two endocardial cushions which are approaching each other.
  4. As the ostium primum becomes closed by the apposition of the septum primum with the fusing endocardial cushions, perforations (apoptosis) appear high in the septum primum. These holes coalesce to form a new opening between the atria, the ostium secundum, thereby maintaining the right to left shunt of blood in the atria. The ostium secundum is the "second" hole in septum primum, the first hole being the ostium primum. The concept and use of "primum" and "secundum" will become important when the Atrial Septal Defects are studied because ASDs can be of "primum" or "secundum" types.

VI. Near the end of the 5th week, the septum secundum, a new and separate crescentic membrane grows down from the anterior-superior wall of the atrium on the right side of the septum primum.

- A. Septum secundum grows (from anterior-superior wall of atrium) toward the fused endocardial cushions thus gradually overlapping the ostium secundum in the septum primum on its right side.
- B. The lower, free, concave edge of the septum secundum extends just beyond the lower margin of the ostium secundum and then stops developing, thus forming an incomplete partition. The free edge of the septum secundum is an important fetal landmark called the crista dividens.
- C. The passage between the two atria is now an obliquely elongated "Z" shaped pathway, the foramen ovale.
- D. Foramen ovale is bounded by:
  1. The upper edge of the persisting lower part of the septum primum
  2. Lower edge of the septum secundum.
- E. The valve of the foramen ovale is formed by the persisting lower part of the septum primum which overlaps the foramen ovale from below on the left.
- F. The valve of the foramen ovale (in the fetus) is forced open (to its left) by the blood moving through the foramen ovale from right to left.

VII. Functional Consideration of the Foramen Ovale

- A. Foramen ovale permits the passage of oxygenated blood from the inferior vena cava to the left atrium through this opening in the interatrial septum and then from the left atrium – left ventricle - systemic circulation.
- B. Thus the foramen ovale aids the ductus arteriosus in shunting blood around the developing lungs and from right heart to left heart – a right to left shunt.
- C. Shortly after birth the lungs inflate, the ductus arteriosus physiologically closes and the placenta, a low resistance organ, is lost; thus, the pulmonary blood pressure decreases while the pressure in the systemic circuit increases.
  - 1. Pressure in the left atrium increases.
  - 2. Pressure in the right atrium decreases.
  - 3. Thus blood attempts to flow from the left atrium into the right atrium.
  - 4. This change in direction of blood (formerly right to left atrium, now left to right atrium) closes the valve of the foramen ovale.
  - 5. In approximately 25% of the adult population the foramen ovale never completely closed or became totally obliterated, this condition is known in gross anatomy as probe patency of the foramen ovale.

#### VIII. Development of the Pulmonary Veins

- A. A single pulmonary vein grows out from the left atrium and joins the plexus of veins of the lungs.
- B. As the left atrium continues to expand, the single common pulmonary vein is resorbed into the wall of the left atrium.
- C. The resorption of the pulmonary vein continues and eventually the proximal branches of the pulmonary vein are resorbed, resulting in four separate pulmonary veins which open into the left atrium.
- D. The smooth-walled portion of the adult left atrium is this resorbed portion of the pulmonary vein(s).

#### IX. Development of Atrioventricular Endocardial Cushions

- A. Two mesenchymal thickenings, the endocardial cushions develop from the antero-superior and postero-inferior borders of the atrioventricular canal.
- B. During the 5th week the two endocardial cushions grow toward each other and fuse, thus separating the original common atrioventricular canal into:
  - 1. A right atrioventricular canal
  - 2. A left atrioventricular canal
- C. This fusion occurs at the time when the free edge of the septum primum reaches and joins with the upper surface of the fusing/fused endocardial cushions, thereby closing the ostium primum.

#### X. Septum formation in the ventricles and in the truncus arteriosus and conus cordis

- A. The common ventricle is partitioned into right and left ventricles.

- B. A muscular ridge, the interventricular septum, grows up from the floor (apex of heart) of the common ventricle.
  1. An external groove, the interventricular groove, marks this internal area.
  2. Growth of the muscular ridge forms the muscular portion of the interventricular septum toward the fusing/fused endocardial cushions, but stops short of fusing with them. This leaves an opening, the interventricular foramen, between the two ventricles.
- C. The space bounded by the free edge of the muscular portion of the interventricular septum and the fused endocardial cushions is the interventricular foramen.
- D. During the 5th week, two opposing ridges of endocardial tissue called bulbar ridges (truncoconal ridges) appear in the bulbus cordis.
  1. The orientation of the bulbar ridges is spiral
  2. The ridges grow toward each other and fuse during the 8th week thus forming the spiral aortico-pulmonary septum.
  3. The spiral aortico-pulmonary septum divides the bulbus cordis into the aorta and the pulmonary trunk.
  4. Because of this developmental spiral arrangement, the pulmonary trunk twists around the ascending aorta forming the adult pattern: PA anterior to aorta, then lateral, then posterior to aorta as they twist around each other from inferior to superior.
- E. Three tissue proliferations, one from each of the inferior ends of the two bulbar ridges (spiral aortico-pulmonary septum) and one from the fused endocardial cushions (your fingers from the underside of your fused fists) close the interventricular foramen thus forming the membranous part of the interventricular septum.
- F. There is good experimental evidence indicating that the spiral aortico-pulmonary septum forms from cervical neural crest. Surgical ablation of appropriate regions (cervical) of neural crest (chick embryo) results in the absence of the spiral aortico-pulmonary septum, i.e., a persistent truncus arteriosus.

## XI. Valve Formation

- A. Atrioventricular valves
  1. Local proliferations of mesenchymal tissue occur around each atrioventricular canal forming the A-V valves.
  2. As myocardium increases on the outside it undergoes diverticulation and trabecular formation on the inside; thus the interior of the adult heart ventricles is markedly trabeculated, the trabeculae carneae. Some of the trabeculae carneae become transformed into the papillary muscles.
  3. The A-V valves thus remain attached to the ventricular wall by cords of dense connective tissue, the chordae tendineae, which are attached to the papillary muscles of the ventricular wall.
- B. Semilunar valves

1. Three tubercles or swellings of the ventricular extremities of the bulbar ridges develop into the aortic and pulmonary semilunar valves.
2. These swellings become hollowed out and reshaped to form three thin-walled cusps or pockets, the semilunar valves.

## ABNORMAL DEVELOPMENT OF THE HEART

- I. Abnormalities of the Atrial Septum (ASD or atrial septal defect)
  - A. Ostium secundum type of ASD
    1. Foramen ovale is patent because of:
      - a. Excessive resorption of septum primum as ostium secundum forms, or
      - b. Defective development of the septum secundum, or
      - c. Complete absence of the inter-atrial septum (no septum primum and no septum secundum form; known as common atrium).
  - B. Ostium primum type of ASD
    1. Free edge of septum primum never fuses with fused endocardial cushions
    2. Leaves a patent ostium primum
  - C. Functional considerations of ASD primum and secundum types – a normal right to left shunt before birth, but this would be an abnormal left to right shunt after birth.
    1. In the fetus this is not life threatening because the defect is functioning like a normal foramen ovale, i.e., right to left shunt.
    2. In the newborn heart the pressure relationships are reversed (now higher on the left than on the right) and a large amount of blood flows from the left atrium into the right atrium through the ASD (a left to right shunt) and thus circulates repeatedly through the right ventricle --- lungs --- left atrium --- right atrium --- right ventricle -- lungs (repeat).
    3. Consequences are pulmonary congestion followed by right ventricular hypertrophy with eventual heart failure.
    4. Treatment
      - a. Sew in a patch to the margins of the ASD
  - E. Premature closure of the foramen ovale
    1. Foramen ovale closes before birth (e.g., no ostium secundum forms)
    2. In the fetus the majority of the blood is now handled by the right heart. This results in massive hypertrophy of the right heart.
    3. Very little blood is moved in and out of the left heart. This results in severe hypoplasia or under development of the left side of the heart (very little blood volume to work/exercise with).  
In general the growth of arteries, veins and chambers of the heart is directly proportional to the workload of these structures. For

example, a severely stenotic pulmonary artery (PA) can't be surgically corrected immediately to adult size because it is not anatomically and physiologically ready to handle the new volume of blood. Many times a palliative shunt is used first for months to years to let the PA “exercise” up to OK morphological size before a more definitive procedure is done.

4. The poorly developed left heart is incapable of handling the volume of blood presented to it immediately after birth and death usually occurs shortly after birth.

## II. Abnormalities of the Atrioventricular Canal

### A. Persistent atrioventricular canal

1. Endocardial cushions fail to fuse. This results in:
  - a. Septum primum cannot fuse with the separated (unfused) endocardial cushions so there must be a patent ostium primum (ASD-primum type).
  - b. Since endocardial cushion material participates in the formation of the membranous portion of the interventricular septum, there must be a ventricular septal defect (VSD) of the membranous type.
  - c. Since endocardial cushion material also participates in the formation of the mitral and tricuspid AV valves, these valves have abnormal leaflets.
  - d. A common AV canal (because endocardial cushions don't fuse).

### B. Tricuspid atresia

1. Right AV canal is obliterated during development; blood cannot enter RV so all of it goes through
2. Patent foramen ovale (small ASD-secundum type) kept open by higher pressure in the right atrium (no atrio-ventricular pathway on the right to the right ventricle) to the left atrium.
3. Hypoplasia of right ventricle because it has little blood to work or exercise with
4. Hypertrophy of left ventricle because it is forced to pump both RA and LA blood
5. Major route to get blood to the lungs is the ductus arteriosus and it is clinically prevented from closing by treating with prostaglandin E1 – this is not as easy as it sounds because this “drug” has significant side effects and the child must be hospitalized during this treatment.
6. This defect is always associated with a VSD so some blood does enter right ventricle and pulmonary trunk, i.e. that which comes from left ventricle to right ventricle through the VSD. Thus, the degree of hypoplasia of the right ventricle is related to how big the VSD is; big VSD = less hypoplasia of right ventricle because it has more blood volume to “work with”.

7. Surgical treatments: Historically corrected using the Fontan procedure in which the right atrium is directly connected to the pulmonary artery thereby providing a route for venous, deoxygenated blood to that lung. If the lungs are normal and therefore of low resistance, right atrial contraction pressure is enough to force blood into the right pulmonary artery to rt. lung. A modification of the original Fontan procedure is now used, i.e. a graft is placed between the superior vena cava and the rt. Pulmonary artery. Prior to performing a definitive and invasive surgical procedure like the Fontan or modified Fontan there is a less invasive way to increase the blood flow from the rt. atrium through the interatrial septum to the left atrium (the only way to get deoxygenated to the left ventricle and through the VSD into the rt. ventricle and to the lungs). Sometimes an atrial septostomy is performed (see transposition of great vessels – treatment – for more information on this clinical procedure).

### III. Abnormalities of the Interventricular Septum (VSD)

- A. Membranous septal defects (VSD-membranous type)
  1. Most common defects of all types of heart defects
  2. Endocardial cushion material fails to fuse with the muscular part of the interventricular septum
- B. Muscular septal defects (VSD-muscular type)
  1. Excessive resorption of myocardial tissue during the formation of the trabeculae carneae
- C. Treatment
  1. Sew a patch over the VSD wherever it is.

### IV. Abnormalities of the Truncus and Conus

- A. Tetralogy of Fallot (if someone *shoves* you, you will *fall* over = SHOVE)
  1. Abnormal partitioning (favoring the aortic side at the expense of the pulmonary side) of the truncus and conus by the spiral aortico-pulmonary septum results in the following anatomical pathophysiological findings:
    - a. Pulmonary Stenosis/infundibular stenosis or narrowing of the infundibulum or conus arteriosus region of rt. ventricle.
    - b. Hypertrophy of right ventricle
    - c. Overriding aorta
    - d. VSD
    - e. Erythropoietin increase, i.e. a polycythemia or an increase in the number of RBCs per cubic mm of blood due to increased levels of erythropoietin because of chronic hypoxia, especially of the kidneys (a source for EP secretion).
  2. Functional considerations

- a. Up to 75% of venous return to the heart may pass from right ventricle into the wide-mouthed aorta thereby bypassing the lungs and no oxygenation, resulting in cyanosis.
- 3. Treatment
  - a. Palliative: Create a functional ductus arteriosus
    - 1) Side to side anastomosis between pulmonary trunk and aorta.
    - 2) Blalock procedure - anastomose subclavian artery to one of the pulmonary arteries.
  - b. Definitive: Excise or enlarge stenotic area in pulmonary trunk/infundibulum and reanastomose ends, close VSD with a patch. Surgeon works through an incision in right atrial wall and then through tricuspid valve for patching of VSD.
- B. Persistent truncus arteriosus
  - 1. The two parts (bulbar ridges) of the spiral aortico-pulmonary septum fail to fuse.
    - a. Always accompanied by a VSD since the spiral septum participates 2/3 tissue contribution) in forming the membranous part of the interventricular septum.
- C. Transposition of the great vessels
  - 1. Spiral aortico-pulmonary septum forms but does not spiral or twist during its partitioning of the truncus arteriosus
    - a. Aorta arises from right ventricle
    - b. Pulmonary trunk arises from the left ventricle
  - 2. Result is two closed circuits
    - a. Systemic – unoxygenated – repeatedly re-circulated
    - b. Pulmonary - oxygenated - repeatedly re-circulated
  - 3. Lethal (no oxygenation of blood) if no anatomical connection exists between the two closed circuits for mixing of blood to get deoxygenated blood to the lungs.  
For days to perhaps weeks after birth there usually is some “normal” mixing of left heart and right heart blood through the foramen ovale, especially during crying, but this is not enough mixing to support life in a child with transposition.
  - 4. Not immediately lethal if some kind of a defect is present which will permit mixing of the systemic and pulmonary circuits, e.g.. a patent ductus arteriosus, VSD, or ASD
  - 5. One treatment is to hold the ductus arteriosus open using prostaglandin. Another treatment is to create a “large” ASD-secundum type by passing a catheter up the inferior vena cava so that the tip of the catheter is pointed at the foramen ovale. The catheter tip is pushed through the foramen ovale. A balloon is then blown up in the left atrium and pulled back into the right atrium through the interatrial septum creating an ASD-secundum type (balloon atrial septostomy – an iatrogenic ASD).

6. Definitive surgical repair involves separating both the aorta and the main pulmonary artery from the base of the heart, twisting and re-anastomosing these free ends with the physiologically appropriate ventricular outflow. The coronary arteries also have to be un-connected and then re-connected to the “new” aorta.
- V. Heart Anomalies Resulting in Cyanosis
- A. Tetralogy of Fallot
  - B. Transposition
  - C. Tricuspid atresia
  - D. Note A-C are right-to-left shunts; in effect bypassing pulmonary perfusion resulting in cyanosis. Left-to-right shunts, on the other hand, are acyanotic, e.g., ASD, VSD, PDA.
- VI. Abnormalities in the Position of the Heart
- A. Dextrocardia
    1. Heart is on right side of thorax
  - B. Ectopia cordis
    1. The lateral body folds fail to meet and fuse in the midline, so that the heart is exposed on the surface of the chest
- VII. Incidence of Congenital Heart Disease (CHD)
- A. In medicine it is important to know the incidences of risk, morbidity and mortality for every disease/clinical situation, e.g. the risk of a woman getting breast cancer without a positive family history vs. the risk with a positive family history, etc. (Note: some disease incidences are so small or so rare that they have been “orphaned” by the pharmaceutical industry).
  - B. For CHD:
    1. Incidence is 8-9 cases/1000 live births = 0.8-0.9% actual, or an easier to remember “about 1%”.
    2. True for all races and all socioeconomic groups in humans, also true for all mammals.
    3. About 40,000 live births/year in Arkansas;  $9 \times 40 = 360$  actual congenital heart anomalies/yr in AR or approximately 400 new cases annually. In AR most of these children are treated at ACH.
    4. 40% of trisomy 21 pts. have CHD.
    5. Most common environmental cause of CHD = alcohol consumption, especially during early pregnancy = 30% incidence of CHD in children born to alcoholic mothers.
    6. Oral contraception taken very early in a pregnancy when the woman does not yet know she is pregnant is associated with transposition of great vessels.

# Gross Anatomy Lecture: Development of great vessels: Normal and Abnormal

Dr. Burns

## **Reading Assignment:**

Langman (9<sup>th</sup>) p 101-103; 255-273.

## **Learning Objectives:**

*Compare and contrast in writing and/or by constructing diagrams, i.e. describe:*

- A. *The steps during the general angiogenesis process*
- B. *The basic plan of the system of bilateral aortic arches*
  1. *The adult derivatives of each aortic arch*
  2. *The major anomalies associated with abnormal development of the aortic arches and their major branches.*
- C. *The basic plan for the major fetal venous structures derived from the vitelline circulation and their adult derivatives.*
- D. *The basic plan for the major fetal arterial branches of the aorta and their adult derivatives*

*Use the outline as your guide for the breadth and depth of your study and reading. Do not learn any material in the text that is not contained in the outline.*

## **Lecture Outline:**

- I. Blood Vessel Formation:
  - A. New blood vessels can be formed by two different processes:
    1. Vasculogenesis
      - a. Vessels arise from mesenchyme - blood islands (now hemangioblasts) - new blood vessel containing primitive blood (stem) cells in center contained in newly differentiating vessel wall (angioblasts).
      - b. Fibroblast growth factor #2 (FGF-2) induces mesenchymal cells to form blood islands
      - c. Vascular endothelial growth factor (VEGF) then causes angioblasts to differentiate into endothelial cells
    2. Angiogenesis: a process initiated in a pre-existing vessels in either the embryo/fetus or the adult (e.g. uterine menstrual cycle, placental formation, wound healing, inflammation).
      - a. New vessels grow/sprout from pre-existing vessels
      - b. VEGF (vascular endothelial growth factor) also involved here – stimulates proliferation and migration of previously formed endothelial cells at branch points where new vessels are needed

- c. Involves degradation of existing basal lamina of the parental vessel where endothelial cell proliferation and migration will occur.
- d. After new capillary tube formed, re-assembly of basal lamina and recruitment of peri-endothelial undifferentiated cells to form smooth muscle and connective tissue of new vessel wall.

B. Tumor angiogenesis

1. Solid tumors have the capability to cause the formation of new blood vessels from existing blood vessels (angiogenesis) so that the tumor will receive an “enhanced” blood supply.
2. Cancer cells secrete endothelial cell growth factors called angiogenic peptides (formerly called TAFs or “tumor angiogenesis factors”) which cause local vessels to sprout new vessels. Without this added “nutrition” solid tumors do not grow and increase in size appreciably.
3. Two anti-angiogenic factors have been isolated:
  - a. endostatin
  - b. angiostatin
  - c. both have been used in animal experimental oncology to stop angiogenesis in tumor-bearing hosts and thereby stop the growth of the tumors. In some cases these factors also cause the dissolution of “tumor blood vessels” resulting in shrinkage to even clinical disappearance of the now “un-fed” tumor.
4. Thalidomide taken by pregnant women apparently prevented angiogenesis of trunk - to -limb vessels thereby causing amelia and meromelia. Thalidomide is being used in clinical experimental oncology (so are endostatin and angiostatin) to compromise or destroy tumor blood vessels.

II. Aortic Arch System

- A. Basic plan of the aortic arches is origin in the aortic sac then course through mesenchyme of the pharyngeal arches on the left and right sides of the foregut to the left and right dorsal aorta.
  1. Gradient of arch formation and disappearance from cranial to caudal, thus the first aortic arches appear first and disappear (except for persisting portions) as the second aortic arches are developing, etc.
- B. First aortic arch
  1. Disappears except for small portion which forms the maxillary artery.
- C. Second aortic arch
  1. Disappears except for small portion which forms the hyoid and stapelial arteries.

- D. Third aortic arch
    - 1. Persists and forms the common carotid artery and the first or proximal part of the internal carotid artery. The distal part of the internal carotid is derived from the cranial extension of the dorsal aorta.
    - 2. The external carotid arteries arise as new branches from the anterior or ventral aspect of the third aortic arches.
  - E. Left fourth aortic arch
    - 1. Becomes the part of the arch of the aorta between the left common carotid and the left subclavian artery.
  - F. Right fourth aortic arch
    - 1. Becomes the proximal part of the right subclavian artery. The remaining portions of the right subclavian artery are derived from a portion of the right dorsal aorta and 7th intersegmental arteries.
  - G. Fifth aortic arch
    - 1. Poorly developed, disappears
  - H. Six aortic arch
    - 1. On the right the distal part disappears, the proximal part becomes the proximal part of the right pulmonary artery which grows into the developing right lung.
    - 2. On the left the distal part does not disappear, but remains as the ductus arteriosus until after birth. The remainder becomes the left pulmonary artery.
    - 3. In the collapsed fetal lung the resistance to blood flow is 5-10 times higher than in the inflated lung. Thus pressure in the pulmonary trunk and arteries is higher than in the aorta. 90% of the right ventricle output flows through the ductus arteriosus into the aorta and very little blood flows through the lungs.
  - I. Differential growth results in the attainment of the adult pattern.
  - J. The brachiocephalic a. and the proximal part of the aortic arch are derived from the aortic sac.
- III. Branches of the Dorsal Aorta
- A. Vitelline arteries
    - 1. Originally supplying the yolk sac
    - 2. Fusion, differential growth, results in -
      - a. Celiac trunk: the artery supplying the developing foregut and its derivatives
      - b. Superior mesenteric artery: the artery supplying the midgut and its derivatives
      - c. Inferior mesenteric artery: the artery supplying the hindgut and its derivatives
  - B. Umbilical arteries
    - 1. Blood supply of the allantois, connecting stalk and developing placenta
    - 2. After birth

- a. Proximally the umbilical arteries become the internal iliac and superior vesicle arteries
- b. Distally the umbilical arteries are obliterated to form fibrous cords, the medial umbilical ligaments.

#### IV. Venous System

##### A. Basic Plan

1. Vitelline veins, from yolk sac
2. Umbilical veins, from placenta
3. Cardinal veins, from body of embryo

##### B. Liver grows into vitelline veins forming:

1. Hepatic sinusoids
2. Portal vein
3. Superior mesenteric
4. Hepatic portion of the inferior vena cava

##### C. Umbilical veins also involved in the growth of the liver. Result is:

1. Only the left umbilical vein present
2. It forms the ductus venosus, a shunt through the liver to the heart so a percentage of the oxygenated blood returning from the placenta will not get lost in the developing hepatic sinusoids and in doing so lose most of its oxygen saturation.
3. After birth the left umbilical vein becomes the ligamentum teres hepatis and the ductus venosus becomes the ligamentum venosum.

#### V. Anomalies of the Great Vessels

##### A. Patent ductus arteriosus or PDA (1:5500): the most common cardiac malformation associated with maternal rubella infection

1. Ductus arteriosus normally closes functionally immediately after birth by contraction of smooth muscle in the tunica media in response to increased oxygen saturation in the blood after the first several breaths. DA histologically closed by about 3 months to become a fibrous strand the ligamentum arteriosum of GA.
2. If these closures fail to occur the ductus arteriosus remains patent
3. In a patient with patent ductus arteriosus about 45-75% of the aortic blood (high pressure) is diverted into the pulmonary stream (left to right shunt), i.e., blood passing from the aorta through the patent ductus arteriosus (lower pressure), into the lungs.
4. Physiological consequences:
  - a. Decrease in systemic blood pressure
  - b. Increase in pulmonary blood pressure
  - c. 45-75% of the left ventricle output is recirculated through the lungs (aorta ---- ductus arteriosus ---- pulmonary arteries ---- lungs ---- pulmonary veins -- -- left atrium ---- left ventricle ---- aorta ---- repeat).
  - d. Left ventricle now pumping 2-3 times the normal cardiac output.

- e. Patient usually appears normal at rest but when exercised he or she becomes weak and may faint, because of relatively little blood in systemic circuit (brain); most blood is "caught" in circuit "C" above.
  - f. Result is left ventricular hypertrophy
  - g. Right ventricle also hypertrophies because of high pulmonary resistance (higher than normal pulmonary blood flow and quantity)
5. Surgical correction is a simple ligation and division
- B. Coarctation of the aorta (1:2000)
- 1. Preductal if the narrowed part is superior to the ductus arteriosus and postductal if the narrowing is inferior to the ductus or ligamentum arteriosum: juxtaductal if in aorta at point when DA enters aorta. Clinically the most common coarctation is juxtaductal.
  - 2. Collateral circulation develops around the coarctation
    - a. B.P. in sup extremities = higher than normal
    - b. B.P. in lower extremities = lower than normal
  - 3. Surgical treatment involves excision of the narrowed portion of the vessel and the rejoining of the proximal and distal ends.
- C. Abnormal origin of the right subclavian (4%)
- 1. Right 4th aortic arch and part of right dorsal aorta disappear (normally remain to form part of the right subclavian artery).
  - 2. Right subclavian now formed from 7th intersegmental artery and a distal portion of right dorsal aorta.
  - 3. Differential growth leads to the adult morphology, i.e., right subclavian crossing the midline behind the esophagus (retroesophageal) to reach the superior extremity.
  - 4. Symptom less or may present as difficulty in swallowing (dysphagia)
- D. Double aortic arch (rare)
- 1. Right dorsal aorta does not disappear between 7th intersegmental artery and left dorsal aorta
  - 2. Vascular ring formed around trachea and esophagus
  - 3. Symptoms are dyspnea sometimes accompanied by cyanosis and dysphagia
  - 4. Since the two arches are usually of unequal diameter the narrower arch is surgically divided when treatment is necessary
- E. Right aortic arch
- 1. The right dorsal aorta remains between the 7th intersegmental artery and the left dorsal aorta. The left dorsal aorta between the left 7th intersegmental and the single dorsal aorta, disappears.

## VI. Variants of the Major Veins.

Abnormal development will provide the explanation for almost all vessel variations encountered in GA. However, these abnormal patterns come in two varieties with very different degrees of clinical significance.

- 1) The variant vessel patterns a surgeon may occasionally encounter performing surgical procedures and therefore he/she obviously needs to be aware of these variations, but which have been of no clinico-pathological significance (clinically silent) to the person/patient.
- 2) The variant vessel patterns which cause clinical problems that bring the person to the attention of a physician, i.e., these variant vessel patterns are not clinically silent.

The abnormal patterns for the superior and inferior vena cavae fall into the first group (clinically silent) and, furthermore, are very rare, i.e., double inferior vena cava at 2% incidence, an IVC on the left side at 0.2% incidence, double superior vena cava at 3% and a single left superior vena cava at 0.3%.

- A. Review the venous return from the embryo to the heart;
  1. Anterior and posterior cardinal veins on each side
  2. ACV and PCV on each side join to form the l & r common cardinal veins
- B. Some additional veins are added to this early pattern
  1. Subcardinal veins, draining the kidneys
  2. Sacrocardinal veins, draining the lower extremities
  3. Supracardinal veins, draining the body wall via the intercostal veins
- C. Anastomoses form and differential growth causes the venous drainage to move to the right side eventually forming both the SVC and IVC on the left at the expense of emphasizing venous return on the left – after all the venous return is “scheduled” to enter the right (not the left) atrium of the heart.
  1. Anastomosis between the two anterior cardinal veins becomes the left brachiocephalic vein channeling most of the blood coming from the left side of the head and the left upper extremity over to the right side
  2. Normal SVC formed from the right common cardinal vein and the proximal part of the right anterior cardinal vein
  3. Double SVC = left anterior cardinal v. persists and no left brachiocephalic v. forms.
  4. Left SVC = Left anterior cardinal v. persists with loss on the right side of the common cardinal v. and the proximal part of the anterior cardinal v.
- D. Reworking the subcardinal vein-anastomoses contributes:
  1. Left renal vein
  2. Left gonadal vein
  3. Remaining subcardinal vein on the right enlarged to become the renal segment of the IVC

- E. Reworking the sacrocardinal veins contributes:
  1. Left common iliac vein
  2. Right sacrocardinal enlarges to become sacrocardinal segment of IVC
- F. Sacrocardinal segment of IVC unites with renal segment of IVC which unites with a remnant of the right umbilical vein forming the hepatic segment of the IVC, we have the IVC formed from 3 major contributions: hepatic, renal and sacrocardinal segments.
- G. Variations of IVC
  1. Double IVC = Left sacrocardinal v. does not lose its connection with the left subcardinal v.
  2. Left IVC = the venous primordia on the left persist and enlarge at the expense of the same on the right.
  3. No IVC = right subcardinal v. does not connect to liver, so blood goes directly into right supracardinal v. In this way venous return to the heart comes in via the azygos to the SVC.

### **Sample Questions: Development of the Cardiovascular System**

1. **The following conditions collectively result in what cardiac anomaly: unfused endocardial cushions, patent foramen primum and a patent interventricular foramen?**
  - A. Tricuspid atresia
  - B. Premature closure of foramen ovale
  - C. Persistent truncus arteriosus
  - D. Persistent atrioventricular canal
  - E. Tetralogy of Fallot
2. **Match:**

<ul style="list-style-type: none"> <li>____. Crista dividens</li> <li>____. Valve of coronary sinus</li> <li>____. Oblique vein of Marshall</li> <li>____. Smooth walled portion of right atrium</li> </ul>	<ul style="list-style-type: none"> <li>A. Superior 1/2 of rt. venous valve of sinus venosus + septum spurium</li> <li>B. Derived from left horn of sinus venosus</li> <li>C. Derived from right horn of sinus venosus</li> <li>D. Inferior edge of septum secundum</li> <li>E. Inferior part of right venous valve of sinus venosus</li> </ul>
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3. **On clinical rounds with a pediatric cardiologist she tells you that a patient you are looking at presented with dysphagia. What anomalous blood vessel pattern(s) could be causing this symptom?**
  - A. Double aortic arch
  - B. Abnormal origin of right subclavian a.
  - C. Right aortic arch
  - D. A and B are correct

- E. B and C are correct
4. **In the OR you watch a cardiovascular surgeon make a side-to-side anastomosis between the aortic and pulmonary trunks. What anomalous condition(s) will benefit from this procedure?**
- Transposition of the great vessels
  - Tetralogy of Fallot
  - Persistent truncus arteriosus
  - A and B are correct
  - A, B and C are correct
5. **The following blood circulation sequence is found in what developmental anomaly of the cardiovascular system: aorta - pulmonary arteries - lungs - pulmonary veins - left atrium - left ventricle - aorta - repeat sequence:**
- Postductal coarctation of the aorta
  - Right aortic arch
  - Persistent and patent ductus arteriosus
  - Abnormal origin of the right subclavian a.
  - Abnormal origin of left common carotid a.
6. **Match - fetal circulation**
- |        |                                  |                          |
|--------|----------------------------------|--------------------------|
| _____. | Inf. vena cava below diaphragm   | A. 80% oxygen saturation |
| _____. | Ductus arteriosus                | B. 26% oxygen saturation |
| _____. | Umbilical artery                 | C. 58% oxygen saturation |
| _____. | Umbilical vein in umbilical cord | D. 67% oxygen saturation |
| _____. | Inf. vena cava above diaphragm   | E. 52% oxygen saturation |
7. **During cardiogenesis, blood is shunted from the right heart circuitry to the left heart circuitry through:**
- Foramen primum
  - Foramen secundum
  - Interventricular foramen
  - A and B are correct
  - A, B and C are correct
8. **At birth, pressure in the right heart (right atrium and right ventricle) decreases while pressure in the left heart (left atrium and left ventricle) increases. What events cause this situation to occur?**
- Loss of the placenta
  - Ductus arteriosus closes thus markedly increasing pulmonary blood flow
  - Lungs inflate, all vessels in the lungs now "open up"
  - A and B are correct
  - A, B and C are correct
9. **The right recurrent laryngeal nerve courses around an adult structure which is a derivative of which aortic arch?**

- A. First arch
- B. Second arch
- C. Third arch
- D. Fourth arch
- E. Sixth arch

**10. Which is not characteristic of Tetralogy of Fallot?**

- A. Cyanosis (blue lips and blue nail beds upon exercise)
- B. Left ventricular hypertrophy
- C. Right ventricular hypertrophy
- D. VSD
- E. Pulmonary stenosis

**11. A defect in the spiral aortico-pulmonary septum will not result in which of the following:**

- A. VSD
- B. Transposition of great vessels
- C. ASD
- D. Persistent truncus arteriosus
- E. Pulmonary stenosis

**12. Formation of interatrial septum:**

- \_\_\_\_. Septum secundum covers foramen secundum
- \_\_\_\_. Foramen secundum forms
- \_\_\_\_. Foramen primum very large
- A\_\_\_\_. Endocardial tubes fuse
- \_\_\_\_. Common atrium

Answers to sample questions on the Development of the Cardiovascular System:

1-D; 2-D,E,B,C; 3-D; 4-D; 5-C; 6-B,E,C,A,D; 7-E; 8-E; 9-D; 10-B; 11-C; 12-Sequence:  
E-D-C-A-B

## Week 6 Schedule: GI and Urinary systems

Day	Date	Time	Modality	Topic	Faculty	Text assignment
M	Nov. 14	10:00	Lecture 25	GI system I	Kielian	B&C Chapter 14 and G&H Chapter 16 (omit teeth; p. 366-374)
M	Nov 14	11:00	Lecture 26	GI system II	Kielian	B&C Chapter 14 and G&H Chapter 17
T	Nov 15	9:00	Lecture 27	GI III	Kielian	B&C Chapter 14 and G&H Chapter 18
T	Nov. 15	10:00	Lab 11	GI system	Stanley, Drew Kielian, Kane	
W	Nov 16	9:00	Lab 12	GI	Kielian, Stanley, Drew, Kane	
W	Nov 16	11:00	Lecture 28	Urinary system	Kane	G&H Ch 19
Th	Nov 17	9:00	Gross Anatomy	Embryology: Development Urinary System	Kane	L Ch 14
Th	Nov 17	10:00	Lab 13	Urinary	Stanley, Kane, Childs, Drew	
Th	Nov 17	4:15	Tutorial	Review as needed		
F	Nov 18	9:00	*Clin lecture 4	Diseases of the Urinary System	Wheeler-Int. Med.	
F	Nov 18	10:00	Tutorial	Catch up in the lab	All lecturers	

**Exam III: Endocrine (all) Heart Histology (not embryology), GI**  
**6.5 lectures + 3.5 labs= 50 questions + 5 review questions. Wednesday 4—midnight; Thursday 4--midnight, Friday, 4—6; Saturday 10-6; Sunday noon—midnight; Monday 4—midnight; Wed 8-midnight; Through the following weekend; final seating is Monday after Thanksgiving.**

# Gross Anatomy Lecture: Embryology: Urinary System

Dr. Kane

## **Reading Assignment:**

Langman, Chapter 14.

## **Learning Objectives:**

Without reference materials, the student should be able to:

1. Identify and define structural elements involved in this stage of human development from representational images. For each structural element, describe:
  - a. The precursors of each structure
  - b. Additional structures to be derived from each structure as development progresses
  - c. The functional significance of each structure
  - d. The functional and regulatory inter-relationships between structures at each stage of development as described in text and lecture

Key figures: 14.1, 14.2, 14.3, 14.4, 14.5, 14.6, 14.7, 14.9, 14.10, 14.11, 14.12, 14.14, 14.15

2. Construct a temporal sequence of significant events during this developmental period
3. Define the structures and processes involved in genesis and differentiation of each organ system
4. Describe the purpose of the key developmental processes during this developmental period. In doing so,
  - a. Define the key tissues, cells and molecules
  - b. Distinguish the key regulators
  - c. Explain the purpose of the process
  - d. Compare and contrast normal and abnormal outcomes

Key developmental processes:

Formation of pronephros, mesonephros, and metanephros

Development of collecting system

Development of excretory system

Ascent of the kidney

Formation of bladder and urethra

5. Extrapolate embryonic structures present during this developmental period into derivative adult structures
6. Distinguish the functional and/or morphological consequences of specific teratologic events during this developmental period as described in the text, lab and lecture

### **Competencies:**

1. Apply knowledge of developmental processes to describe in detail the construction of an adult human from male and female gametes to
  - a) the general public
  - b) professional peers
2. Communicate knowledge-based information to patients regarding risk of birth defects and prevention of birth defects
  - a) In relation to relevant causative mechanisms, both genetic and epigenetic
  - b) In relation to relevant cellular and molecular processes of development
  - c) In relation to temporal periods of prenatal development
3. Given patients with either common or rare developmental anomalies, apply state-of-the-art knowledge of developmental processes to correctly diagnose and explain in detail the underlying cause of the structural and/or functional teratology

### **Sample questions:**

1. Which of the following congenital malformations of urinary system development is common (1/600) and frequently goes undetected because it does not lead to dysfunction?
  - A. Congenital polycystic kidney
  - B. Horseshoe kidney
  - C. Renal agenesis
  - D. Exstrophy of the bladder
  - E. Urachal fistula

Answer: B

2. Normal reciprocal induction between the epithelium of the ureteric bud and the mesenchyme of the metanephric blastema involves all of the following regulatory factors, EXCEPT:
  - A. EGF
  - B. FGF2
  - C. BMP7
  - D. WNT4
  - E. PAX2

Answer: A

### **Study Guide:**

Read and outline Sadler text Chpt 14, pp. 321-336 before lecture

Note: Content of p. 337-361 will be covered in the context of reproductive system development.

Emphasize clinical correlates (pp. 328-329, 332-333 and 335-336)

Solve practice problem #1 p. 361 (Answers p. 493)

## Week 7 Schedule: Study week and Vacation

Day	Date	Time	Modality	Topic	Faculty	Text assignment
M	Nov 21					
T	Nov. 22			Gross Anatomy exam		
W	Nov 23					

Thursday and Friday: Thanksgiving Holiday

## Week 8 Schedule: Reproductive Biology

Day	Date	Time	Modality	Topic	Faculty	Text assignment
M	Nov 28	8:00	Exam	Exam III last seating		
M	Nov 28	10:00	Lecture 29	Female Reproductive System I (Ovary)	Childs	B&C 199-215; G&H 461-486
M	Nov 28	11:00	Lecture 30	Female Reproductive System II (Uterus and tubes)	Childs	
						See above
T	Nov 29	9:00	Lecture 31	Placenta	Childs	See above
T	Nov 29	1000	Lab 14	Female Reproductive system	Childs Stanley, Burns, Kane	
W	Nov 30	9:00	Lecture 32	Male Reproductive System	Childs	B& C 190-198; G&H 487-508
W	Nov 30	1000	Clinical	Maternal-Fetal Medicine	Dr. Helen Kay	
Th	Dec 1	9:00	Gross Anatomy	Development of Reproductive system	Childs	L 321-362
Th	Dec 1	10:00	Lab	Male Reproductive system	Childs Stanley, Burns, Kane	
Th	Dec 1	4:15	Tutorial	Review as needed		
F	Dec 2	9:00	Movie	Journey into Life		
		10:00	Lab 16	(Catch up in lab)	Childs Stanley, Burns, Kane	

Key: Blue= Microanatomy-Gross Anatomy correlates; Red=Embryology; Green=tutorials  
B&C=Burns and Cave; G&H=Gartner and Hiatt; L=Langman

### Exam IV: Urinary and Reproductive System

7 lectures + 3 laboratories=50 questions + 5 review=55 questions

Self schedule beginning 12/2/2005 4—6; 12/3/2004 10—6; 12/4/2004 noon—midnight; 12/5/2004; 8- midnight; 12/6/2004 8—midnight Allow 2 hours Over Urinary and Reproductive Last seating in LRC: Tuesday 8 AM.

# Gross Anatomy Lecture: Development of the reproductive system

Dr. Childs

## **Reading Assignment:**

pp 337-362, Langman.

## **Learning Objectives and Lecture outline:**

1. Discuss the point at which sex is determined.
2. Describe the location, timing, and process of germ cell origination and migration
3. Discuss the differences in the very early formation of follicles or seminiferous tubules.
4. Describe the early formation of the duct system including the factors that promote expression of gender differences.
5. Describe and distinguish the development of the testes from the development of the ovary.
6. Describe and distinguish the later development of the duct systems in males and females.
7. Describe and distinguish the development of the external genitalia.
8. Compare and contrast the descent of the male and female gonads.

## **Sample questions:**

1. Germ cells that eventually populate the genital ridge arise originally from:
  - a. cytotrophoblast cells
  - b. mesonephros
  - c. ventral wall of coelomic cavity
  - d. endoderm of yolk sac
  - e. syncytiotrophoblast

answer: d

2. A baby was born with ambiguous genitalia caused by the absence of an enzyme in the adrenal needed to produce cortisol. This resulted in too much ACTH which stimulated the production of adrenal androgens. She was genotypically female. If you were the surgeon, you would expect to find the following signs of masculinization during reconstructive surgery:

- a. fused labia majora over an enlarged genital tubercle
  - b. absence of mullerian duct derivatives
  - c. ovotestes
  - d. a and c
  - e. a, b, and c.
- d. is answer

3. The following cells types in the testes are responsible for the resorptiom of the Mullerian duct
- a. Leydig cells
  - b. Primary spermatocytes
  - c. Myoid cells
  - d. Sertoli cells
  - e. Cells of the mesonephric duct.

D is answer.

# Gross Anatomy Lecture: Development of the Eye and Ear: Normal and Abnormal

Dr. Burns

To be given in January, Gross Anatomy

## **Reading Assignment:**

Langman (9<sup>th</sup>): 403-411 (omit external ear defects): 413-422 (omit “molecular---“); 424-426

## **Learning Objectives:**

*Compare and contrast in writing and/or by constructing diagrams, i.e. describe:*

- A. *The normal developmental steps taken and the adult derivatives of the primordia for the Ear.*
- B. *The normal developmental steps taken and the adult derivatives of the primordia for the Eye.*
- C. *The developmental basis for the anomalies listed in the syllabus.*

Include in your study all of the content contained in the outline whether it is included in the embryology text or not and omit all content contained in the text book that is not contained in the outline,

## **Lecture Outline**

### **I. General Plan**

- A. Derived from surface ectoderm (otocyst)
  1. Cochlear duct, hair cells, organ of Corti, semicircular ducts, maculae, sensory nerves and ganglia.
  2. Epithelial lining of the external auditory canal and ext. surface of tympanic membrane
  3. Lumen of ext. auditory canal is derived from the lumen of the first branchial groove
- B. Derived from mesoderm
  1. Ossicles
    - a. Malleus (first arch)
    - b. Incus (first arch)
    - c. Stapes (second arch)
    - d. Lateral to medial = MIS
  2. Skeletal muscle
    - a. Tensor tympani
    - b. Stapedius
  3. Core of tympanic membrane
  4. Bony labyrinth

- C. Derived from endoderm
  1. Eustachian tube lining
  2. Middle ear cavity lining
  3. Epithelial covering of ossicles
  4. Cavity of the middle ear and the lumen of the Eustachian or auditory tube are derived from the lumen of the first pharyngeal pouch.
- D. The critical period of development begins early in 4th week and extends to 8 1/2 weeks. Rubella infection during this time period can result in deafness.

## II. Internal Ear

- A. Otic placode, a thickening of surface ectoderm appears at beginning of 4th week.
  1. Invagination forms otic pit
  2. Ectodermal surface seals over forming otic vesicle, the primordium of the membranous labyrinth
- B. Otic vesicle forms 2 regions
  1. Dorsal utricular part
  2. Ventral saccular part
- C. Utricular part forms
  1. Utricle
  2. Semicircular canals
  3. Endolymphatic duct
- D. Saccular part forms
  1. Saccule
  2. Cochlear duct
    - a. An elongation which spirals 2.5 turns
    - b. Organ of Corti differentiates from the wall of cochlear duct, therefore, all of the subcomponents/parts of the organ of Corti are ectodermal derivatives.
- E. Surrounding the entire otic vesicle is head mesenchyme which forms a cartilage model of the future bony labyrinth inside of which the membranous labyrinth differentiates. Spaces form (apoptosis of mesenchymal cells) in the cartilage between the membranous labyrinth and the future definitive bony labyrinth.
  1. These spaces are filled with perilymph
    - a. Scala vestibule
    - b. Scala tympani
    - c. Unnamed spaces which are outside of membranous labyrinth but inside of bony labyrinth
      - 1) e.g., Perilymph surrounds semicircular ducts, fills semicircular canals
- F. All spaces within membranous labyrinth are filled with endolymph
  1. Cochlear duct
  2. Semicircular ducts

3. Sacculle
4. Utricle

### **III. Middle Ear**

- A. Enlargement of the distal end of the 1st pharyngeal endodermal pouch becomes the middle ear cavity.
- B. Epithelium lining the auditory tube and the middle ear cavity is, therefore, of endodermal origin. This endodermal epithelial layer eventually envelops the ossicles, tendons, ligaments, chorda tympani n. and becomes the inner (medial) lining of the tympanic membrane.

### **IV. External Ear**

- A. First branchial groove (an ectodermal invagination) gives rise to the ext. auditory canal and meatus. The ectoderm lining this invagination forms the lining of the canal.
- B. Inner-most aspect of the ectodermal lining of the first branchial groove forms the epithelium on the external surface of tympanic membrane.
- C. Auricle forms from 6 swellings or hillocks which form at margins of ext. auditory meatus.

## **EYE**

### **I. General**

- A. Formed from surface ectoderm
  1. Lens
  2. Corneal and bulbar conjunctiva
- B. Formed from neuroectoderm of brain
  1. Retina
  2. Optic n.
- C. Formed from mesoderm interposed between and surrounding A and B
  1. Choroid
  2. Sclera
  3. Extraocular muscles
  4. Substantia propria and endothelium (not endoderm) of cornea
- D. The critical period of development begins at the end of the 3rd week and extends through the middle of the 8th week

### **II. Two (left and right) Optic Vesicles form as evaginations from the wall of the forebrain**

- A. Distal ends expand but proximal ends narrow forming optic stalks (future optic n.).
- B. Optic vesicle surrounded by head mesenchyme
- C. Optic vesicle induces a thickening in overlying surface ectoderm, the lens placode
- D. Lens vesicle is formed by invagination of lens placode
  1. Surface connection lost, resealed

2. Lens vesicle becomes lens
  3. Lens vesicle causes optic vesicle to fold in on itself forming the optic cup
- E. Optic cup is, therefore, a double walled structure (folded on itself)
1. Groove forms in inferior surface of optic cup and stalk, i.e., choroid fissure
  2. Choroid fissure filled with mesenchyme and hyaloid a. & v. differentiate here
  3. Outer layer of the optic cup forms the pigmented layer of the retina
  4. Inner layer of the optic cup forms the other 9 layers of the 10 layered retina
  5. The space between the inner and outer layers of the optic cup is the intraretinal space. It is obliterated during the differentiation of the retina, but remains a potential space which can be reopened or reappear in the adult as in the case of an intra-retinal hemorrhage (detached retina).

**III. Vitreous body is derived from the mesoderm interposed between the retina and the lens**

**IV. Ciliary body and its processes are formed from**

- A. Mesoderm which gives rise to the ciliary m. and C.T.
- B. Ectodermal extension of certain layers of the retina
  1. Pigmented layer of the ciliary retina is formed by the outer layer of the optic cup, i.e., the pigmented layer of the retina
  2. Non-pigmented layer of the ciliary retina represents the neural retina or an extension of the inner layer of the optic cup

**V. Iris is formed from**

- A. The edge of the optic cup
- B. The epithelium on the posterior aspect of the iris represents extensions of both inner and outer layers of the optic cup, but here both of these layers are pigmented (iridial retina).
- C. The chromatophores of the iris develop from area mesenchyme
- D. The dilator and sphincter pupillae muscles are, oddly enough, derived from neuroectoderm of the outer layer of the optic cup

**VI. Anterior and posterior chambers develop as spaces formed by apoptosis of the mesenchymal cells in these areas**

**VII. Cornea**

- A. Most of the cornea is formed from mesenchyme
  1. Endothelium
  2. Substantia propria
- B. The external surface of the cornea is derived from ectoderm
  1. Stratified squamous wet epithelium

- C. The basement membranes under the stratified squamous wet epithelium (Bowman's membrane) and under the endothelium (Descemet's membrane) are produced in the usual fashion, i.e., components are derived from the epithelial cells and from the adjacent connective tissue cells.

**VII. Malformations**

- A. Coloboma of the iris
  - 1. Failure of the choroid fissure to close properly in this region
- B. Persistent pupillary membrane
  - 1. Not all of the mesenchyme anterior to the lens disappears during the apoptotic formation of the anterior chamber
  - 2. This leaves a fishnet like arrangement of connective tissue anterior to the pupil
- C. Congenital cataract
  - 1. Rubella infection during critical period of development
- D. Anophthalmos
  - 1. Agenesis of the eye due to:
    - a. No formation of optic vesicle but brain OK.
    - b. No formation of optic vesicle because of defective brain development
- E. Aniridia
  - 1. Deletion on chromosome #11
  - 2. Also associated with Wilm's tumor (cancer of kidney in newborn)

**Sample Questions**

1. Development of the Eye and Ear

- |        |   |    |                      |
|--------|---|----|----------------------|
| _____. | Persistent optic fissure                                  | A. | Aniridia             |
| _____. | Fishnet strands of connective tissue in posterior chamber | B. | Anophthalmia         |
| _____. | Wilm's tumor  | C. | Coloboma iridis      |
| _____. | Developmental absence of an eye membrane                  | D. | Deafness             |
| _____. | Congenital fixation of a bone derived from the hyoid arch | E. | Persistent pupillary |

2. Place an "A" beside derivatives of ectoderm; "B" beside derivatives of mesoderm; and "C" beside derivatives of endoderm.

- \_\_\_\_\_. Outer hair cells
- \_\_\_\_\_. Macula of utricle
- \_\_\_\_\_. Epithelium lining Eustachian tube
- \_\_\_\_\_. Bone of incus
- \_\_\_\_\_. Endothelium on posterior aspect of cornea
- \_\_\_\_\_. Non-photosensitive retinal cells covering ciliary process
- \_\_\_\_\_. Smooth muscle of sphincter of the pupil

- \_\_\_\_. Lens fibers
- \_\_\_\_. Epithelium lining inner aspect of tympanic membrane
- \_\_\_\_. Membranous semicircular duct

Answers to sample questions on The Development of the Eye and Ear:  
1-C,E,A,B,D; 2-A,A,C,B,B,A,A,A,C,A

# Gross Anatomy Lecture: Development of the Head and Neck: Normal and Abnormal

Dr. Burns

## Reading Assignment:

Langman (9<sup>th</sup>): 363-375 (omit “molecular---“); 378-395 (omit Teeth, however, know ameloblast cells only); 399-400.

## Learning Objectives:

Compare and contrast in writing and/or by constructing diagrams, i.e. describe:

- A. The normal developmental steps taken and the adult derivatives of the:
  - 1. Branchial arches, branchial grooves and the pharyngeal pouches
  - 2. Processes and prominences of the face, mouth, hard and soft palate, nasal chambers and the tongue
- B. The developmental anomalies associated with the development of the body regions mentioned in objective “a”.

Include in your study the content contained in the outline whether it is included in the embryology text or not and omit all content contained in the text book that is not contained in the outline, e.g. do not study the components of the Treacher-Collins syndrome, Robin syndrome, Goldenhar syndrome and DiGeorge syndrome but you do need to note however, that DiGeorge syndrome contains a lack or absence of development of the thymus gland and these individuals have immunological problems, especially with the T cell component of the immune system.

## Lecture Outline

### NECK

#### I. General Plan

- A. Branchial or pharyngeal arches
  - 1. Masses of mesoderm with ectoderm on the outside, endoderm on the inside. Enlarged by migration of neural crest cells into region, plus contributions from somite and lateral plate mesoderm.
  - 2. Each contains a specific cranial nerve and an aortic arch; this explains the innervation of the derivatives of each arch.
    - a. BA #1 contains aortic arch #1; cranial nerve #5
    - b. BA #2 " " #2; " " #7

- c. BA #3 " " #3; " " #9
- d. BA #4 " " #4; " " #10
- B. Branchial or pharyngeal grooves
  1. Ectodermal depressions into surface caudal to the corresponding branchial arch, e.g. branchial groove #1 is immediately caudal to branchial arch #1.
  2. Phylogenetic "gill slits"
- C. Pharyngeal pouches
  1. Evaginations of endoderm directed outward (medial to lateral) from center of pharyngeal foregut toward corresponding branchial groove, e.g. pharyngeal pouch #1 faces branchial groove #1 forming branchial membrane #1 (the future tympanic membrane).
- D. Branchial or pharyngeal membranes
  1. Ectoderm of branchial groove
  2. Endoderm of pharyngeal pouch
  3. Mesoderm between 1 & 2
- E. Stomodeum
  1. Ectodermal depression toward lumen of pharynx (foregut)
  2. Ectoderm tightly opposed to endoderm of pharynx; the previous prochordal plate. No mesoderm between these 2 epithelial plates.
  3. This sandwich of ectoderm - endoderm is the oro - or bucco - pharyngeal membrane. It ruptures on or about day 24 of development. Then amniotic fluid can pass into foregut region and eventually be swallowed. Likewise cells sloughing off from epithelial surfaces of pharynx, tracheo-bronchial tree, etc., can gain access to amniotic fluid. These cells can be retrieved via amniocentesis, grown *in vitro* and consequently the fetus can be karyotyped (e.g. diagnosis of fetus with trisomy 21). In the adult the location of the buccopharyngeal membrane is in the Waldeyer ring area in the adult (a ring of lymphoid tissue at posterior aspect of the oral cavity).

## II. Derivatives of the Branchial Arches (mesodermal core)

- A. Branchial arch #1 has 2 major subdivisions, the mandibular and maxillary processes. They give rise to:
  1. Maxilla, zygoma, squamous pt. of temporal bone
  2. Mandible
  3. Malleus and incus
  4. Muscles of mastication plus tensor tympani, tensor veli palatini, mylohyoid and anterior belly of digastric
  5. Sphenomandibular ligament and ant. lig. of malleus
- B. Branchial arch #2 (hyoid)
  1. Stapes, styloid process, lesser horn of hyoid bone and superior part of body of hyoid bone
  2. Muscles of facial expression plus stapedius, stylohyoid and posterior belly of digastric

3. Stylohyoid ligament
- C. Branchial arch #3
  1. Greater horn and inferior part of body of hyoid bone
  2. Stylopharyngeus
- D. Branchial arches #4 (#5 doesn't really form) & #6.
  1. Laryngeal cartilages
  2. Intrinsic muscles of larynx plus levator veli palatini, pharyngeal constrictors and cricothyroideus.
  3. Epiglottis and extreme posterior part of tongue (CN. #X)

### III. Derivatives of the Branchial Grooves

- A. Branchial groove #1
  1. External auditory meatus and canal
  2. External epithelium of tympanic membrane and the skin and its glands lining the ext. auditory canal
- B. Branchial grooves #2 and the rest of them
  1. Are overgrown by developing hyoid arch
  2. This obliterates these branchial grooves
  3. Sometimes the grooves are not normally obliterated resulting in external branchial sinuses or fistulas which may communicate through a degenerated branchial membrane with a remnant of a pharyngeal pouch. In this way branchial fistulas and sinuses are formed and mucus can appear at the external opening on the neck.

### IV. Derivatives of the Pharyngeal Pouches

- A. Pharyngeal Pouch #1
  1. Tympanic cavity and lumen of Eustachian tube
  2. Endoderm lining tympanic cavity forms epithelium covering medial (inside) of tympanic membrane and the epithelial lining of the Eustachian tube.
  3. Endoderm lining tympanic cavity also forms a cuboidal epithelium covering the ossicles (MIS) of the middle ear.
- B. Pharyngeal Pouch #2
  1. Epithelial crypts of the palatine tonsil
  2. Adjacent mesenchyme differentiates into lymphatic tissue of palatine tonsil.
- C. Pharyngeal Pouch #3
  1. Dorsal expansion becomes inferior parathyroid
  2. Ventral expansion becomes epithelial reticular cells of thymus; adjacent mesenchyme differentiates into T lymphocytes; some branchial ectoderm "trapped" during development of thymus=becomes Hassall's corpuscles.
  3. Primordia of thymus and inferior parathyroids lose their connections with the lumen of pouch #3 and migrate caudally to their normal adult position. These parathyroid primordia travel caudally with the thymic primordia, lose their attachment to the

thymus and eventually attach to the posterior surface of the thyroid.

- D. Pharyngeal Pouch #4
  - 1. Dorsal expansion becomes superior parathyroid
  - 2. Ventral expansion is called the ultimobranchial body; it eventually fuses with the thyroid diverticulum from the tongue forming the calcitonin cells of the thyroid.
- E. Much of the mesenchyme of this pharyngeal region is derived from neural crest and forms the stromal elements of the adult glands and structures derived from this region. Experimental ablation of these neural crest cells can result in a wide variety of congenital defects in the structures normally derived from this branchial region, e.g., thymic agenesis.
- F. The surgical search for the missing parathyroid adenoma
  - 1. Patient has a diagnosis of a benign, functioning (excessive amounts of parathyroid hormone) tumor of a parathyroid gland. Too much PTH results in an increase in serum calcium and a decrease in serum phosphate, x-ray of bones = "uniform osteoporosis appearance" or extensive decalcification-forming cysts; calcium deposits in the kidney (nephrocalcinosis).
  - 2. If the 4 parathyroid glands are in their normal adult position on the posterior side of the thyroid, the surgeon usually has no trouble finding the one that is enlarged by the presence of the adenoma.
  - 3. However, if, during embryonic development, one of the parathyroids (the one in which the adenoma formed) did not migrate normally, the surgeon now has to find "the missing gland" in the neck.
  - 4. If it is one of the inferior parathyroids that is missing the surgeon dissects in the neck along the (adult) anatomical pathways the gland should have taken. This may include entering the mediastinum and searching in the thymus or its remains or its migratory path for the "missing" parathyroid gland. A similar concept, but different adult anatomy exists for the "missing" parathyroid if it was a pouch #4 derivative, i.e., a superior parathyroid.

## FACE

### I. General Plan

- A. Named Prominences Formed Around Stomodeum
  - 1. Single frontonasal p.
  - 2. Paired maxillary p. (subdivision of first branchial arch)
  - 3. Paired mandibular p. ( " " )
- B. Prominences enlarge and "move" due to proliferation of head mesenchyme and arrival of migratory neural crest cells. This has the net effect of "moving" the buccopharyngeal membrane (prochordal plate of

the early embryo) posteriorly by adding tissue mass anterior to it. Face formed between 5th to 8th wks.

- C. Ectoderm/Endoderm sandwich, the oro-or buccopharyngeal membrane ruptures on about day 24.

## **II. Medial and Lateral Nasal Prominences**

- A. Subdivisions of frontonasal p. caused by formation of nasal placodes/pits
- B. Lateral nasal p. demarcated from maxillary p. by an external groove, the nasolacrimal groove extending from the Stomodeum to the medial corner of the eye.
- C. Medial nasal p. merge with each other in midline forming a mass of mesenchyme, the intermaxillary segment which gives rise to:
  - 1. Philtrum of the lip
  - 2. Premaxillary part of the maxilla
    - a. Forms alveolar ridge and upper 4 incisors
    - b. Vestibule between 1 and 2
  - 3. Primary palate
- D. If the midline merging fails the result is MEDIAN (not medial) cleft lip (true "hare lip") and/or a bifid nose.

## **III. Maxillary p. merges with both Medial and Lateral Nasal Prominences**

- A. Forms lip lateral to philtrum (the site of the collision between max.p and medial nasal p.)
- B. Forms cheek
- C. Obliterates nasolacrimal groove
  - 1. Ectoderm at floor of nasolacrimal g. becomes a solid cord.
  - 2. Separates from surface
  - 3. Canalized to form the nasolacrimal duct which will eventually drain into nasal cavity.
  - 4. Superior end of this duct expands and differentiates into the lacrimal sac.
- D. If this developmental process fails the result is an oblique facial cleft or a cleft lip.

## **IV. Mandibular p. Merge Together in Midline Forming Lower Jaw**

## **V. Angle of the Mouth Formed by Merging of Maxillary p. and Mandibular p.**

- A. Excessive merging results in microstoma
- B. Less than a normal degree of merging results in macrostomia
- C. Micro-and macro-stoma can be unilateral

## **VI. Palate and Nasal Chamber**

- A. Primary palate formed from internal part of intermaxillary segment
- B. Secondary palate (hard and soft)
  - 1. Horizontal shelves of mesenchyme grow from lateral to medial from internal surface of each maxillary p.

2. These palatine shelves meet and fuse with each other in midline
    - a. Anterior segment forms hard palate
    - b. Posterior segment forms soft palate and uvula
  3. Palatine shelves also fuse with primary palate
  4. Absence of these fusions of the palatine shelves results in the wide varieties of cleft palate
- C. Formation and fusion of palatine shelves divides this part of the pharynx into an inferior oral cavity and a superior nasal cavity
1. Nasal septum forms in midline from superior to inferior
  2. Eventually fuses with the developing palate (crossing an upside down “T or I”)
  3. This divides the single nasal cavity into a left and right nasal chamber.
- D. Development of the palate causes primitive choanae to “move” posteriorly attaining the adult position for the choanae (the paired openings between the nasal cavity and the nasopharynx).

## TONGUE

### I. General Plan

- A. Many named mesenchymal elevations develop from floor of pharynx. Several of these are overgrown and eventually disappear, hence no need to discuss these.
- B. Distal tongue buds form (left and right)
  1. Merge together in midline
  2. Become anterior 2/3 of tongue
- C. Single posterior tongue bud, the hypobranchial eminence, forms the posterior 1/3 of the tongue
- D. Where B & C meet is the terminal sulcus.

### II. Innervation

- A. Distal or lateral tongue buds (lingual swellings) arise from 1st and 2nd branchial arches, therefore:
  1. CN V & CN VII involved in tongue innervation
    - a. CN V = general sensory to ant. 2/3
    - b. CN VII = taste (taste buds) for ant. 2/3
- B. Post. tongue bud arises from 3rd branchial arch, therefore:
  1. CN IX innervates post. 1/3, including circumvallate papillae because during final development of tongue, post. tongue bud tissue moves slightly forward or anteriorly.
- C. The extreme posterior part of the tongue is derived from 4th arch and therefore carries CN X innervation Occipital myotomes, innervated by CN XII, migrate from paraxial position into substance of tongue. Myoblasts originating from this mesoderm form essentially all of the skeletal muscle of the tongue. This migration during development explains the gross anatomical course the 12th CN takes as it innervates the tongue.

### III. Germ Layers and Adult Derivatives: Tongue and Mouth

- A. In the adult mouth the junction between ectoderm and endoderm is behind all of the teeth, i.e.
  - 1. Posterior to front teeth
  - 2. Medial to lateral teeth
- B. Thus all of the teeth are of ectodermal origin
- C. The epithelia of the tongue, epiglottis, submandibular and sublingual glands are of endodermal origin (endodermal lined floor of the buccal cavity).
- D. The wet epithelium of the cheeks is, therefore, of ectodermal origin.
- E. Since the parotid gland develops from an evagination from the cheek epithelium, its parenchyma is of ectodermal origin. The sublingual and submandibular glands, however, begin by evaginations from the endoderm lining of the floor of the mouth, their parenchymal elements are endodermally derived.

#### Pituitary Gland

##### I. Two different primordia, but both are of ectodermal origin

- A. Rathke's pouch
  - 1. Evagination from roof of mouth, grows superiorly
  - 2. Eventually loses its "ductal" connection to epithelial lining of roof of mouth
  - 3. "Ductless" sac is formed which differentiates into the adenohypophysis
- B. Infundibulum
  - 1. Evagination from the diencephalon (floor of the third ventricle) of the developing brain, grows inferiorly
  - 2. Distal region differentiates into the neurohypophysis
  - 3. Proximal region becomes infundibular recess (small pit) of adult 3<sup>rd</sup> ventricle

##### II. Pathology

- A. Craniopharyngioma (Rathke's pouch tumor)
  - 1. Second most common neoplasm of the pituitary gland; pituitary adenoma is most common
  - 2. More common in children and young adults
  - 3. Derived from vestigial elements of Rathke's pouch
  - 4. Therefore can be found in the gland itself OR any where along the migratory path that Rathke's pouch took, i.e. craniopharyngiomas can be found in the hard palate
  - 5. Many times the histology of a craniopharyngioma mimics that of a developing tooth, an oral ectodermal derivative. Since the cells in the tooth bud which make enamel are called ameloblasts, craniopharyngiomas with this histology are called ameloblastomas.

#### Miscellaneous

- I. Ectodermal Dysplasias**
- A. ED's are a group of related syndromes in which ectodermal development is defective.
    - 1. Absence of teeth often leads to diagnosis
    - 2. Lack of sweat glands; poor body temperature regulation; if fever occurs in such a child can be fatal
    - 3. Vision and hearing problems
    - 4. Hair and skin problems
  - B. 20-30 neonates/year in Arkansas are effected
  - C. ACH is one of 5 regional centers for diagnosis and treatment

**Sample Questions:**

- 1. All of the following are adult derivatives of the merged medial nasal prominences except:**
- A. Philtrum of upper lip
  - B. Lacrimal sac
  - C. Upper 4 incisors
  - D. Part of vestibule between upper 4 incisors and philtrum of upper lip
  - E. Primary palate
- 2. Place:**
- A - if a 1st branchial arch derivative
  - B - if a 2nd branchial arch derivative
  - C - if a 3rd branchial arch derivative
  - D - if a 4-6th branchial arch derivative
- \_\_\_\_. Muscles of mastication
  - \_\_\_\_. Thyroid cartilage
  - \_\_\_\_. Stapes
  - \_\_\_\_. Muscles of facial expression
  - \_\_\_\_. Incus
  - \_\_\_\_. Greater horn of hyoid bone
  - \_\_\_\_. Stapedius
  - \_\_\_\_. Stylopharyngeus muscle
- 3. You see a child at Children's Hospital who has the following history and physical: "IQ of 72, thin upper lip, poorly developed philtrum, microcephaly and hyperactivity". The diagnosis is:**
- A. Spina bifida
  - B. Anencephaly
  - C. Fetal alcohol syndrome
  - D. Trisomy 21
  - E. Neonatal abstinence syndrome

**Answers to sample questions on the Development of the Face and Pharynx:**

**1-B 2-A,D,B,B,A,C,B,C; 3-C**