ANAT2341 Embryology 2009

From Embryology

Welcome to Embryology 2009!


Dr Mark Hill, course coordinator

The course coordinator is Dr Mark Hill, my office is located in Wallace Wurth ground floor room G20.

Welcome to Embryology in 2009 and thank you for choosing your next stage in your own development with me! In the past 20 years as a researcher I have seen enormous changes in our understanding of this topic and the methods we employ to further our knowledge. This topic and its associated methodologies are now found at the core of scientific investigations and current medical research.

This current page will introduce the current course and link to related online course resources (bookmark this as your start page). This is a new online resource, content and links will be added during your current course.

Contents

Course Links

- UNSW Course Outline 2009 ANAT2341 Embryology PDF (8 pages, 500 Kb) this is a link to the PDF version of the current course handout.
- ANAT2341 Course Timetable 2009 the current planned course timetable.
- 2009 Lecture Audio Recordings page with links to the Lectopia recording page (requires login).
- Student Pages page containing links to all individual student pages and group project pages.
- Quizzes page containing links to some simple quizzes on course theory.

Course Outline

- Course Staff - Dr Mark Hill, Office: Wallace Wurth Building, room G20 (ground floor), Email: m.hill@unsw.edu.au
- Student Contact - University policy concerning student contact: ” When a student is enrolled into University of New South Wales, he or she will be automatically issued with a University email account. The School will use that email account as the official electronic channel to communicate with each student.” Appointments with Dr Mark Hill should be made initially by email or through the SOMS office, Wallace Wurth Building, room MG14 (ground floor).
- Course Information - UNSW Online Handbook entry (http://www.handbook.unsw.edu.au/undergraduate/courses/2009/ANAT2341.html) , 6 Units of credit, Science/Anatomy program. Prerequisite: ANAT2200 or ANAT2241.

Course Timetable

The course consists of two lectures and a single laboratory each week of UNSW Semester 2, Weeks 2-7,8-13. UNSW Academic Calendar (https://my.unsw.edu.au/student/resources/AcademicCalendar.html)

- ANAT2341 Course Timetable 2009
- 2009 Lecture Audio Recordings

Weekly Timetable

- Lecture 1 Mon 12:00 - 1:00pm Central Lecture Block 5
- Lecture 2 Tue 12:00 - 1:00pm Biomedical Theatre E
- Laboratory Thu 1:00 - 3:00pm Wallace Wurth 106/108
    - Note- this is a swipecard access only laboratory

Course Aims

- To present the current theories and applications of embryology.
- To cover early embryonic then fetal development through to birth.
- To describe the developmental anatomy of the organ systems.
- To examine the common principles and differences underlying normal and abnormal development of vertebrates.
- To cover emerging technologies, such as stem cells, genomic analysis and the use of transgenic and dysfunctional mouse mutants in research.

In Lectures and Labs I will clearly identify any examinable material. In addition, the final lecture is an opportunity to review course material and ask questions about difficult concepts. As part of the course I also encourage you to develop the general scientific skills of critical thinking, analysis and scientific writing.

The new UNSW semester structure means that there will be some reorganization of previous course content material, I apologize for any inconvenience during this transition time. This year I will also be asking you to participate in assessing and providing feedback on a medical student's Independent Learning Project (ILP) on online education in cardiac development.

Student Contact

- University policy concerning student contact is:

  " When a student is enrolled into University of New South Wales, he or she will be automatically issued with a University email account. The School will use that email account as the official electronic channel to communicate with each student."

- Appointments with Dr Mark Hill should be made initially by email or through the Anatomy office (room G11).

Student Online Pages

Each student in the current course has their own Wiki page Student Pages for assessment items and course feedback. In addition groups of students have a group project page to be prepared online as part of their assessment.

Assessment

There will be three parts to the course assessment.

1. Group Assignment - An online written assignment. 20%
2. Laboratory - Progressive assessments throughout session. 20%
3. Theory - A written test held during the examination period. 60%

- Assessment design has been structured to develop and examine the following graduate attributes and specific learning skills:
  - Student independent learning/research abilities
  - Student scientific writing and referencing skills
  - Student teamwork in small groups
  - Student group work contribution
  - Student ability to plan time and meet assessment deadlines
  - Student acquired knowledge from lecture/lab presentations
  - Student application of knowledge to problem solving

- For more information see also UNSW Guidelines on Learning (http://www.guidelinesonlearning.unsw.edu.au/guidelinesHome.cfm)

Examiner The course organizer (Dr Mark Hill) will be the examiner. The course assessor is Prof Edna Hardeman.

Group Assessment will be an online small group (4-5 student) embryology project prepared throughout the semester, assessed by peers and the course coordinator. Detailed information will be available online and in the laboratory times.

Laboratory Assessment will be a series of short answer questions prepared throughout the semester relating to embryology lecture and laboratory content.

Theory examination will be an internal exam within the session two exam period and will conform to University examination guidelines. Students absent through illness or misadventure should immediately contact UNSW Student Central (https://my.unsw.edu.au/student/atoz/UNSWStudentCentral.html) . For more information see UNSW A-Z Guide Special Consideration (https://my.unsw.edu.au/student/atoz/SpecialConsideration.html) .

Supplementary examinations will only be offered if the student is unable to attend the final examination for medical or misadventure reasons.

Assignment and Lab Project Dates Current planned submission and project assessment dates are shown in the printed course schedule (page 6).

Textbooks

- Either of the textbooks listed below are recommended for this course and page references to both are given in each lecture. There are additional embryology textbooks that can also be used, consult course organizer.
  - The Developing Human: Clinically Oriented Embryology (http://www.us.elsevierhealth.com/product.jsp?isbn=9781416037064) (8th Edition) by Keith L.

Moore and T.V.N Persaud
- Larsen's Human Embryology (http://www.elsevier.com/wps/find/bookdescription.cws_home/713963/description#description) by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West

Lecture Recordings

- ANAT2341 Embryology 2009 Lecture Recordings page with links to all current recordings.
- Available from both UNSW Embryology and http://lectopia.elearning.unsw.edu.au/lectopia Lectopia] (formally iLecture), online sound recording system making UNSW Lectures available in several formats (including Podcast).
    - Lecture recordings are grouped by the id of the lecture, usually the course code.

Academic Honesty and Plagiarism

Please Read - Plagiarism & Academic Integrity www.lc.unsw.edu.au/plagiarism **What is Plagiarism?** Plagiarism is the presentation of the thoughts or work of another as one's own.(1)

Examples include:

- direct duplication of the thoughts or work of another, including by copying material, ideas or concepts from a book, article, report or other written document (whether published or unpublished), composition, artwork, design, drawing, circuitry, computer program or software, web site, Internet, other electronic resource, or another person's assignment without appropriate acknowledgement;
- paraphrasing another person's work with very minor changes keeping the meaning, form and/or progression of ideas of the original;
- piecing together sections of the work of others into a new whole;
- presenting an assessment item as independent work when it has been produced in whole or part in collusion with other people, for example, another student or a tutor; and
- claiming credit for a proportion a work contributed to a group assessment item that is greater than that actually contributed.†

For the purposes of this policy, submitting an assessment item that has already been submitted for academic credit elsewhere may be considered plagiarism. Knowingly permitting your work to be copied by another student may also be considered to be plagiarism. Note that an assessment item produced in oral, not written, form, or involving live presentation, may similarly contain plagiarised material.

The inclusion of the thoughts or work of another with attribution appropriate to the academic discipline does not amount to plagiarism. The Learning Centre website is main repository for resources for staff and students on plagiarism and academic honesty. These resources can be located via: www.lc.unsw.edu.au/plagiarism

The Learning Centre also provides substantial educational written materials, workshops, and tutorials to aid students, for example, in:

- correct referencing practices;
- paraphrasing, summarising, essay writing, and time management;
- appropriate use of, and attribution for, a range of materials including text, images, formulae and concepts.
- Individual assistance is available on request from The Learning Centre.

Students are also reminded that careful time management is an important part of study and one of the identified causes of plagiarism is poor time management. Students should allow sufficient time for

research, drafting, and the proper referencing of sources in preparing all assessment items.

(1) Text above based on that proposed to the University of Newcastle by the St James Ethics Centre. Used with kind permission from the University of Newcastle † Adapted with kind permission from the University of Melbourne.

Administrative Matters

Attendance Requirements

- Students are required to attend each lecture and laboratory unless given special permission.
- Students seeking special consideration should be able to provide medical certificates.

Human Swine Flu (H1N1 Influenza 09) UNSW Health Advice (http://www.unsw.edu.au/gen/pad/healthadvice.html)

> "Anyone with an acute respiratory illness and a fever should stay at home until they have not had a fever for 24 hours (this means a 24 hour fever-free period without medications such as paracetamol and cold and flu tablets)."

- Students must wear a white lab coat and closed footwear in research laboratories and comply at all times with SOMS occupational health and safety requirements (found on SOMS website).

Group Assignment Submission

- Late Assignments will be penalized by 5% / day late.

Occupational Health and Safety (OHS)

- The University policies and expectations can be found currently at: http://www.hr.unsw.edu.au/ohswc/ohs/pdf/statement_OHS_policy.pdf
- The School of Medical Sciences (SOMS) also maintains important student specific OHS information. SOMS OHS (http://medicalsciences.med.unsw.edu.au/somsweb.nsf/page/OHS)

Equity and Diversity

- Those students who have a disability that requires some adjustment in their teaching or learning environment are encouraged to discuss their study needs with the course convener prior to, or at the commencement of, their course, or with the Equity Officer (Disability) in the Equity and Diversity Unit (9385 4734) or on the web:

  http://www.studentequity.unsw.edu.au

- Issues to be discussed may include access to materials, signers or note-takers, the provision of services and additional exam and assessment arrangements.
- Early notification is essential to enable any necessary adjustments to be made.

Links

- **UNSW Embryology** http://embryology.med.unsw.edu.au/ is an online resource I have developed to aid your own independent learning, please explore its content. It not only has the usual lecture slides, but also podcast broadcasts, lab project support, online external resources (included complete

ANAT2341 Course Timetable 2009

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  - Note- this is a swipecard access only laboratory
- 2009 Lecture Audio Recordings

Week	Date	Lecture 1 Mon 12:00 - 1:00pm Central Lecture Block 5	Lecture 2 Tue 12:00 - 1:00pm Biomedical Theatre E	Laboratory Thu 1:00 - 3:00pm Wallace Wurth 106/108
2	27 Jul	Embryology Introduction	Cell Division/Fertilization	Cell Division/Fertilization
3	3 Aug	Week 1&2 Development	Week 3 Development	Lab 2
4	10 Aug	Mesoderm Development	Ectoderm, Early Neural, Neural Crest	Lab 3
5	17 Aug	Early Vascular Development	Placenta	Lab 4
6	24 Aug	Endoderm, Early Gastrointestinal	Respiratory Development	Lab 5
7	31 Aug	Head Development	Neural Crest Development	Lab 6
	7 Sep	**Mid-semester break**		
8	14 Sep	Musculoskeletal Development	Limb Development	Lab 7
9	21 Sep	Kidney	Genital	Lab 8
	24 Sep	**Updated Group Project Due Date**		
10	28 Sep	Sensory - Ear	Integumentary	Lab 9
11	5 Oct	**Public Holiday** Sensory - Eye	Endocrine	Lab 10
12	12 Oct	Heart	Fetal	Lab 11
13	19 Oct	Birth, Postnatal	Revision	Lab 12
	24 Oct	Study Week		
	30 Oct to 17 Nov	Examination- Wed 04/11		

Theory Exam ANAT2341 Embryology Date: Wed 04/11 Time: 8:45 - 12:00 Location: WEBST 334 (K-G14-334)

Supplementary exams It is intended that supplementary exams for School of Medical Sciences courses in Semester 2, 2009 will be held in the week commencing Monday 7th December, 2009. SOMS Supplementary exams (http://medicalsciences.med.unsw.edu.au/SOMSWeb.nsf/page/Science+Current+Students#SupExam)

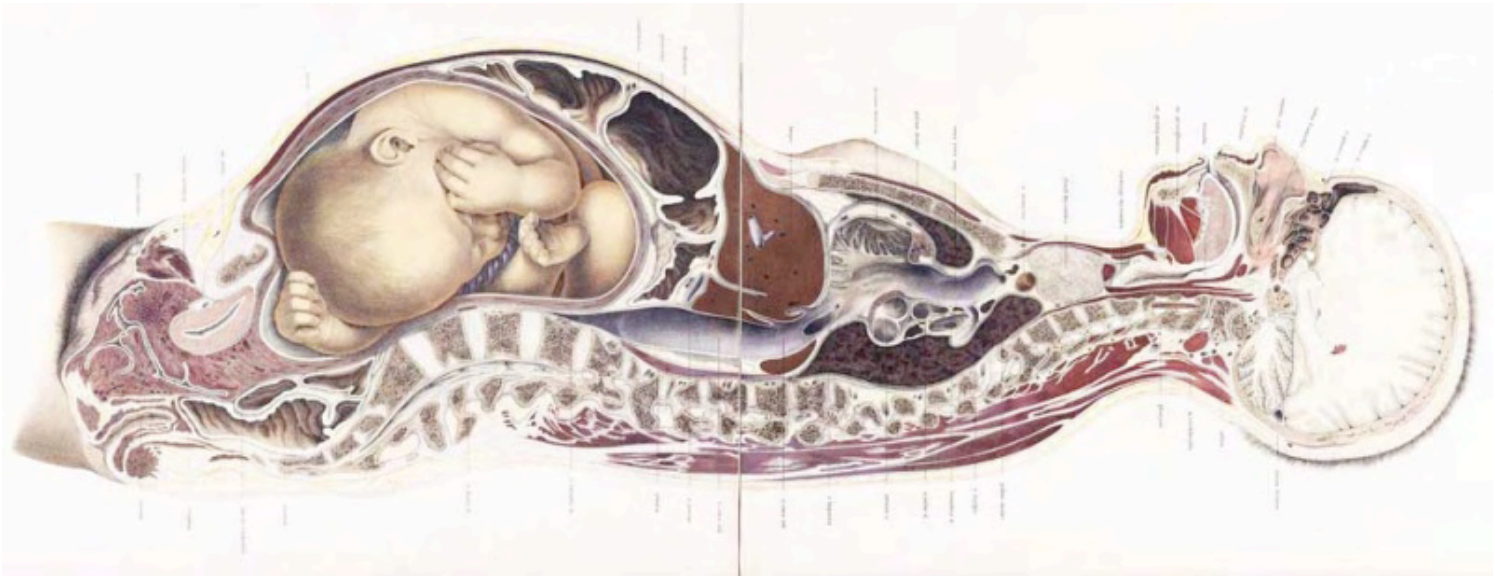
Categories: 2009ANAT2341 | Science-Undergraduate

2009 Lecture 1

From Embryology

Contents

A Course Introduction



Anatomical image of late pregnancy by Wilhelm Braune (1831-1892): Topographisch-anatomischer Atlas : nach Durchschnitten an gefrornen Cadavern, Leipzig: Verlag von Veit & Comp., 1867-1872. (Topographic-anatomical Atlas) Wilhelm Braune (1831-1892) (http://embryology.med.unsw.edu.au/History/page11.htm#Braune)

This first lecture will be a general introduction to the course and the subject of Embryology.

> **Firstly**, an introduction to the course, its content and assessment and an opportunity to ask questions.
>
> **Secondly**, some historic background to the subject and related current Australian trends.

MH - I do not expect you to remember specific historic dates or statistical data, this is provided as an introduction to the topic.

Lectopia Lecture Audio Lecture Date: 27-07-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Course Introduction (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48823)

ANAT2341 Course Background 2009

I will spend the first half going through the current course design, online support and assessment criteria. This is an opportunity to ask the course coordinator questions about the course.

Links: Course Homepage | UNSW Embryology (http://embryology.med.unsw.edu.au/)

History

Long Ago

- A series of Anatomies from Early History 1600-1700 (http://embryology.med.unsw.edu.au/History/page11.htm) .
- Harvey (http://embryology.med.unsw.edu.au/History/page2b.htm)
- Leeuwenhoek (http://embryology.med.unsw.edu.au/History/page2c.htm)
- 18C Anatomy and Physiology (http://embryology.med.unsw.edu.au/History/page2.htm#18canatomy)

19th Century

- **1824** - Rolando cut chemically hardened (fixed) pieces of brain tissues into thin sections for microscopical examination
- **1859** - Darwin - On the Origin of Species Evolution Darwin (http://embryology.med.unsw.edu.au/History/page4g.htm)
- **1880** - image excerpts from a historic study of German embryologist Wilhelm His (1831-1904) Anatomie menschlicher Embryonen (1880) (http://embryology.med.unsw.edu.au/History/page1880.htm) .
- **1889** - Camille Golgi discovered a method of silver staining hardened brain tissues Brain and Mind (http://embryology.med.unsw.edu.au/History/page5c.htm) Brain Structure (http://embryology.med.unsw.edu.au/History/page5d.htm)

Early 20th Century

- **1914** - image excerpts from a historic study of The Anatomy of a 17.8 mm Human Embryo by Thyng, FW 1914 (http://embryology.med.unsw.edu.au/History/page1914.htm) ,
- **1918** - links to images from Anatomy of the Human Body by Gray, W 1918 (http://embryology.med.unsw.edu.au/History/page1918.htm)
- **1935** - Hans Spemann's 1935 nobel speech (http://embryology.med.unsw.edu.au/History/page1935.htm) .

Development in the early 20th century can also be seen in some Historic Movies 1920-1960 (http://embryology.med.unsw.edu.au/Movies/historic.htm) .

Late 20th Century

There are too many embryological breakthroughs in the late 20th century to briefly list here. Some key women in development 1953 Virginia Apgar (http://embryology.med.unsw.edu.au/Child/apgar.htm) , Rita Levi-Montalcini (http://nobelprize.org/nobel_prizes/medicine/laureates/1986/index.html) and 1965 Le Douarin (http://embryology.med.unsw.edu.au/History/page1965.htm) .

- **1953** - Apgar Test Virginia Apgar (http://embryology.med.unsw.edu.au/Child/apgar.htm) .
- **1965** - Neural Crest Research Nicole Le Douarin (http://embryology.med.unsw.edu.au/History/page1965.htm) .
- **1978** - First IVF baby born. In Vitro Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5b.htm)

Nobel Prizes

Much of the modern history of Medicine/Embryology is documented in the Nobel Prizes for Medicine (http://nobelprize.org/nobel_prizes/medicine/laureates/) . Remember that these award dates reflect findings that have proven to be scientific key breakthroughs from earlier dates.

- **1986** discoveries of growth factors (http://nobelprize.org/nobel_prizes/medicine/laureates/1986/index.html)
- **1995** genetic control of early embryonic development (http://nobelprize.org/nobel_prizes/medicine/laureates/1995/index.html)
- **2002** cell cycle (http://nobelprize.org/nobel_prizes/medicine/laureates/2001/index.html)
- **2002** cell death (http://nobelprize.org/nobel_prizes/medicine/laureates/2002/index.html)
- **2007** embryonic stem cells (http://nobelprize.org/nobel_prizes/medicine/laureates/2007/index.html)

21st Century

- **2000** - Human Genome Complete
- **2001** talk given by Robert Winston "Engineering Reproduction: Will We Still Be Human At The End of the 21st Century (http://embryology.med.unsw.edu.au/History/page2001.htm) ".
- **2009** - Induced pluripotent stem (iPS) Stem Cells (http://embryology.wordpress.com/category/stem-cell/) Embryology Blog 2009 (http://embryology.wordpress.com/)

Australian Statistics

The data below are highlights from the AIHW National Perinatal Statistics Unit recent annual publication: "**Australia's mothers and babies 2005**"

> **267,793** women gave birth to **272,419** babies, **15,214** more births (5.9%) than reported in Australia for 2004.

Mothers

- **29.8** years was the mean maternal age, continuing an upward trend. (More? Australian Statistics (http://embryology.med.unsw.edu.au/Stats/page2.htm) | Australian Maternal Statistics (http://embryology.med.unsw.edu.au/Stats/page2a.htm))
- **9,867** were of Aboriginal or Torres Strait Islander origin, making up 3.7% of all mothers.
- **17.4%** reported smoking at all during pregnancy. (More? Smoking (http://embryology.med.unsw.edu.au/Defect/smoking.htm))
- **58.5%** had a spontaneous vaginal birth (0.4% vaginal breech birth, 3.5% forceps and 7.2% vacuum extractions). (More? Birth Overview (http://embryology.med.unsw.edu.au/Child/birth3.htm))
- **30.3%** gave birth by caesarean section (19.5% in 1996) (More? Caesarean Delivery (http://embryology.med.unsw.edu.au/Child/birth6.htm))
- **83.2%** had previously had a caesarean section
- **1.7%** had a multiple pregnancy (More? Twinning (http://embryology.med.unsw.edu.au/Defect/twin.htm))
- **3.0 days** median length of stay in hospital (caesarean section 5.0 days)

Babies

- **8.1%** were preterm (less than 37 weeks gestation) (More? [../Child/birthpremature.htm Premature Birth] | [../Child/birthweight.htm Low Birth Weight])
- **6.4%** of liveborn babies were of low birthweight (less than 2,500 grams) (More? [../Child/birthweight.htm Low Birth Weight] | [../Defect/page10.htm Fetal Origins Hypothesis])
- 105.5 male / 100 female live births
- **15.5%** of liveborn babies admitted to a special care nursery or neonatal intensive care unit.
- **6,044** were admitted to level III neonatal intensive care units in Australia and met ANZNN‚Äôs high risk criteria, of which **78.0%** were preterm.
- **7.3 /1,000** births fetal death rate (More? [../Child/birth7.htm Stillbirth and Perinatal Death])
- **3.2 /1,000** neonatal death rate / live births
- **10.5 /1,000** perinatal death rate / births

Assisted Reproduction Technology

Assisted Reproduction Technology (ART) may include more techniques than, but is sometimes also used to identify, In vitro Fertilization (IVF) (More? [../Notes/week1_5b.htm In Vitro Fertilization]).

- **51,017 treatment cycles** reported to ANZARD in Australia and New Zealand in 2005.
  - 91.1% were from Australian fertility and 8.9% from New Zealand centres (an increase of 13.7% of ART treatment cycles from 2004).
- **35.5** years average age of women (35.2 years in 2002).
- Women aged older than 40 years has increased from 14.3% in 2002 to 15.3% in 2005.

Single Embryo Transfers (SET)

- Significant increase in the number of SET embryos transfer cycles: 2002 28.4%; 2005 48.3%
- increase of SET cycles resulted more singleton deliveries (singleton deliveries 2005 was 85.9%)
- Single-embryo transfer babies had better outcomes compared to babies born to women who had a double-embryo transfer (DET).
- Singletons babies 96.1% SET, 61.6% DET
- Preterm babies, 11.7% SET, 30.6% DET
- Low birthweight liveborn babies, 8.0% SET, 25.0% DET

(Reference: AIHW National Perinatal Statistics Unit Assisted Reproduction Technology in Australia and New Zealand 2005 (http://www.npsu.unsw.edu.au/NPSUweb.nsf/page/art11))

Australian Developmental Abnormalities

Ten most frequently reported birth defects in Victoria between 2003-2004 (More? Australian Statistics - Victoria (http://embryology.med.unsw.edu.au//Defect/page3c.htm))

1. **Hypospadias** (More? Genital Abnormalities - Hypospadia (http://embryology.med.unsw.edu.au/Notes/genital2.htm#Hypospadia))
2. **Obstructive Defects of the Renal Pelvis** (More? Urogenital Abnormalities (http://embryology.med.unsw.edu.au/Notes/urogen2.htm#top))
3. **Ventricular Septal Defect** (More? Cardiovascular Abnormalities - Ventricular Septal Defect (http://embryology.med.unsw.edu.au/Notes/heart2.htm#vsd))
4. **Congenital Dislocated Hip** (More? Musculoskelal Abnormalities - Congenital Dislocation of the Hip (CDH) (http://embryology.med.unsw.edu.au/Notes/skmus2.htm#HIPDISLOCATION))
5. **Trisomy 21 or Down syndrome** - (More? Abnormal Development - Trisomy 21 (http://embryology.med.unsw.edu.au//Defect/page21.htm))
6. **Hydrocephalus** (More? Neural Abnormalities - Hydrocephalus (http://embryology.med.unsw.edu.au/Notes/neuron2.htm#Hydrocephalus))
7. **Cleft Palate** (More? Head Abnormalities (http://embryology.med.unsw.edu.au/Notes/head2.htm#Cleft))
8. **Trisomy 18 or Edward Syndrome** - multiple abnormalities of the heart, diaphragm, lungs, kidneys, ureters and palate 86% discontinued (More? Abnormal Development - Trisomy 18 (http://embryology.med.unsw.edu.au/Defect/page18.htm))
9. **Renal Agenesis/Dysgenesis** - reduction in neonatal death and stillbirth since 1993 may be due to the more severe cases being identified in utero and being represented amongst the increased proportion of terminations (approximately 31%). (More? Kidney Abnormalities - Renal Agenesis (http://embryology.med.unsw.edu.au/Notes/urogen2.htm#Renal_Agenesis))
10. **Cleft Lip and Palate** - occur with another defect in 33.7% of cases. (More? Head Abnormalities (http://embryology.med.unsw.edu.au/Notes/head2.htm#Cleft))

Links: Historical Embryology (http://embryology.med.unsw.edu.au/News/history.htm) | The History of Childbirth (http://www.umanitoba.ca/outreach/manitoba_womens_health/hist1.htm) | Classic Papers in Neonatal Medicine (http://www.neonatology.org/classics/default.html) | Australian Data (http://embryology.med.unsw.edu.au/Medicine/BGD2tutorial.htm)

UNSW Embryology Links

- Lecture 1 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture01.htm)
- Historical Embryology (http://embryology.med.unsw.edu.au/News/history.htm)
- detailed History (http://embryology.med.unsw.edu.au/history/page1.htm)
- Australian Data (http://embryology.med.unsw.edu.au/Medicine/BGD2tutorial.htm)

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Original Glossary (http://embryology.med.unsw.edu.au/Notes/Index/Index.htm)

2009 Lecture 2

From Embryology

Contents

Cell Division and Fertilization

This lecture will introduce two key concepts of biology, cell division and cellular sexual development. Both these concepts will also be explored further in the Thursday laboratory.

--MarkHill 15:44, 27 July 2009 (EST) Lecture notes in preparation (notice removed when complete)

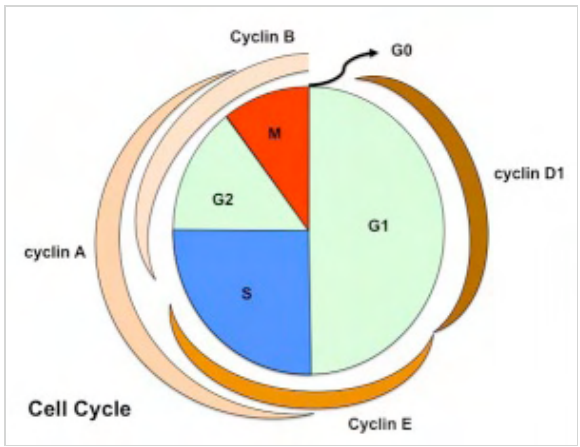
Textbooks

- The Developing Human: Clinically Oriented Embryology (8th Edition) by Keith L. Moore and T.V.N Persaud - Chapter 2
- Larsen's Human Embryology - Chapter 1

Lectopia Lecture Audio Lecture Date: 28-07-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Cell Division and Fertilization (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48835)

Cell Cycle

- Cell Division (m phase) is only a brief moment in the functional life (interphase) of most eukaryotic cells.
- The eukaryotic cell cycle is regulated by 2 protein families known as cyclins and cyclin-dependent kinases.



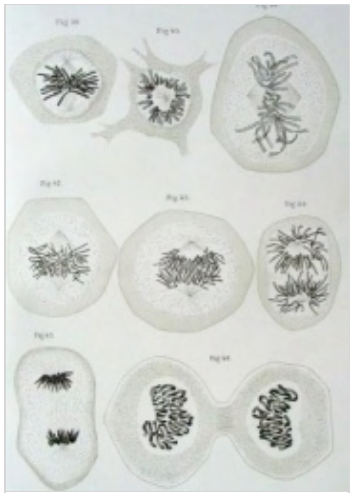
The Cell Cycle

Cell Division

- Cell Division Milestones

(http://www.nature.com/celldivision/milestones/index.html) Recent

(http://www.nature.com/celldivision/milestones/index.html) ; Recent Nobel Prizes


Historic drawing of mitosis

Features Two Mechanical Processes

- Mitosis - microtubule based segregation of chromosomes and formation of 2 nuclei
- Cytokinesis - microfilament based splitting of the cell cytoplasmic contents as a whole into 2 daughter cells

Features Two Types

- Mitosis - occurs in all cells, producing genetically identical progeny.
- Meiosis - occurs only in germ cells (sperm=spermatozoa and egg=oocyte), producing genetically different progeny.
  - progeny = daughter cells, offspring

Cell Changes

- Nucleus
  - Chromosome condensation
  - Nuclear envelope breakdown

- Cytoplasm
  - Cytoskeleton reorganization
  - Spindle formation (MT) Contractile ring (MF)
  - Organelle redistribution

Mitosis

MCB Movie - The stages of mitosis and cytokinesis in an animal cell (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mcb.figgrp.5500)

- Based on light microscopy of living cells light and electron microscopy of fixed and stained cells
- 5 Phases - prophase, prometaphase, metaphase, anaphase, and telophase
- Cytokinesis 6th stage overlaps the end of mitosis

Note that DNA duplication has occurred earlier in the S Phase of the cell cycle.

Prophase

- Chromosome DNA has been earlier duplicated (S Phase)
- Chromosomes begin condensing
- Chromosome pairs (chromatids) held together at centromere
- Microtubules disassemble
- Mitotic spindle begins to form
- Prophase ends when nuclear envelope breaks down

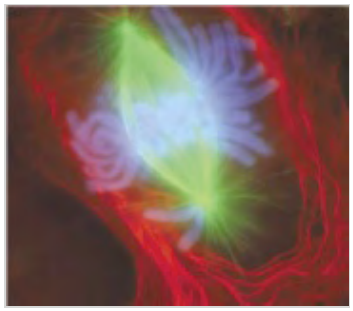
Prometaphase

MCB Movie - Centromeric attachment of microtubules (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mcb.figgrp.5509) |

- Microtubules now enter nuclear region
- Nuclear envelope forms vesicles around mitotic spindle
- Kinetochores form on centromere attach to some MTs of spindle
- Prometaphase ends when chromosomes move to metaphase plate

Metaphase

- Kinetochore MTs align chromosomes in one midpoint plane
- Metaphase ends when sister kinetochores separate



Metaphase fluorescent image of Mitotic spindle and Chromosomes

Anaphase

- Separation of sister Kinetochores
- shortening of Kinetochore microtubules pulls chromosome to spindle pole
- Anaphase ends as nuclear envelope (membrane) begins to reform

Telophase

- Chromosomes arrive at spindle poles
- Kinetochore MTs lost
- Condensed chromosomes begin expanding
  - Continues through cytokinesis

Cytokinesis

- Division of cytoplasmic contents
- Contractile ring forms at midpoint under membrane
- Microfilament ring Contracts forming cleavage furrow
- Eventually fully divides cytoplasm

Cell Organelles

- Mitochondria - Divide independently of cell mitosis, distributed into daughter cells
- Peroxisomes - localise at spindle poles
- Endoplasmic Reticulum - associated with the nuclear envelope vesicles.
- Golgi Apparatus- Golgi stack undergoes a continuous fragmentation process, fragments are distributed into daughter cells, then reassembled into new Golgi stacks

Meiosis

Meiosis Germ cell division (haploid)

- Reductive division
- Generates haploid gametes (egg, sperm)
- Each genetically distinct from parent

- Genetic recombination (prophase 1)
  - Exchanges portions of chromosomes maternal/paternal homologous pairs
- Independent assortment of paternal chromosomes (meiosis 1)

Homologous chromosomes pairing unique to meiosis

- Each chromosome duplicated and exists as attached sister chromatids before pairing occurs
- Genetic Recombination shown by chromosomes part red and part black
  - chromosome pairing in meiosis involves crossing-over between homologous chromosomes

Meiosis I and II

- Meiosis I separates the pairs of homologous chromosomes, reduces the cell from diploid to haploid.
- Meiosis II separates each chromosome into two chromatids (chromosome behavior in meiosis II is like that of mitosis).

Figure 14.32. Comparison of meiosis and mitosis (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?

&rid=cooper.figgrp.2486)

Prophase I

- The homologous chromosomes pair and exchange DNA to form recombinant chromosomes.
- Prophase I is divided into five phases:
  - **Leptotene** - chromosomes start to condense.
  - **Zygotene** - homologous chromosomes become closely associated (synapsis) to form pairs of chromosomes consisting of four chromatids (tetrads).
  - **Pachytene** - crossing over between pairs of homologous chromosomes to form chiasmata (form between two nonsister chromatids at points where they have crossed over)
  - **Diplotene** - homologous chromosomes begin to separate but remain attached by chiasmata.
  - **Diakinesis** - homologous chromosomes continue to separate, and chiasmata move to the ends of the chromosomes.

Prometaphase I

- Spindle apparatus formed, and chromosomes attached to spindle fibres by kinetochores.

Metaphase I

- Homologous pairs of chromosomes (bivalents) arranged as a double row along the metaphase plate. The arrangement of the paired chromosomes with respect to the poles of the spindle apparatus is random along the metaphase plate. (This is a source of genetic variation through random assortment, as the paternal and maternal chromosomes in a homologous pair are similar but not identical. The number of possible arrangements is 2n, where n is the number of chromosomes in a haploid set. Human beings have 23 different chromosomes, so the number of possible combinations is 223, which is over 8 million.)

Anaphase I

The homologous chromosomes in each bivalent are separated and move to the opposite poles of the cell.

Telophase I

The chromosomes become diffuse and the nuclear membrane reforms.

Cytokinesis I

- Cellular cytoplasmic division to form two new cells, followed by Meiosis II.

Prophase II

- Chromosomes begin to condense, nuclear membrane breaks down and spindle forms.

Metaphase II

- Spindle fibres attach to chromosomes, chromosomes align in cell centre.

Anaphase II

- Chromosomes separate and move to the opposite poles of the cell.

Telophase II

- Chromosomes reach spindle pole ends and the nuclear membrane reforms.

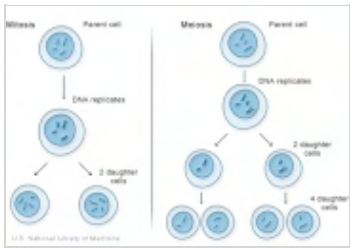
Cytokinesis

Cellular cytoplasmic division to form new cells.

Comparison of Meiosis/Mitosis

McGraw-Hill Animation comparing Mitosis and Meiosis (http://highered.mcgraw-hill.com/olcweb/cgi/pluginpop.cgi?it=swf::535::535::/sites/dl/free/0072437316/120074/bio17.swf::Comparison%20of%20Meiosis%20and%20Mitosis)

- After DNA replication 2 nuclear (and cell) divisions required to produce haploid gametes
- Each diploid cell in meiosis produces 4 haploid cells (sperm) 1 haploid cell (egg)
- Each diploid cell mitosis produces 2 diploid cells



Comparison of Mitosis and Meiosis

Meiosis Differences

Female - Oogenesis

The Cell - Figure 14.37. Meiosis of vertebrate oocytes (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=cooper.figgrp.2492)

- Meiosis initiated once in a finite population of cells
- 1 gamete produced / meiosis
- Completion of meiosis delayed for months or years
- Meiosis arrested at 1st meiotic prophase and reinitiated in a smaller population of cells
- Differentiation of gamete occurs while diploid in first meiotic prophase
- All chromosomes exhibit equivalent transcription and recombination during meiotic prophase

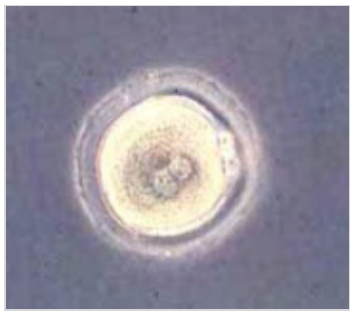
Male - Spermatogenesis

MBoC - Figure 20-27. The stages of spermatogenesis (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3734)

- Meiosis initiated continuously in a mitotically dividing stem cell population
- 4 gametes produced / meiosis
- Meiosis completed in days or weeks
- Meiosis and differentiation proceed continuously without cell cycle arrest
- Differentiation of gamete occurs while haploid after meiosis ends
- Sex chromosomes excluded from recombination and transcription during first meiotic prophase

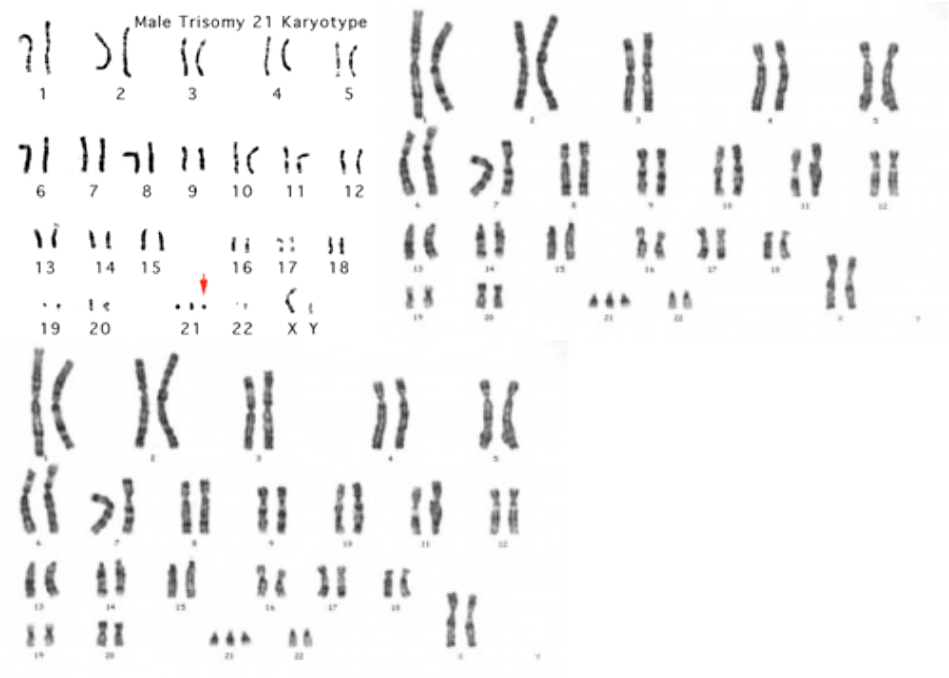
Polar Bodies

- In female gametogenesis only a single (1) haploid egg is produced from meiosis. In male gametogenesis four (4) haploid sperm are produced from meiosis. So what happens to all the extra DNA in producing this single egg?
  - In Meiosis 1 the "extra" DNA is excluded to the periphery as a 1st polar body, which encloses the extra DNA.
  - In Meiosis 2 the "extra" DNA is once again excluded as a 2nd polar body. The first polar body may also under go meiosis 2 producing a 3rd polar body.
- These polar bodies are not gametes.
- Polar bodies appear to have no other function other than to dispose of the extra DNA in oogenesis.
  - Recent research in mice suggest that the position of oocyte polar body may influence fertilization site.



Early zygote showing polar bodies

Abnormalities



- The most common chromosome abnormality is **aneuploidy**, the gain or loss of whole chromosomes.
- Caused by **meiotic nondisjunction**, the failure of chromosomes to correctly separate homologues during meiosis I or sister chromatids during meiosis II.
- Down Syndrome - caused by an extra copy of chromosome 21. Abnormal Development - Trisomy 21 (Down Syndrome) (http://embryology.med.unsw.edu.au/Defect/page21.htm)

- **Chromosomal translocations** occur when there is an inappropriate exchange of chromosomal material. Philadelphia chromosome (http://visualsonline.cancer.gov/retrieve.cfm?imageid=7153&dpi=72&fileformat=jpg)
- Philadelphia chromosome - piece of Chr9 exchanged with Chr22 Generates truncated abl, overstimulates cell production, leads to chronic myelogenous leukemia

Fertilization

MH - Gamete formation, menstrual cycle and fertilization will also be covered in this week's Laboratory. We may not complete all content shown below within the lecture.

Fertilization is the complete process resulting in the fusion of haploid gametes, egg and sperm, to form the diploid zygote. The recent development of aided fertilization is described as in vitro fertilization (in vitro = "in glass", outside the body, IVF). Clinically, all these aided fertilization techniques are grouped as Assisted Reproductive Technologies or ART.

UNSW Embryology Links: Week 1 - Spermatogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3b.htm) | Week 1 - Oogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3a.htm) | Week 1 - Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5.htm) | In Vivo Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5a.htm) | In Vitro Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5b.htm)

Fertilization Preparation

Prior to the fertilization process commencing both the gametes oocyte (egg) and spermatozoa (sperm) require completion of a number of biological processes.

- **Oocyte Meiosis** - completes Meiosis 1 and commences Meiosis 2 (arrests at Metaphase II).
- **Spermatozoa Capacitation** - following release (ejaculation) and mixing with other glandular

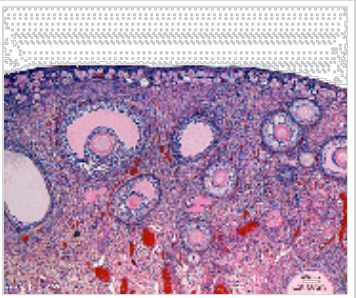
secretions, activates motility and acrosome preparation.
- **Migration** - both Oocyte and Spermatozoa.
  - oocyte ovulation and release with associated cells, from ovary into fimbria then into uterine tube (oviduct, uterine horn, fallopian tube) and epithelial cilia mediated movement.
  - spermatozoa ejaculation, deposited in vagina, movement of tail to "swim" in uterine secretions through cervix, uterine body and into uterine tube, have approximately 24-48h to fertilize oocyte.

Endocrinology - Diagram of the comparative anatomy of the male and female reproductive tracts (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972&rendertype=box&id=A1230)

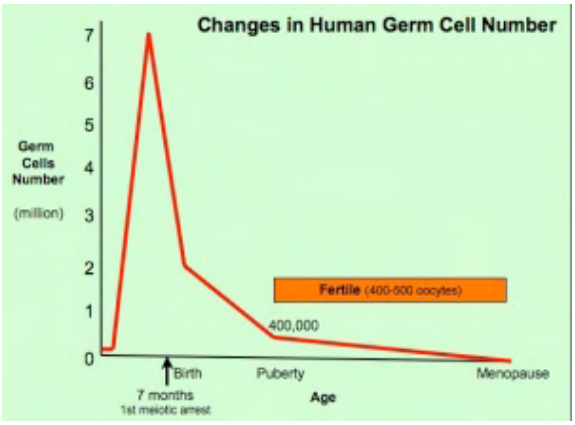
Oogenesis

Week 1 - Oogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3a.htm)

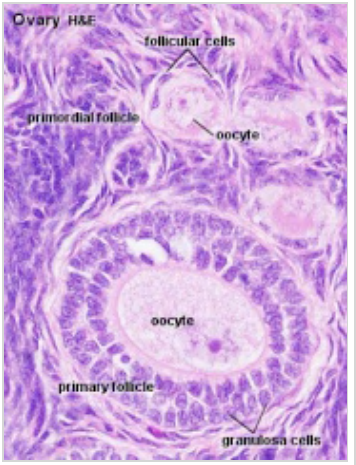
- Process of oogonia mature into oocytes (ova, ovum, egg)
- all oogonia form primary oocytes before birth, therefore a maturation of preexisting cells in the female gonad, ovary



Histology of the Ovary



- humans usually only 1 ovum released every menstrual cycle (IVF-superovulation)
- oocyte and its surrounding cells = follicle
- primary -> secondary -> ovulation releases



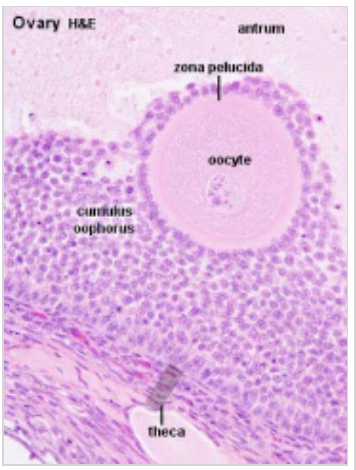
Preantral Follicle

Ovary- Histology - whole transverse section (cortex, medulla)

Menstrual Cycle

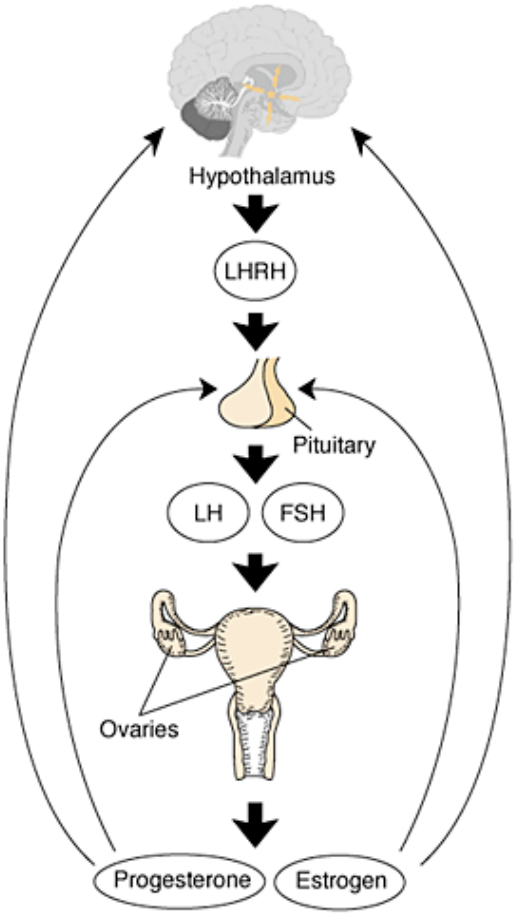
- Primary Oocyte - arrested at early Meiosis 1
  - diploid: 22 chromosome pairs + 1 pair X chromosomes (46, XX)
  - autosomes and sex chromosome

- Oogenesis- pre-antral then antral follicle (Graafian follicle is mature antral follicle released)
- Secondary oocyte
  - 1 Day before ovulation completes (stim by LH) Meiosis 1
  - haploid: 22 chromosomes + 1 X chromosome (23, X)
  - nondisjunction- abnormal chromosome segregation
  - begins Meiosis 2 and arrests at metaphase
  - note no interphase replication of DNA, only fertilization will complete Meiosis 2



Antral Follicle and Oocyte

Ovulation (HPG Axis)



- Hypothalmus releases gonadotropin releasing hormone (GRH, luteinizing hormone–releasing hormone, LHRH) -> Pituitary releases follicle stimulating hormone (FSH) and lutenizing hormone (LH) -> ovary follicle development and ovulation.
  - release of the secondary oocyte and formation of corpus luteum
  - secondary oocyte encased in zona pellucida and corona radiata
- Ovulation associated with follicle rupture and ampulla movement.

Zona Pellucida

MBoC - Figure 20-21. The zona pellucida (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3722)

- glycoprotein shell ZP1, ZP2, ZP3
- mechanical protection of egg
- involved in the fertilization process
- sperm binding
- adhesion of sperm to egg
- acrosome reaction
  - releases enzymes to locally breakdown
- block of polyspermy
  - altered to prevent more than 1 sperm penetrating
  - may also have a role in development of the blastocyst

Corona Radiata

- granulosa cells and extracellular matrix
- protective and nutritional role for cells during transport
- cells are also lost during transport along oviduct

Gamete formation- Spermatogenesis

Week 1 - Spermatogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3b.htm)

- process of spermatagonia mature into spermatazoa (sperm)
- continuously throughout life occurs in the seminiferous tubules in the male gonad- testis (plural testes)
- at puberty spermatagonia activate and proliferate (mitosis)
- primary spermatocyte -> secondary spermatocyte-> spermatid->sperm
- Seminiferous Tubule is site of maturation involving meiosis and spermiogenesis

- Spermatogenesis- Meiosis
- meiosis is reductive cell division
    - 1 spermatagonia (diploid) 46, XY (also written 44+XY) = 4 sperm (haploid); 23, X 23, X 23, Y 23, Y

Spermiogenesis

- morphological (shape) change from round spermatids to elongated sperm
- loose cytoplasm
- Transform golgi apparatus into acrosome (in head)
- Organize microtubules for motility (in tail, flagellum)
- Segregate mitochondria for energy (in tail)

Ejaculate

- By volume <10 % sperm and accessory glands contribute majority of volume (60 % seminal vesicle, 10 % bulbourethral, 30 % prostate)
- 3.5 ml, 200-600 million sperm
- Capacitation is the removal of glycoprotein coat and seminal proteins and alteration of sperm mitochondria
- Infertility can be due to Oligospermia, Azoospermia, Immotile Cilia Syndrome
    - Oligospermia (Low Sperm Count) - less than 20 million sperm after 72 hour abstinence from sex
    - Azoospermia (Absent Sperm) - blockage of duct network
    - Immotile Cilia Syndrome - lack of sperm motility

Fertilization Site

- Fertilization usually occurs in first 1/3 of oviduct
- Fertilization can also occur outside oviduct, associated with In Vitro Fertilization (IVF, GIFT, ZIFT...) and ectopic pregnancy
- The majority of fertilized eggs do not go on to form an embryo

Fertilization - Spermatozoa

- **Sperm Binding** - zona pellucida protein ZP3 acts as receptor for sperm
- **Acrosome Reaction** - exyocytosis of acrosome contents (Calcium mediated) MBoC - Figure 20-31. The acrosome reaction that occurs when a mammalian sperm fertilizes an egg (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mboc4.figgrp.3741)
    - enzymes to digest the zona pellucida
    - exposes sperm surface proteins to bind ZP2
- **Membrane Fusion** - between sperm and egg, allows sperm nuclei passage into egg cytoplasm

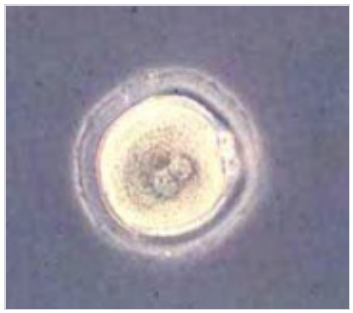
Fertilization- Oocyte

- **Membrane Depolarization** - caused by sperm membrane fusion, primary block to polyspermy
- **Cortical Reaction** - IP3 pathway elevates intracellular Calcium, exocytosis of cortical granules MBoC - Figure 20-32. How the cortical reaction in a mouse egg is thought to prevent additional sperm from entering the egg (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mboc4.figgrp.3743)
    - enzyme alters ZP3 so it will no longer bind sperm plasma membrane
- **Meiosis 2** - completion of 2nd meiotic division

- forms second polar body (a third polar body may be formed by meiotic division of the first polar body)

Formation of the Zygote

- Pronuclei - Male and Female haploid nuclei approach each other and nuclear membranes break down
- chromosomal pairing, DNA replicates, first mitotic division



Early human zygote showing Pronuclei

- Sperm contributes - centriole which organizes mitotic spindle
- Oocyte contributes - mitochondria (maternally inherited)

Sex Determination

- based upon whether an X or Y carrying sperm has fertilized the egg, should be 1.0 sex ratio.
- actually 1.05, 105 males for every 100 females, some studies show more males 2+ days after ovulation.
- cell totipotent (equivalent to a stem cell, can form any tissue of the body)

Men - Y Chromosome

- Y Chromosome carries Sry gene, protein product activates pathway for male gonad (covered in genital development)

Women - X Chromosome

- Gene dosage, one X chromosome in each female embryo cell has to be inactivated
- process is apparently random and therefore 50% of cells have father's X, 50% have mother's X
- Note that because men only have 1 X chromosome, if abnormal, this leads to X-linked diseases more common in male that female where bothe X's need to be abnormal.

UNSW Embryology Links

- Lecture 2 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture02.htm)
- Week 1 - Spermatogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3b.htm)
- Week 1 - Oogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3a.htm)
- Week 1 - Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5.htm) | In Vivo Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5a.htm) | In Vitro Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5b.htm)
- Abnormal Development - Trisomy 21 (Down Syndrome) (http://embryology.med.unsw.edu.au/Defect/page21.htm)
- ANAT3231 Cell Division (http://php.med.unsw.edu.au/cellbiology/index.php?title=2009_Lecture_16)

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Chapter 2
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 1

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000Figure 2.9. Summary of meiosis (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=meiosis&rid=dbio.figgrp.200) | fusion of egg and sperm plasma membranes

(http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.1360)

- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 - IV. Internal Organization of the Cell Chapter 17. The Cell Cycle and Programmed Cell Death Programmed Cell Death (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.chapter.3167) | An Overview of the Cell Cycle (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.section.3169) | Figure 17-1. The cell cycle (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.figgrp.3168) | Fertilization (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.section.3738)
- **Molecular Cell Biology** by Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James E. New York: W. H. Freeman & Co.; c1999 Chapter 13. Regulation of the Eukaryotic Cell Cycle Regulation of the Eukaryotic Cell Cycle (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mcb.chapter.3432) | Overview of the Cell Cycle and Its Control (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mcb.section.3463) | Figure 13-2. Current model for regulation of the eukaryotic cell cycle (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mcb.figgrp.3467) | **Movies** Proposed alternative mechanisms for chromosome congression. (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mcb.figgrp.5522) | Centromeric attachment of microtubules. (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mcb.figgrp.5509) | The stages of mitosis and cytokinesis in an animal cell. (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mcb.figgrp.5500)

- **The Cell - A Molecular Approach** by Cooper, Geoffrey M. Sunderland (MA): Sinauer Associates, Inc.; c2000- IV. Cell Regulation Chapter 14. The Cell Cycle The Eukaryotic Cell Cycle (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=cooper.section.2433) | Figure 14.1. Phases of the cell cycle (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=cooper.figgrp.2435) | Figure 14.32. Comparison of meiosis and mitosis (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=cooper.figgrp.2486) | Figure 14.37. Meiosis of vertebrate oocytes (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=cooper.figgrp.2492)
- **HSTAT** - In Vitro Fertilization As A Medical Treatment For Male or Female Infertility (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=hstat6.section.1395#1396)

Search

- **Bookshelf** cell division (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=cell+division) | mitosis (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=mitosis) | meiosis (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=meiosis) | fertilization (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=fertilization)

- **Pubmed** cell division (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=cell+division) | mitosis (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=mitosis) | meiosis (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=meiosis) | fertilization (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=fertilization)

Reviews

- Cell cycle studies based upon quantitative image analysis. Stacey DW, Hitomi M. Cytometry A. 2008 Apr;73(4):270-8. Review. PMID: 18163464 (http://www.ncbi.nlm.nih.gov/pubmed/18163464)
- Analysis of cell cycle phases and progression in cultured mammalian cells. Schorl C, Sedivy JM. Methods. 2007 Feb;41(2):143-50. Review. PMID: 17189856 (http://www.ncbi.nlm.nih.gov/pubmed/17189856)

Articles

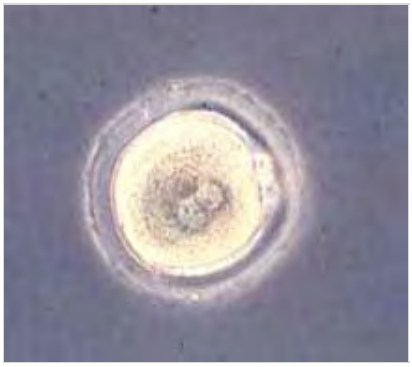
External Links

- JCB - Movie Collection Mitosis (http://jcb.rupress.org/misc/annotatedvideo.shtml#Mitosis) |

2009 Lecture 3

From Embryology

Contents



Early zygote showing polar bodies

Week 1 and 2

Introduction

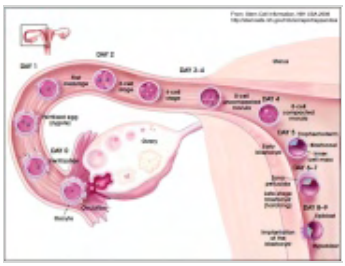
Following fertilization the first week is a series of rapid cell divisions, still contained within the zona pellucida, and still floating and being propelled within the uterine tube towards the uterine body. At the end of the first week and within the second week the process of implantation and early differentiation of cells that will form the embryo and the placenta.

Human Development Overview (http://embryology.med.unsw.edu.au/Movies/human_dev/human_dev.mov)

- **Lectopia Lecture Audio** Lecture Date: 03-08-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Week 1 and 2 (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48824)

Lecture Overview

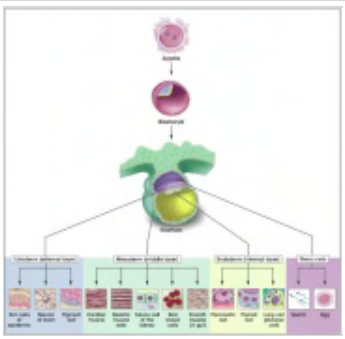
- Week 1-2 of human development
- Fertilization options - In vitro fertilization
- Zygote, Morula, Blastocyst
- Cell layers - Trophoblast, Syncytiotrophoblast, Cytotrophoblast, Embryoblast
- Implantation - Normal, Ectopic, Uterine changes, Blastocyst implantation changes



Week 1 Human Development Overview

Fertilization Options

- Natural sex
- Artificial insemination of mother with father's sperm, with mother with donor sperm, with egg and sperm donors, using surrogate mother
- In vitro fertilization (IVF) using egg and sperm of parents
  - Intra-Cytoplasmic Sperm Injection (ICSI), frozen embryos, pre-implantation Genetic Diagnosis (PGD), egg donor, sperm donor, egg and sperm donor, surrogate using parents' egg and sperm, surrogate and egg donor, surrogate and sperm donor, surrogate using her egg and sperm from baby's father, surrogate using egg and sperm donors



Inner cell mass

Week 1 - Formation of Zygote

Pronuclear Fusion (http://embryology.med.unsw.edu.au/Movies/week1/pronuclear_fusion.mov) | Movie Parental Genomes (http://embryology.med.unsw.edu.au/Movies/week1/genome.htm)

- male and female pronuclei, 2 nuclei approach each other and nuclear membranes break down
- DNA replicates, first mitotic division
- sperm contributes centriole which organizes mitotic spindle

Conceptus - term refers to all material derived from this fertilized zygote and includes both the embryo and the non-embryonic tissues (placenta, fetal membranes).

Cleavage of Zygote

Early Cell Division Movie (http://embryology.med.unsw.edu.au/Movies/week1/earlydiv.htm) | Cell Cleavage (http://embryology.med.unsw.edu.au/Movies/week1/week1.mov)

- cleavage of zygote forms 2 blastomeres and is cleavage with no cytoplasm synthesis
  - special "embryonic" cell cycle S phases and M phases alternate without any intervening G1 or G2 phases (MSMSMSMS, adult MG1SG2) therefore individual cell volume decreases
- cell division is initially synchronous, then asynchronously
  - slow- centre cells, larger fast- peripheral cells

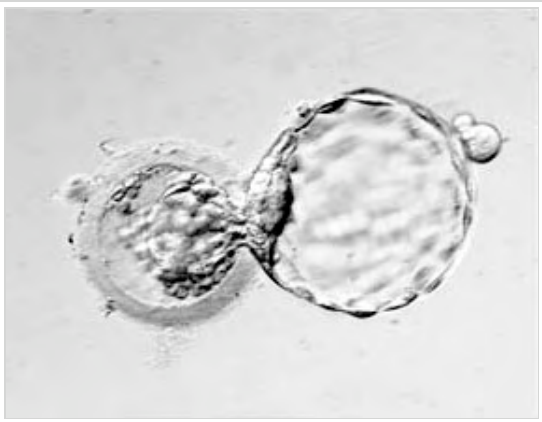
Morula

Early Cell Division Movie (http://embryology.med.unsw.edu.au/Movies/week1/earlydiv.htm) | Figure 8.19. Changes in DNA methylation during mammalian development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=hmg.figgrp.928)

- about **day 4** is a solid ball of 16-20 cells with peripheral cells flattened against zona pellucida
- compaction occurs forming a cavity and leading to the next blastocyst stage

Blastocyst

- about **day 5** have 2 identifiable cell types and a fluid-filled cavity (blastoceol)
  - **trophoblast layer** - peripheral flattened cells, forms the placenta and placental membranes
  - **inner cell mass** - embryoblast, mass of rounder cells located on one wall of the blastocoel, forms entire embryo



Hatching Blastocyst

Figure 21-69. The blastula (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3927) **Blastula Cell Communication** - two forms of cellular junctions

- gap junctions, allow electrically couple cells of epithelium surrounding a fluid-filled cavity
- tight junctions, close to outer surface create a seal, isolates interior of embryo from external medium

Blastocyst Hatching - zona pellucida lost, ZP has sperm entry site, and entire ZP broken down by uterine secretions and possibly blastula secretions. **Uterine Glands** - secretions required for blastocyst motility and nutrition

Week 2 - Implantation

Movie - Implantation (http://embryology.med.unsw.edu.au/Movies/week2/week2.mov) The second week of human development is concerned with the process of implantation and the differentiation of the blastocyst into early embryonic and placental forming structures.

- implantation commences about **day 6 to 7**
- **Adplantation** - begins with initial adhesion to the uterine epithelium
  - blastocyst then slows in motility, "rolls" on surface, aligns with the inner cell mass closest to the epithelium and stops
- **Implantation** - migration of the blastocyst into the uterine epithelium, process complete by about **day 9**
- **coagulation plug** - left where the blastocyst has entered the uterine wall **day 12**

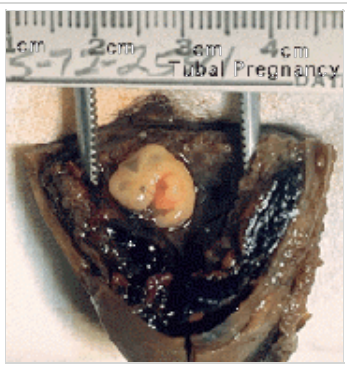
Normal Implantation Sites - in uterine wall superior, posterior, lateral

Abnormal Implantation

Ectopic Pregnancy (http://embryology.med.unsw.edu.au/Notes/week2_2.htm) | Movie - Ectopic pregnancy ultrasound (http://embryology.med.unsw.edu.au/Movies/usoundab/Ectopic1.htm)

Abnormal implantation sites or Ectopic Pregnancy occurs if implantation is in uterine tube or outside the uterus.

- sites - external surface of uterus, ovary, bowel, gastrointestinal tract, mesentry, peritoneal wall
- If not spontaneous then, embryo has to be removed surgically

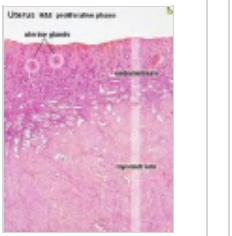


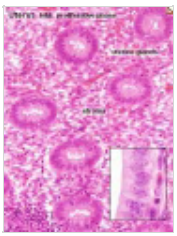
Ectopic tubal pregnancy

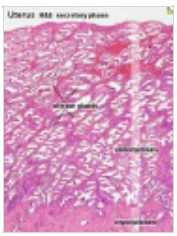
Tubal pregnancy - 94% of ectopic pregnancies

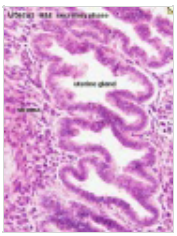
- if uterine epithelium is damaged (scarring, pelvic inflammatory disease)
- if zona pellucida is lost too early, allows premature tubal implantation
- embryo may develop through early stages, can erode through the uterine horn and reattach within the peritoneal cavity

Uterus


Uterus proliferative phase


Uterine gland proliferative phase


Uterus secretory phase


Uterine gland secretory phase

- Endometrium - 3 layers in secretory phase of menstrual cycle: compact, spongy, basal
- Myometrium - muscular layer outside endometrium, contracts in parturition
- Perimetrium - tunica serosa of the uterus continuous with the peritoneal wall

Endometrial Layers

- Compact - implantation occurs in this layer, dense stromal cells, uterine gland necks, capillaries of spiral arteries
- Spongy - swollen stromal cells, uterine gland bodies, spiral arteries
- Basal - not lost during menstruation or childbirth, own blood supply

Decidual Reaction

- occurs initially at site of implantation and includes both cellular and matrix changes
- reaction spreads throughout entire uterus, not at cervix
- deposition of fibrinoid and glycogen and epithelial plaque formation (at anchoring villi)
- presence of decidual cells are indicative of pregnancy

Cervix - at mouth of uterus, secretes mucus (CMP), forms a plug/barrier, mechanical and antibacterial
Vascular - increased number of blood vessels

Decidua

The endometrium becomes the decidua and forms 3 distinct anatomical regions (at approx 3 weeks)

- Decidua Basalis at implantation site
- Decidua Capsularis enclosing the conceptus
- Decidua Parietalis the remainder of uterus
    - Decidua Capsularis and Parietalis fuse eventually fuse and uterine cavity is lost by 12 weeks

Uterus Abnormalities

Endometriosis endometrial tissue located in other regions of the uterus or other tissues. This misplaced tissue develops into growths or lesions which respond to the menstrual cycle hormonal changes in the same way that the tissue of the uterine lining does; each month the tissue builds up, breaks down, and sheds. Endometriosis (http://embryology.med.unsw.edu.au/wwwhuman/mcycle/Mcycle.htm#Endometriosis)

Bilaminar Embryo

Week 2 Bilaminar Embryo (http://embryology.med.unsw.edu.au/Movies/week2/chorcav.mov)

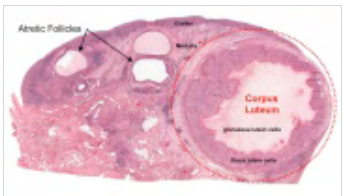
- about **day 8 to 9**

Pregnancy Test Kit

The outer trophoblast and inner embryoblast layers now both differentiate to form two distinct cellular layers. The trophoblast layer forms the syncitotrophoblast and cytotrophoblast layers. The embryoblast (inner cell mass) forms the epiblast and hypoblast layers. This early stage of embryo development is referred to as the bilaminar embryo.

Syncitiotrophoblasts

- secrete proteolytic enzymes, enzymes break down extracellular matrix around cells
- Allow passage of blastocyst into endometrial wall, totally surround the blastocyst
- generate spaces that fill with maternal blood- lacunae
- secrete Human Chorionic Gonadotropin (hCG), hormone, maintains decidua and Corpus Luteum, basis of pregnancy diagnostic test, present in urine is diagnostic of pregnancy
    - Later in development placenta will secrete hCG



Ovary corpus luteum

MH - more information in lecture 4 and laboratory.

Human Chorionic Gonadotropin

- levels peak at 8 to 10 weeks of pregnancy, then decline and are lower for rest of pregnancy

0-1 week: 0-50 mIU/ml
1-2 weeks: 40-300 mIU/ml
3-4 weeks: 500-6,000 mIU/ml
1-2 months: 5,000-200,000 mIU/ml
2-3 months: 10,000-100,000 mIU/ml
2nd trimester: 3,000-50,000 mIU/ml

3rd trimester: 1,000-50,000 mIU/ml

Non-pregnant females: <5.0 mIU/ml Postmenopausal females: <9.5 mIU/ml

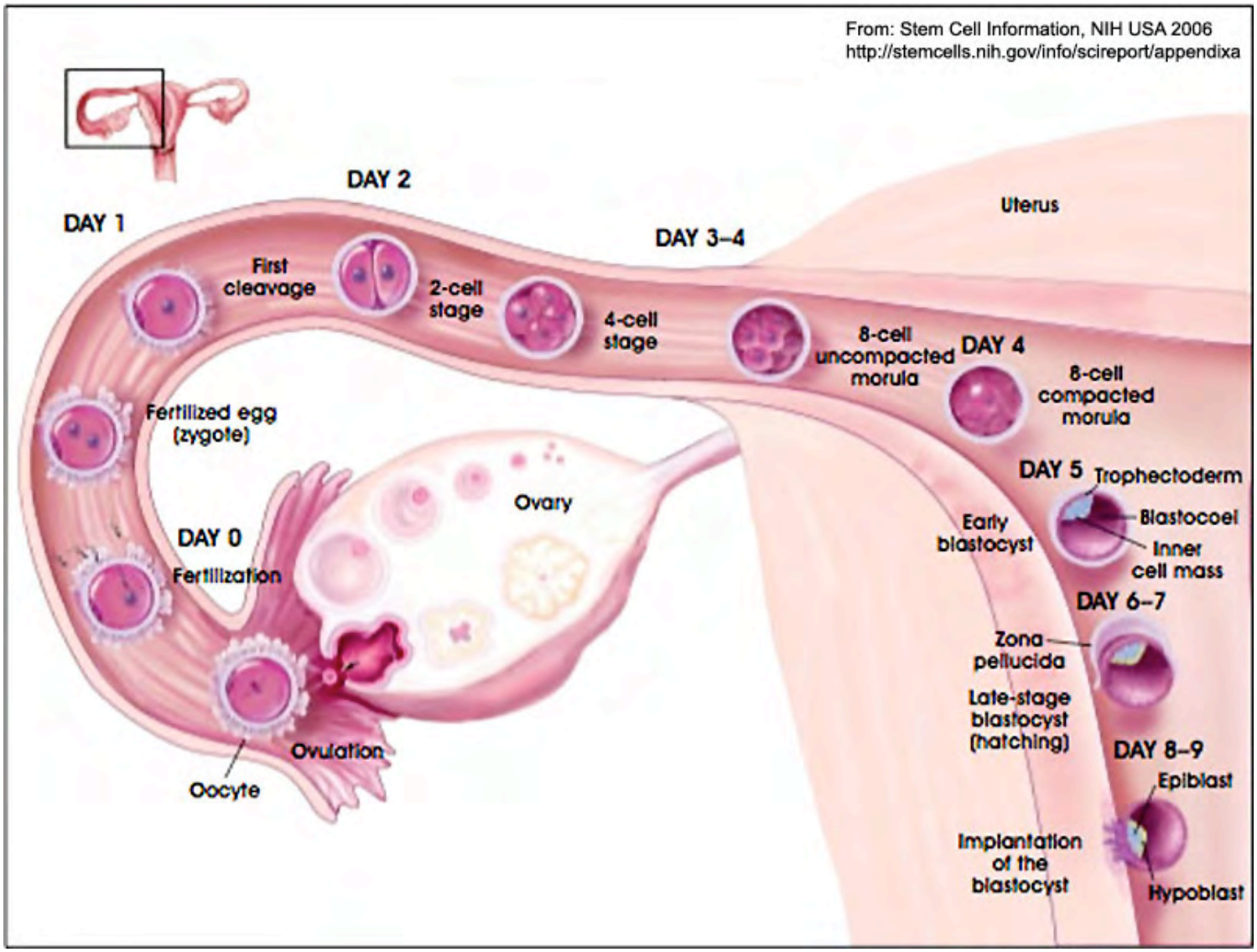
Twinning

Twinning can be due to two separate fertilization events (dizygotic twins) or as an abnormality of a single fertilization (monozygotic twins) event during the early weeks of development. Twinning (http://embryology.med.unsw.edu.au/Defect/twin.htm)

- In **dizygotic twinning** the genetic material is different and implantation and placentation is also different.
- In **monozygotic twinning** the genetic material is initially identical and degree of twinning will depend upon the timing (early to late) from separate fetal membranes and placenta to conjoined twins.
  - morula stage (diamniotic dichorionic), early blastocyst (diamniotic monochorionic), late blastocyst to bilaminar (monoamniotic monochorionic), bilaminar to trilaminar embryo (conjoined)
- Monozygotic twins are a unique research resource for comparing environmental effects on development and health.
- Congenital abnormality statistics for twins is generally increased in various conditions.

MH - twinning will be covered in more detail in this weeks laboratory.

Week 1 Human Development Overview



Movies


Ovulation


Fertilization


Pronuclear Fusion


Week 1

UNSW Embryology Links

- **Week 1 and 2 Slides** Lecture 3 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture03.htm) | Lecture 3 2008 Slides (http://embryology.med.unsw.edu.au/pdf/ANAT2341L3Week1s1.pdf)
- **Week 1 and 2 Movies** Week 1 Movies (http://embryology.med.unsw.edu.au/Movies/week1.htm) | Pronuclear Fusion (http://embryology.med.unsw.edu.au/Movies/week1/pronuclear_fusion.mov) | Early Cell Division Movie (http://embryology.med.unsw.edu.au/Movies/week1/earlydiv.htm) | Cell Cleavage (http://embryology.med.unsw.edu.au/Movies/week1/week1.mov) | Implantation (http://embryology.med.unsw.edu.au/Movies/week2/week2.mov) | Week 2 Bilaminar Embryo (http://embryology.med.unsw.edu.au/Movies/week2/chorcav.mov) | Movie - Ectopic Pregnancy Ultrasound 1 (http://embryology.med.unsw.edu.au/Movies/usoundab/Ectopic1.htm) | Movie - Ectopic Pregnancy Ultrasound 2 (http://embryology.med.unsw.edu.au/Movies/usoundab/Ectopic1.htm) | Chorionic cavity (http://embryology.med.unsw.edu.au/Movies/week2/chorcav.mov)
- **Week 1 and 2 Notes** Gamete Formation (http://embryology.med.unsw.edu.au/Notes/week1_3.htm) | Oogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3a.htm) | Corpus Luteum (http://embryology.med.unsw.edu.au/Notes/week1_3d.htm) | Spermatogenesis (http://embryology.med.unsw.edu.au/Notes/week1_3b.htm) | Capacitation (http://embryology.med.unsw.edu.au/Notes/week1_3c.htm) | Cell division (http://embryology.med.unsw.edu.au/Notes/week1_4.htm) | Mitosis (http://embryology.med.unsw.edu.au/Notes/week1_4a.htm) | Meiosis (http://embryology.med.unsw.edu.au/Notes/week1_4b.htm) | Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5.htm) | In Vivo Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5a.htm) | In Vitro Fertilization (http://embryology.med.unsw.edu.au/Notes/week1_5b.htm) | Zygote (http://embryology.med.unsw.edu.au/Notes/week1_6.htm) | Genomes Parental Genome Organization (http://embryology.med.unsw.edu.au/Notes/week1_6.htm#Parental) | Chromosome Location (http://embryology.med.unsw.edu.au/Notes/week1_12.htm) | Blastocyst (http://embryology.med.unsw.edu.au/Notes/week1_7.htm) | Twinning (http://embryology.med.unsw.edu.au/Defect/twin.htm) | Ectopic Pregnancy (http://embryology.med.unsw.edu.au/Notes/week2_2.htm) | Male sex determination (http://embryology.med.unsw.edu.au/Notes/week1_8.htm) | X inactivation (http://embryology.med.unsw.edu.au/Notes/week1_9.htm) | Cloning Issues (http://embryology.med.unsw.edu.au/Notes/week1_10.htm) | Molecular (http://embryology.med.unsw.edu.au/Notes/week1_11.htm) | WWW Links (http://embryology.med.unsw.edu.au/Notes/week1_link.htm) | Prenatal Diagnosis (http://embryology.med.unsw.edu.au/Defect/page7.htm)

Internet Links

- Australian Twin Registry (http://www.twins.org.au/index.php?page=31)

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Chapter 2
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 2

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Figure 11.22. The cleavage of a single mouse embryo in vitro (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.2615) | Figure 11.25. Mouse blastocyst hatching from the zona pellucida (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.2618) | Figure 11.20. Development of a human embryo from fertilization to implantation (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=implantation&rid=dbio.figgrp.2612) | Figure 11.24. Implantation of the mammalian blastocyst into the uterus (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=blastocyst&rid=dbio.figgrp.2617)
- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 - Fertilization (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.section.3738) | Figure 21-84. Scanning electron micrographs of the early mouse embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3955) | Figure 21-69. The blastula (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3927)
- **Molecular Cell Biology** by Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James E. New York: W. H. Freeman & Co.; c1999 Chapter 13. Regulation of the Eukaryotic Cell Cycle
- **The Cell - A Molecular Approach** by Cooper, Geoffrey M. Sunderland (MA): Sinauer Associates, Inc.; c2000 Figure 14.37. Meiosis of vertebrate oocytes (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=cooper.figgrp.2492)
- **HSTAT** - In Vitro Fertilization As A Medical Treatment For Male or Female Infertility (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=hstat6.section.1395#1396)
- **Human Molecular Genetics 2** Strachan, Tom and Read, Andrew P. New York and London: Garland Science; c1999 Figure 8.19. Changes in DNA methylation during mammalian development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=morula&rid=hmg.figgrp.928)

Search

- **Bookshelf** blastocyst (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=blastocyst) | morula (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=morula) | implantation (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=implantation) | ectopic pregnancy (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=ectopic_pregnancy)

- **Pubmed** blastocyst (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=blastocyst) | implantation (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=implantation) | ectopic pregnancy (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=ectopic_pregnancy) |

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Original Glossary (http://embryology.med.unsw.edu.au/Notes/Index/Index.htm)

Course Content 2009

Embryology Introduction | Cell Division/Fertilization | Cell Division/Fertilization | **Week 1&2 Development** | Week 3 Development | Lab 2 | Mesoderm Development | Ectoderm, Early Neural, Neural Crest | Lab 3 | Early Vascular Development | Placenta | Lab 4 | Endoderm, Early Gastrointestinal | Respiratory Development | Lab 5 | Head Development | Neural Crest Development | Lab 6 | Musculoskeletal Development | Limb Development | Lab 7 | Kidney | Genital | Lab 8 | Sensory - Ear |

2009 Lecture 4

From Embryology

Contents

Week 3 Development

Introduction

This lecture will continue from the second week into the third week and discuss early placentation and gastrulation. Note that we will be covering only the early events of placentation and a later lecture will cover this topic in more detail.

- **Lectopia Lecture Audio**

Lecture Overview

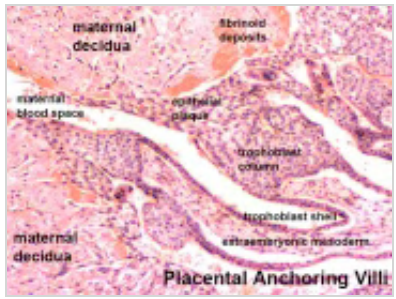
- Understand broadly the events of week 2-3 of human development
- Understand the process early placentation, villi formation
- Understand the process of gastrulation
- Understand the process of axis formation

Early Placentation

Movie - Implantation (http://embryology.med.unsw.edu.au/Movies/week2/week2.mov)

The trophoblast layer has now differentiated into two morphologically distinct cellular layers.

- **Syncitiotrophoblast**s - form a multinucleated cytoplasmic mass by cytotrophoblast cell fusion and both invade the decidua and secrete hCG
- **Cytotrophoblasts** - form a cellular layer around the blastocyst, proliferates and extends behind syncitiotrophoblasts



Early placenta anchoring villi

Early Utero-Placental exchange - transfer of nutrition from maternal lacunae filled with secretions from uterine glands and maternal blood from blood vessels. The development of trophoblast villi extending into the uterine decidua.

There are three stages of villi development:

- Primary Villi - cytotrophoblast
- Secondary Villi - cytotrophoblast + extraembryonic mesoderm

- Tertiary Villi - cytotrophoblast + extraembryonic mesoderm+ blood vessels

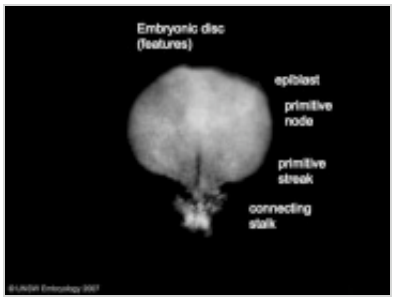
There are two main types of early villi:

- Anchoring villi - attached to decidua
- Floating villi - not attached to decidua, floating in maternal lacunae.

Gastrulation

Movie - Gastrulation (http://embryology.med.unsw.edu.au/Movies/larsen/gast.mov)

Gastrulation, (Greek = belly) means the formation of gut, but has been used in a more looser sense to to describe the formation of the trilaminar embryo. The epiblast layer, consisting of totipotential cells, derives all 3 embryo layers: endoderm, mesoderm and ectoderm. The primitive streak is the visible feature which represents the site of cell migration to form the additional layers.



Embryonic Disc showing primitive streak

Historically, gastrulation was one of the earliest observable morphological event occurring in the frog embryo. Currently, the molecular and physical mechanisms that regulate patterning and migration during this key event are being investigated in several different animal models. In humans, it is proposed that similar mechanisms regulate gastrulation to those found in other vertebrates.

- **primitive node** - region in the middle of the early embryonic disc epiblast from which the primitive streak extends caudally (tail)
  - nodal cilia establish the embryo left/right axis
  - axial process extends from the nodal epiblast
- **primitive streak** - region of cell migration from the epiblast layer forming sequentially the two germ cell layers (endoderm and mesoderm)

Epithelial to Mesenchymal Transition

Epithelial Mesenchymal Transition (http://embryology.med.unsw.edu.au/Notes/mechanism1.htm)

Epithelial cells (organised cellular layer) which loose their organisation and migrate/proliferate as a mesenchymal cells (disorganised cellular layers) are said to have undergone an Epithelial Mesenchymal Transition (EMT). Mesenchymal cells have an embryonic connective tissue-like cellular arrangement, that have undergone this process may at a later time and under specific signaling conditions undergo the opposite process, mesenchyme to epithelia. In development, this process can be repeated several times during tissue differentiation.

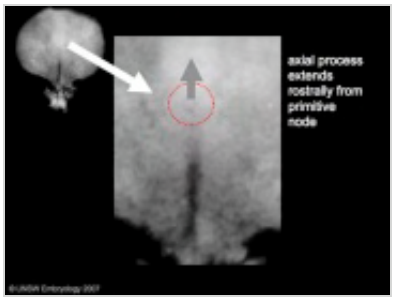
This process occurs at the primitive streak where epiblast cells undergo an epithelial to mesenchymal transition in order to delaminate and migrate.

MH - there are a number of common cellular changes that occur during embryonic development at different times and in different tissues, which we can classify into "developmental mechanisms". Mechanisms (http://embryology.med.unsw.edu.au/Notes/mechanism.htm)

Notochord

Movie - notochord 1 (http://embryology.med.unsw.edu.au/Movies/larsen/notoch.mov) | - notochord 2 (http://embryology.med.unsw.edu.au/Movies/larsen/noto.movMovie)

The notochord is a structure which has an early mechanical role in embryonic disc folding and a major signaling role in patterning surrounding embryonic tissue development. This signaling role patterns many different tissues (neural plate, neural tube, somites, endodermal organs). It has its own sequence of development from a primitive axial process and is a developmental feature not present in the adult anatomy.



Stage7 axial process

- **axial process** an initial epiblast hollow epithelial tube which extends in the midline from the primitive pit, cranially in the embryonic disc (toward the oral membrane).
    - **neuroenteric canal** is a transient communication between the amnionic cavity and the yolk sac cavity formed by the axial process.
- **notochordal plate** forms from the axial process merging with the endoderm layer.
- **notochord** forms from the notochordal plate which then separates back into the mesoderm layer as a solid column of cells lying in the midline of the embryonic disc and running rostro-caudally (head to tail).
    - An alternate name for the notochord is "axial mesoderm".

MH - Much of our knowledge of this structure comes from the study of animal models of development.

UNSW Embryology Links

- **Week 3 Slides** Lecture 4 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture04.htm) | Lecture 4 2008 slides (http://embryology.med.unsw.edu.au/pdf/ANAT2341L3Week1s1.pdf)
- **Week 3 Movies** Movie - Implantation (http://embryology.med.unsw.edu.au/Movies/week2/week2.mov) | Movie - Gastrulation (http://embryology.med.unsw.edu.au/Movies/larsen/gast.mov) | Chorionic cavity (http://embryology.med.unsw.edu.au/Movies/week2/chorcav.mov) Movie - notochord 1 (http://embryology.med.unsw.edu.au/Movies/larsen/notoch.mov) | - notochord 2 (http://embryology.med.unsw.edu.au/Movies/larsen/noto.movMovie) | Extracoelomic cavity (http://embryology.med.unsw.edu.au/Movies/week2/exoves.mov) | Nodal Cilia Movement (http://embryology.med.unsw.edu.au/Movies/week3/week3NodeCilia.htm)
- **Week 3 Notes** Week 3 (http://embryology.med.unsw.edu.au/Notes/week3.htm) | Gastrulation (http://embryology.med.unsw.edu.au/Notes/week3_3.htm) | Trilaminar Embryo (http://embryology.med.unsw.edu.au/Notes/week3_4.htm) | Neural Tube Formation (http://embryology.med.unsw.edu.au/Notes/week3_5.htm) | Early Somite Formation (http://embryology.med.unsw.edu.au/Notes/week3_6.htm) | Developmental Mechanisms (http://embryology.med.unsw.edu.au/Notes/mechanism.htm) | Epithelial Mesenchymal Transition (http://embryology.med.unsw.edu.au/Notes/mechanism1.htm) | Molecular Development (http://embryology.med.unsw.edu.au/MolDev/MolDev.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/week3_2.htm) |

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- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 3

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- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Figure 11.22. The cleavage of a single mouse embryo in vitro (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.2615) | Figure 11.25. Mouse blastocyst hatching from the zona pellucida (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.2618) | Figure 11.20. Development of a human embryo from fertilization to implantation (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=implantation&rid=dbio.figgrp.2612) | Figure 11.24. Implantation of the mammalian blastocyst into the uterus (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=blastocyst&rid=dbio.figgrp.2617)
- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 - Fertilization (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.section.3738) | Figure 21-84. Scanning electron micrographs of the early mouse embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3955) | Figure 21-69. The blastula (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3927)
- **Molecular Cell Biology** by Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James E. New York: W. H. Freeman & Co.; c1999 Chapter 13. Regulation of the Eukaryotic Cell Cycle
- **The Cell - A Molecular Approach** by Cooper, Geoffrey M. Sunderland (MA): Sinauer Associates, Inc.; c2000 Figure 14.37. Meiosis of vertebrate oocytes (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=cooper.figgrp.2492)
- **HSTAT** - In Vitro Fertilization As A Medical Treatment For Male or Female Infertility (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=hstat6.section.1395#1396)
- **Human Molecular Genetics 2** Strachan, Tom and Read, Andrew P. New York and London: Garland Science; c1999 Figure 8.19. Changes in DNA methylation during mammalian development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=morula&rid=hmg.figgrp.928)

Search

- **Bookshelf** placentation (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=placentation) | placenta (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=placenta) | implantation (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=implantation) | gastrulation (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=gastrulation) | notochord (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=notochord)

- **Pubmed** placentation (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=placentation) | placenta (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=placenta) | implantation (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=implantation) | gastrulation (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=gastrulation) | notochord (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=notochord)

Movies

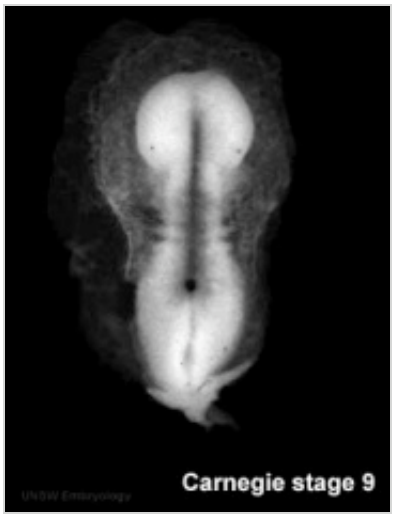
2009 Lecture 5

From Embryology

Contents

Mesoderm Development

Introduction



Carnegie stage 9 showing somite formation

We have seen the following processes during early human development so far: fertilization and blastocyst development in the first week, implantation in the second week, early placentation and bilaminar to trilaminar in the third week. In the third to fourth week we will now follow the development of the trilaminar embryo as each layer begins to differentiate into the primordia of different tissues within the embryo. From this point onward the lectures will not be in a strict timeline format as we will have to follow each layer (**ectoderm, mesoderm, endoderm**) forward through its early development, and then jump back to discuss the next layer.

This lecture will look at mesoderm development and formation of the body cavities.

Mesoderm means the "middle layer" and it is from this layer that nearly all the bodies connective tissues are derived. In early mesoderm development a number of transient structures will form and then be lost as tissue structure is patterned and organised. Humans are vertebrates, with a "backbone", and the first mesoderm structure we will see form after the notochord will be **somites**.

Carnegie stage 9 scanning electron microscope image showing somite formation

Coelom, meaning "cavity", and major fluid-filled cavities can be seen to form both within the embryo (intraembryonic coelom) and outside the embryo (extraembryonic coelom). The **intraembryonic coelom** is the single primitive cavity that lies within the mesoderm layer that will eventually form the 3 major anatomical body cavities (**pericardial, pleural, peritoneal**).

- **Lectopia Lecture Audio** Lecture Date: 10-08-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Mesoderm (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48825)

Objectives

- Understanding of events during the third week of development
- Understanding the process of notochord formation
- Understanding the process of early somite development
- Understanding the process of body cavity formation
- Understanding the future fate of mesoderm components
- Brief understanding of early heart formation

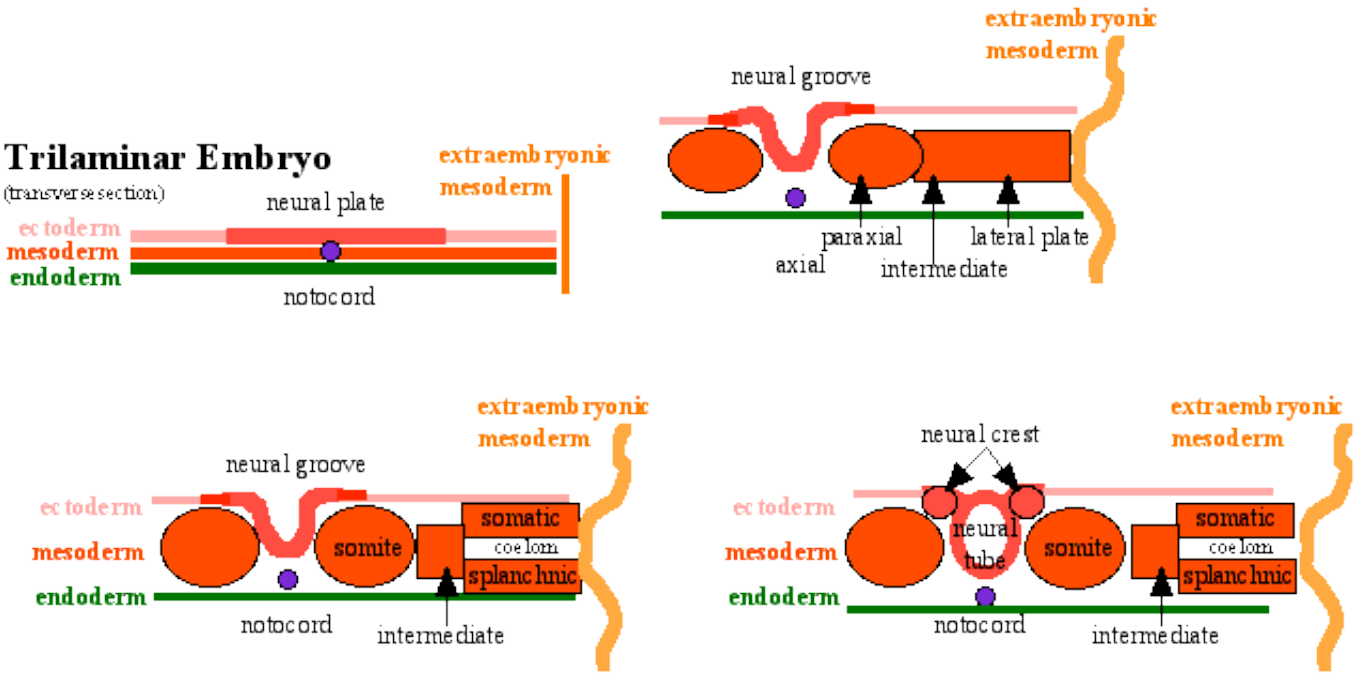
UNSW Embryology Links

- **Mesoderm Slides** Mesoderm Lecture 2008 - 1 slide/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L6Mesoderms1.pdf) | Lecture 3 2008 Slides - 4 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L6Mesoderms4.pdf) | Mesoderm Lecture 2008 Slides - 6 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L6Mesoderms6.pdf)

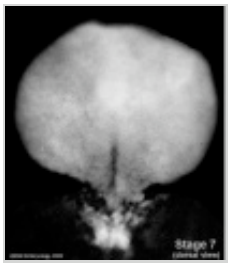
- **Mesoderm** Week 4 Movies (http://embryology.med.unsw.edu.au/Movies/week4.htm) | Mesoderm Movies (http://embryology.med.unsw.edu.au/Movies/mesoderm.htm) |
- **Mesoderm Notes** Week 4 (http://embryology.med.unsw.edu.au/Notes/week4.htm) | Week 4 - Somites (http://embryology.med.unsw.edu.au/Notes/week4_4.htm) | Coelomic Cavity Development (http://embryology.med.unsw.edu.au/Notes/coelom.htm) | Musculoskeletal Development (http://embryology.med.unsw.edu.au/Notes/skmus.htm) |

Lecture Summary

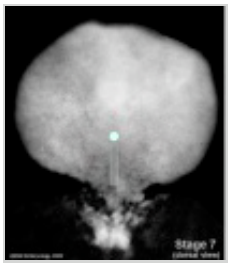
The following text is extracted and modified from 2008 lecture slides and should be used as a "trigger" to remind you of key concepts.



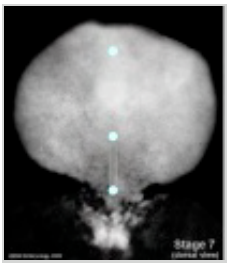
Notochord (Axial mesoderm)



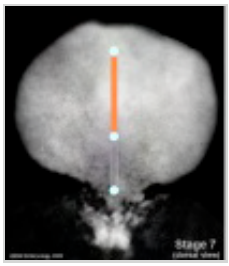
Stage 7 embryonic disc



Stage 7 primitive-streak-node



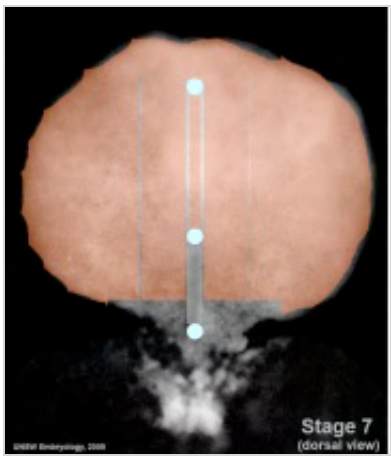
Stage 7 cloacal-oral-membranes



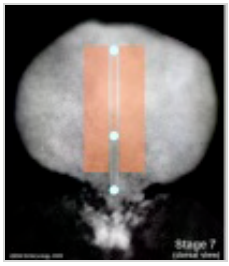
Stage 7 notochord

Mesoderm

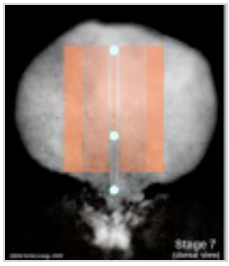
- generated from epiblast cells migrating through the primitive streak
- epiblast cells expressing fibroblast growth factor (FGF2)
- forms a layer between ectoderm and endoderm with notochord down midline
- present before neural tube formation
- divides initially into 3 components



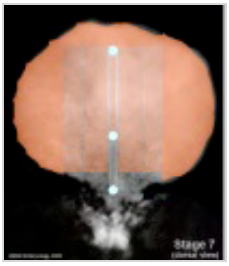
Stage 7 mesoderm



Stage 7 paraxial mesoderm

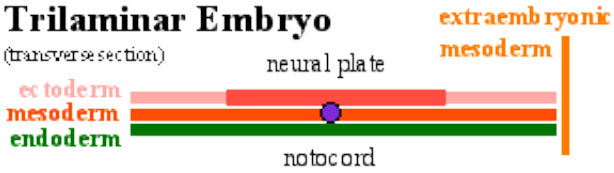


Stage 7 intermediate mesoderm



Stage 7 lateral plate

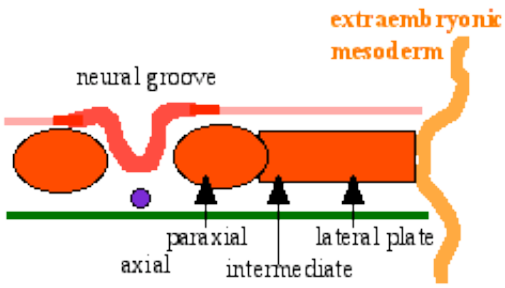
- Paraxial mesoderm - somites - musculoskeletal structures
- Intermediate mesoderm - kidney
- Lateral plate mesoderm - body wall structures



Mesenchyme

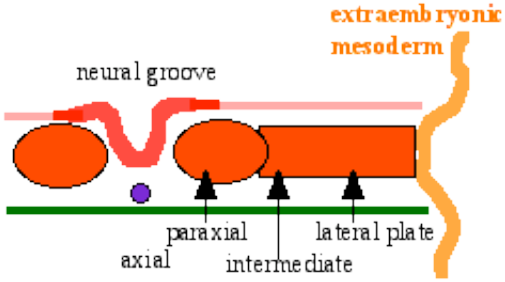
- Embryonic connective tissue, describes the cell morphology (Histology is not epithelial organization)
  - epithelial to mesenchymal transitions
  - mesenchymal to epithelial transitions

Paraxial Mesoderm



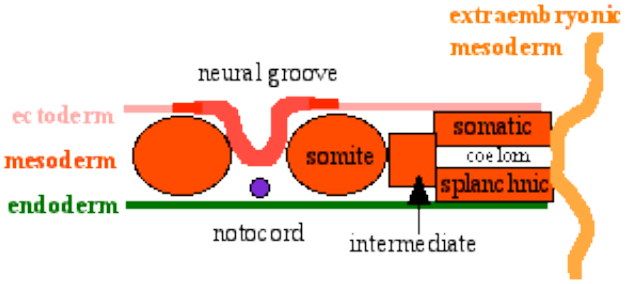
- lies adjacent to notochord
- Forms 2 components
  - Head - unsegmented paraxial mesoderm
  - Body - segmented paraxial mesoderm
- Generates trunk muscles, skeleton, dermis of skin, blood vessels, connective tissue
- Segmented Paraxial Mesoderm
  - segments called somites
  - first pair of somites (day 20)
  - segmentation imposes a pattern on
  - nerves, vasculature, vertebra....
  - somites appear in ordered sequence cranial to caudal
  - appearance so regular used to stage the embryo
  - Hamburger & Hamilton 1951- chicken
- thought to be generated by a "clock" (1 pair every 90 minutes)
- neural tube begins to close at 4th somite level
- 44 pairs of somites

Intermediate Mesoderm



- lies between paraxial and lateral mesoderm
- generates urogenital system
  - Wolffian duct, kidney
  - **MH** - covered in Kidney Development Lecture/Laboratory

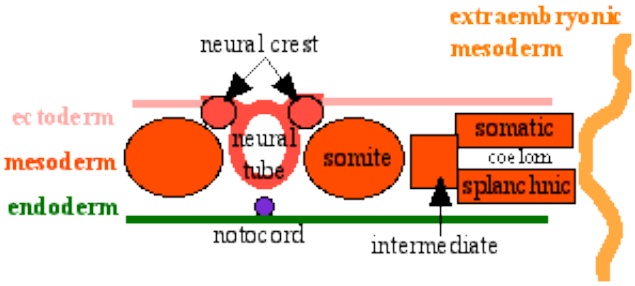
Lateral Plate Development



The intraembryonic coelom divides the lateral plate into 2 portions

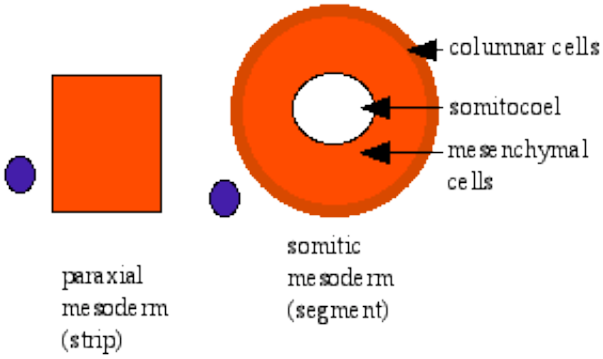
- **Somatic mesoderm**- closest to ectoderm
  - body wall osteogenic, chrondrogenic and fibrogenic
  - except ribs and scapula
- **Splanchnic mesoderm** - closest to endoderm
  - heart and smooth muscle of GIT and blood vessels

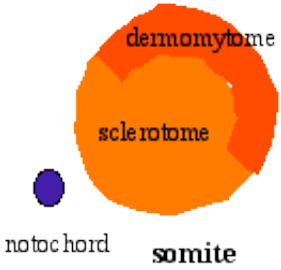
Intraembryonic Coelom

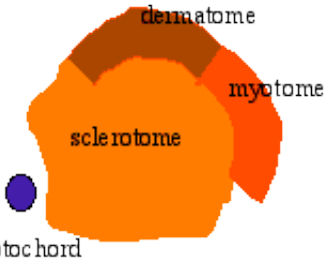


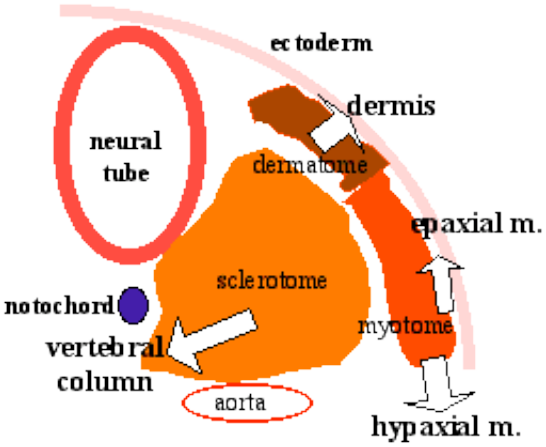
- small spaces (vacuoles) begin appearing within the lateral plate mesoderm
- small spaces enlarge forming a single cavity within the lateral plate mesoderm
  - divides into 2 parts at about day 18-19
- this cavity is called the **Intraembryonic Coelom**
  - coelom is a general term for a "cavity" and can lie within the embryo (intraembryonic) and outside the embryo (extraembryonic)
  - later anatomical spaces within the embryo and fetus can also be described as coeloms
- later when the embryonic disc folds the intraembryonic coelom in the lateral plate mesoderm will later form all 3 major body cavities
  - Pericardial
  - Pleural
  - Peritoneal

Somite Formation









Mesoderm Movies (http://embryology.med.unsw.edu.au/Movies/mesoderm.htm)

- ball forms through epithelialization and interactions (cell-cell, cell-extracellular matrix, ECM) fibronectin, laminin
- has 2 populations of cells - peripheral columnar and central mesenchymal
- early somite has cavity- somitocoel, cavity is lost during growth
- somite enclosed by ECM connected to nearby tissues

Somite Specification

- Different segmental level somites have to generate different segmental body structures?
- somite has to form different tissues?
- Somite Differentiation
- Compartmentalization accompanied by altered patterns of expression of Pax genes within the somite

Somite initially forms 2 main components

-
  - ventromedial- **sclerotome** forms vertebral body and intervertebral disc
  - dorsolateral - **dermomyotome** forms dermis and skeletal muscle

Somite Axial Specification

- rostro-caudal axis appears regulated by Pax/Hox expression, family of DNA binding transcription factors
- Movie: Somite Development

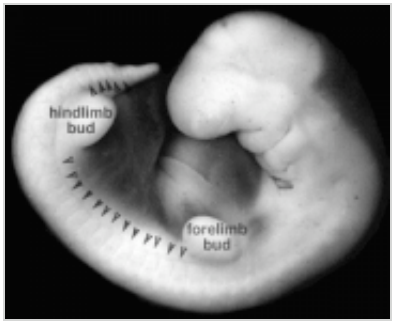
Sclerotome

- sclerotome later becomes subdivided
- rostral and caudal halves separated laterally by von Ebner's fissure
  - half somites contribute to a single vertebral level body
  - other half intervertebral disc

- therefore final vertebral segmentation ,"shifts"

Muscle

- Myoblast determining transcription factor MyoD is first expressed in the dorsomedial quadrant of the still epithelial somite whose cells are not yet definitely committed
  - basic Helix Loop Helix
  - form myotome
- Myotome component of Somite
  - epaxial myotome (dorsomedial quarter) forms the dorsal epimere (erector spinae)
  - hypaxial myotome (dorsolateral quarter) forms the ventral hypomere, 3 primary muscle layers which are different at neck, thorax and abdomen



Stage 14 Embryo showing somites and limb buds (Week 5)

- Chick Embryo Mesoderm
- Body Musculature - Myotome derivatives-mouse embryo
- Lateral Plate Mesoderm
- Limb Musculature
- Dermomyotome- Muscle (MyoD)
- MyoD Pax 3
- Somite Differentiation
  - migrating neural crest cells enter cranial half, will form dorsal root ganglia (DRG)
  - sclerotome bulges ventro-medially towards notochord, then surround and engulf notochord
    - not movement of sclerotome, growth of surrounding tissues
    - notochord forming nucleus pulposus of IVD

Dermomyotome

- lateral myotome edge migrates at level of limbs
- upper limb first then lower
- mixes with somatic mesoderm
- dermotome continues to contribute cells to myotome

Muscle Development Abnormalities

- Duchenne Muscular Dystrophy
  - Embryonic muscle development normal and changes occur postnatally
  - X-linked dystrophy, large gene encoding cytoskeletal protein - Dystrophin
  - progressive wasting of muscle, die late teens
- Becker Muscular Dystrophy, milder form, adult onset

Axial Segmentation - Somite Specification Signals

Chicken Model - Somite formation

- Somitomere to Somite
- Chicken Stages -regular appearance of somites allowed early experimenters to accurately stage the embryo
- Chicken
  - Advantages - accessible, easy to manipulate, limb grafts/removal, chimeras, developmental processes

    - taxon-Gallus gallus
    - develops and hatches in 20-21 days
    - Fertilized eggs easily maintained in humidified incubators
    - Embryo Staged growth
    - Series of Embryonic Chicken Growth
    - Hamburger & Hamilton J. Morphology, 88 49 - 92, 1951 [1] (http://embryology.med.unsw.edu.au/OtherEmb/chick1.htm)
- Zebrafish, Xenopus
- Paraxial Segmentation
- Stage 13/14 Embryo

Take the Quiz

1. Mesenchyme refers to the middle layer of the trilaminar embryo

- ○ true
- ○ false

2. The intraembryonic coelom forms within :

- ○ somites
- ○ lateral plate
- ○ neural tube
- ○ intermediate mesoderm

3. All paraxial mesoderm segments into somites.

- ○ true
- ○ false

4. Somites are developmental structures that contribute the following adult structures :

- ○ vertebra, notochord, dermis, skeletal muscle
- ○ vertebra, intervertebral discs, dermis, skeletal muscle
- ○ kidney, body wall connective tissue, sensory ganglia
- ○ kidney, gastrointestinal tract smooth muscle, mesentry

Submit

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Mesoderm Ch15,16: p405-423, 426-430 Body Cavities Ch9: p174-184
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Mesoderm Ch11 p311-339 Body Cavities Ch6 p127-146

Additional Textbooks

- Before We Are Born (5th ed.) Moore and Persaud Ch16,17: p379-397, 399-405
- Essentials of Human Embryology Larson Ch11 p207-228
- Human Embryology Fitzgerald and Fitzgerald Body Cavities Ch5 p29-32, Ch7 p47,48
- Human Embryology and Developmental Biology ?Carlson Ch9,10: p173-193, 209-222 Body Cavities Ch5 p29-32, Ch7 p47,48

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Paraxial Mesoderm: The Somites and Their Derivatives (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3455) | Lateral Plate Mesoderm (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=mesoderm&rid=dbio.section.3693) | Snapshot Summary: Paraxial and Intermediate Mesoderm (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=mesoderm&rid=dbio.section.3519) |

- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 - Figure 21-78. Somite formation in the chick embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3943) | Figure 21-34. Origin of the mesoderm from cells expressing twist (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3857)

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Movies


Mesoderm


Somite Structures


Vertebra

UNSW Embryology Links

2009 Lecture 6

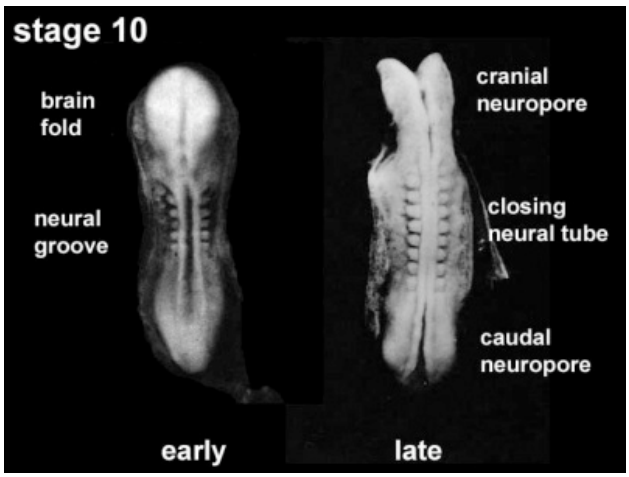
From Embryology

Contents

Ectoderm Development

Introduction

This lecture will cover the early development of the ectoderm layer of the trilaminar embryo. Note that we will be returning later to discuss neural (central nervous system; brain and spinal cord) and neural crest (peripheral nervous system; sensory and sympathetic ganglia). Epidermis (integumentary, skin contribution) development will be briefly mentioned due to its ectoderm origin, but will also be covered later in the current course.



- **Lectopia Lecture Audio** Lecture Date: 11-08-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Ectoderm

(http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48837)

Lecture Objectives

- Understanding of events during the third and fourth week of development
- Understanding the process of notochord formation
- Understanding the process of early neural development
- Brief understanding of neural crest formation
- Brief understanding of epidermis formation
- Understanding of the adult components derived from ectoderm
- Brief understanding of early neural abnormalities

Textbook References

- Human Embryology (3rd ed.) Chapter 5 p107-125
- The Developing Human: Clinically Oriented Embryology (6th ed.)

Other textbooks

- Moore and Persaud Chapter 18 p451-489
- Essentials of Human Embryology Larson Chapter 5 p69-79
- Before We Are Born (5th ed.) Moore and Persaud Chapter 19 p423-458

UNSW Embryology Links

- **Ectoderm Slides** Neural Lecture 5 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture05.htm) | Neural Lecture 2008 - 1 slide/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L5Neurals1.pdf) | Neural 2008 Slides - 4 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L5Neurals4.pdf) | Neural Lecture 2008 Slides - 6 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L5Neurals6.pdf)
- **Ectoderm Movies** Notochord (http://embryology.med.unsw.edu.au/Movies/larsen/notoch.mov) | Notochord (http://embryology.med.unsw.edu.au/Movies/larsen/noto.mov) | Neural Plate (http://embryology.med.unsw.edu.au/Movies/larsen/neuralplt.mov) | Neurulation (http://embryology.med.unsw.edu.au/Movies/larsen/neurul.mov) | Secondary Neurulation (http://embryology.med.unsw.edu.au/Movies/larsen/2neuro.mov)
- **Ectoderm Notes** Timeline - Embryonic Week 3 | Carnegie Stages | Stages - scanning electron micrographs (http://embryology.med.unsw.edu.au/wwwhuman/Stages/Stagesem.htmlCarnegie) | Neural Notes (http://embryology.med.unsw.edu.au/Notes/neuron.htm) | Neural Crest Notes (http://embryology.med.unsw.edu.au/Notes/ncrest.htm) | Neural Abnormalities (http://embryology.med.unsw.edu.au/Notes/neuron2.htm) | Integumentary Development (http://embryology.med.unsw.edu.au/Notes/skin.htm) | Folic Acid and Neural Tube Defects (http://embryology.med.unsw.edu.au/Defect/page5e.htm) | Week 3 (http://embryology.med.unsw.edu.au/Notes/week3.htm) |

Development Overview

Notochord

Movie - Notochord (http://embryology.med.unsw.edu.au/Movies/larsen/notoch.mov) | Movie - Notochord 2 (http://embryology.med.unsw.edu.au/Movies/larsen/noto.mov)

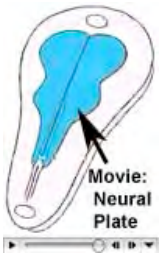
- forms initially as the Axial Process, a hollow tube which extends from the primitive pit , cranially to the oral membrane
- the axial process then allow transient communication between the amnion and the yolk sac through the neuroenteric canal.
- the axial process then merges with the Endodermal layer to form the Notochordal Plate.
- the notochordal plate then rises back into the Mesodermal layer as a solid column of cells which is the Notochord.

Ectoderm

- 2 parts
- midline neural plate
  - columnar
- lateral surface ectoderm
  - cuboidal
  - sensory placodes
  - epidermis of skin, hair, glands, anterior pituitary, teeth enamel

Neural Plate

Movie - Neural Plate (http://embryology.med.unsw.edu.au/Movies/larsen/neuralplt.mov)

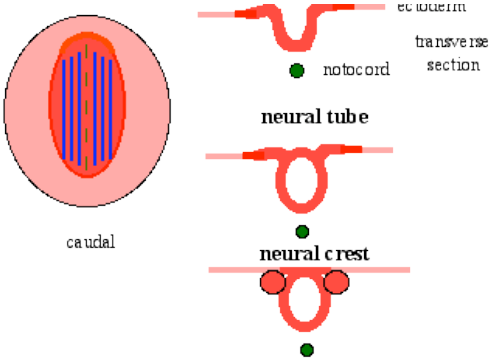


- extends from buccopharyngeal membrane to primitive node
- forms above notochord and paraxial mesoderm
- neuroectodermal cells
  - broad brain plate
  - narrower spinal cord
- 3 components form: floor plate, neural plate, neural crest

Neural Determination- neuronal populations are specified before plate folds

- signals from notochord and mesoderm - secrete noggin, chordin,follistatin

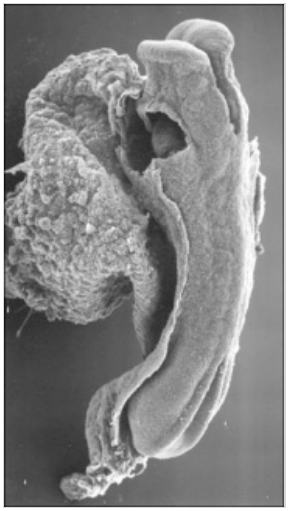
    - all factors bind BMP-4 an inhibitor of neuralation
    - bone morphogenic protein acts through membrane receptor
- lateral inhibition generates at spinal cord level 3 strips of cells
- expression of delta inhibits nearby cells, which express notch receptor, from becoming neurons
- Delta-Notch inetraction- generates Neural strips



Neural Groove

Movie - Neurulation (http://embryology.med.unsw.edu.au/Movies/larsen/neurul.mov)

- forms in the midline of the neural plate (day 18-19)
- either side of which are the neural folds which continues to deepen until about week 4
- neural folds begins to fuse, beginning at 4th somite level


Stage 11 neural groove to tube

Neural Tube

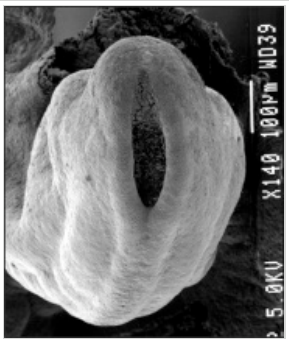
- the neural tube forms the brain and spinal cord
- fusion of neural groove extends rostrally and caudally
- begins at the level of 4th somite
- closes neural groove "zips up" in some species.
    - humans appear to close at multiple points along the tube.
- leaves 2 openings at either end - **Neuropores**
    - cranial neuropore closes before caudal

Failure for the neural tube to close correctly or completely results in a **neural tube defect**.

Secondary Neuralation

Movie - Secondary Neurulation (http://embryology.med.unsw.edu.au/Movies/larsen/2neuro.mov)

- caudal end of neural tube formed by secondary neuralation
- develops from primitive streak region
- solid cord canalized by extension of neural canal
- mesodermal caudal eminence



Stage 12 caudal neuropore

Neural Crest

Neural Crest Notes (http://embryology.med.unsw.edu.au/Notes/ncrest.htm)

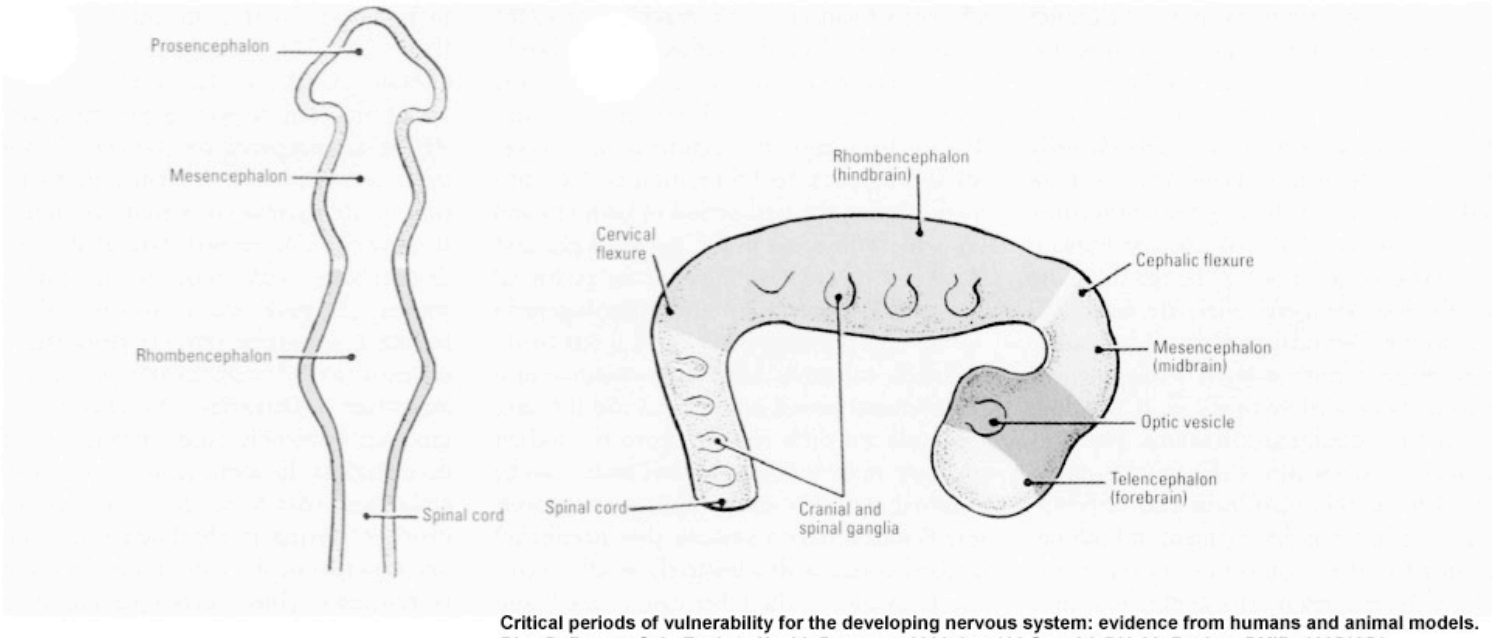
- a population of cells at the edge of the neural plate that lie dorsally when the neural tube fuses
    - dorsal to the neural tube, as a pair of streaks
    - pluripotential, forms many different types of cells
    - cells migrate throughout the embryo
    - studied by quail-chick chimeras
    - transplanted quail cells have obvious nucleoli compared with chicken

Neural Crest Derivitives

- dorsal root ganglia
- autonomic ganglia
- adrenal medulla
- drg sheath cells, glia
- pia-arachnoid sheath
- skin melanocytes
- connective tissue of cardiac outflow
- thyroid parafollicular cells
- craniofacial skeleton
- teeth odontoblasts

Early Brain Structure

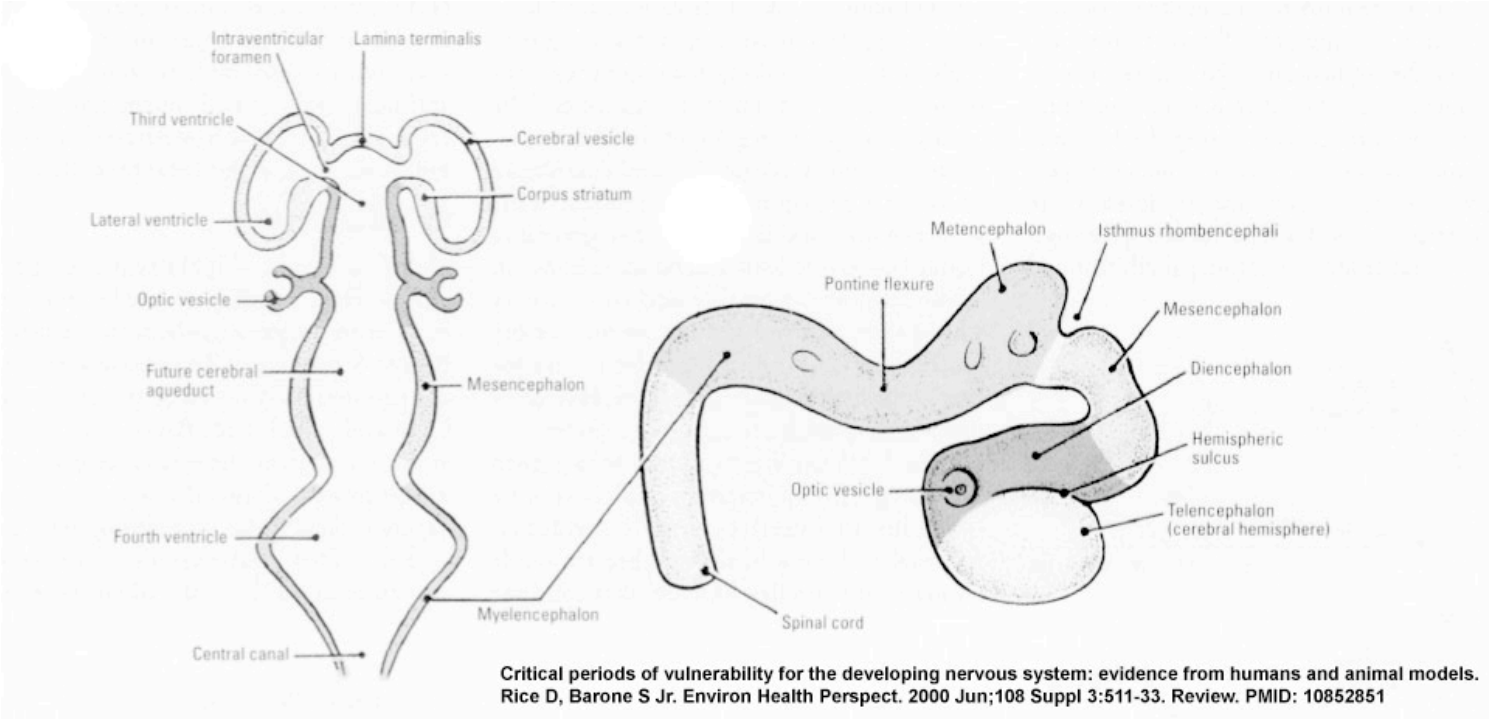
Primary Vesicles



Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Rice D, Barone S Jr. Environ Health Perspect. 2000 Jun;108 Suppl 3:511-33. Review. PMID: 10852851

- rostral neural tube forms 3 primary brain vesicles (week 4)
- 3 primary vesicles: **prosencephalon** (forebrain), **mesencephalon** (midbrain), **rhombencephalon** (hindbrain)

Secondary Vesicles



Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Rice D, Barone S Jr. Environ Health Perspect. 2000 Jun;108 Suppl 3:511-33. Review. PMID: 10852851

From the 3 primary vesicles developing to form 5 secondary vesicles

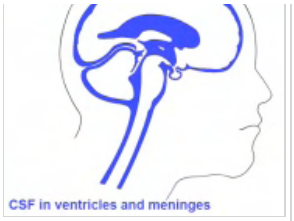
- prosencephalon- **telencephalon** (endbrain, forms cerebral hemispheres), **diencephalon** (betweenbrain, forms optic outgrowth)
- **mesencephalon**
- rhombencephalon- **metencephalon** (behindbrain), **myelencephalon** (medullabrain)

Ventricles

MH - this will be covered in detail in later neural development

- cavity within tube will form the contiguious space of the ventricules

of the brain and central canal of spinal cord
- this space is filled initially with amniotic fluid, later with CerebroSpinal Fluid (CSF)
- CSF is secreted by a modified vascular structure, the **chorioid plexus**, lying within the ventricles
  - (More? [Notes Chorioid Plexus (http://embryology.med.unsw.edu.au/Notes/neuron6.htm))



CNS ventricles

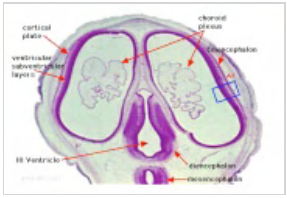
Brain Flexures

Rapid growth folds the neural tube forming 3 brain flexures

- **cervical flexure** - between brain stem and spinal cord
- **midbrain flexure** - pushes mesencephalon upwards
- **pontine flexure** - generates 4th ventricle

Neural Layers

- neural stem cells lie in the layer closest to the ventricular space, the **ventricular layer**
  - this layer generates both neuroblasts and glioblasts


Stage 22 developing head cross section

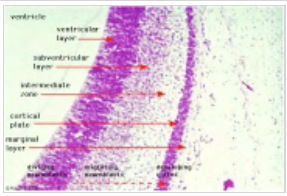
Neuroblasts - neurons arise first as neuroblasts and migrate along radial gial, their migration stops at cortical plate. **Glioblasts** - glia arise later as glioblasts

Both neurons and glia undergo a complex process of growth, differentiation and interaction over a long developmental time period.

Spinal Cord Axes

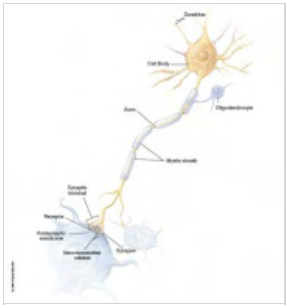
Identified by experimental manipulation of interactions.

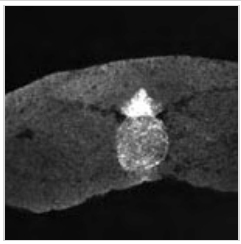
- Initial experiments looked at how isolated tissues may influence the development of the spinal cord.
- Repositionining of specific tissues both in vivo and in vitro
- specific markers of or alteration of differentiation. **Notocord Induction**


Stage 22 developing cortex

Ventral Axis

- Sonic Hedgehog (SHH) - notochord secretes sonic hedgehog
- Gene expression studies (ISH) showed shh gene expression occured in a subset of inducing tissues
- has a patterning role elsewhere (limb, sclerotome, lung)
- 2 signaling activities acting (locally and at a distance) Ventral- Sonic Hedgehog
- Binds to cell surface receptor patched
- without shh, patched (Ptc) binds smoothened (Smo)
- with shh shh-Ptc releases Smo activating G protein pathway **Gene Diseases**
- shh Human mutation- holoprosencephaly 3
  - characteristic faces of the severe form of HPE which included a single fused eye (cyclopia) and a nose-like structure (proboscis) above the eye
  - Downstream targets of Sonic hedgehog signalling:
    - transcription factors like Gli3 (responsible for Greigs polycephalosyndactyly in humans)
    - d Hoxd13 (responsible for polysyndactyly)


Neuron and supporting glial cells


Notochord secreting sonic hedgehog

Dorsal Axis

- Dorsalin - ectoderm secretes a growth factor shown to controls patterning in embryonic mesoderm (frog)
  - Transforming Growth factor beta, (TGF b), related factors BMP-2, BMP-4, BMP-7, radar (flies related protein determines dorsoventral)
  - homology search of vertebrate library identified protein of same family.
  - dorsalin-1 (dsl-1) (Basler, Cell 73, p687, 1993) Dorsalin-1
  - From overlying ectoderm
  - Naming comes from the obvious reason that it promotes the differentiation of neural crest cells.
  - Also signal for dorsal signal of neural tube.

- Inhibits the differentiation of motoneurons.
- Implication is that dsl-1 and shh act antagonistically, or competitively to establish d-v axis of neural tube.

Rostro-Caudal Axis

- Brain rostro-caudal axis is generated by differential expression of Hox genes (transcriptional activators)
  - corresponding to genetic order on chromosome. (Wilkinson, Nature, 341, p405, 1989) Hox Genes
  - Stands for **H**omeob**ox** domain Genes
  - A family of transcription factors
  - Discovered in flies and conserved between all species. [../OtherEmb/fly.htm#antennapedia antennapedia]
  - Expressed in sequence along the embryo rostro-caudal axis.
  - Regulate many other aspects of development.
  - 180aa region binds DNA and regulate gene expression
  - large family of genes organized and expressed in sequence on the chromosome
  - Nkx-2.2 first detected at 1 somite stage
  - Lim hox gene expressed at spinal cord level

Ectodermal Placodes

- Specialized ectodermal "patches" in the head region
- Contribute sensory structures - otic placode (otocyst), nasal placode, lens placode
- Contribute teeth

Human Neuralation - Early Stages

The stages below refer to specific Carneigie stages of development.

- **stage 8** (about 18 postovulatory days) neural groove and folds are first seen
- **stage 9** the three main divisions of the brain, which are not cerebral vesicles, can be distinguished while the neural groove is still completely open. Stage 9 SEM (http://embryology.med.unsw.edu.au/wwwhuman/Stages/stage9sem.htm)
- **stage 10** (two days later) neural folds begin to fuse near the junction between brain and spinal cord, when neural crest cells are arising mainly from the neural ectoderm Stage 10 SEM (http://embryology.med.unsw.edu.au/wwwhuman/Stages/stage10sem.htm)
- **stage 11** (about 24 days) the rostral (or cephalic) neuropore closes within a few hours; closure is bidirectional, it takes place from the dorsal and terminal lips and may occur in several areas simultaneously. The two lips, however, behave differently. Stage 11 SEM (http://embryology.med.unsw.edu.au/wwwhuman/Stages/stage11sem.htm)
- **stage 12** (about 26 days) The caudal neuropore takes a day to close Stage 12 SEM (http://embryology.med.unsw.edu.au/wwwhuman/Stages/stage12sem.htm)
- the level of final closure is approximately at future somitic pair 31
- corresponds to the level of sacral vertebra 2
- **stage 13** (4 weeks) the neural tube is normally completely closed Stage 13 SEM (http://embryology.med.unsw.edu.au/wwwhuman/Stages/stage13sem.htm)

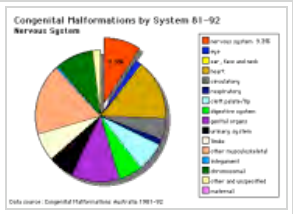
Secondary neurulation begins at stage 12 - is the differentiation of the caudal part of the neural tube from the caudal eminence (or end-bud) without the intermediate phase of a neural plate.

(Stage text modified from: Neurulation in the normal human embryo. O'Rahilly R, Muller F Ciba Found Symp 1994;181:70-82)

Abnormalities

See also Neural Abnormalities (http://embryology.med.unsw.edu.au/Notes/neuron2.htm)

Neural Tube Defects (NTD)

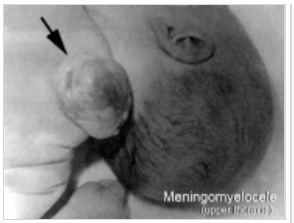


Australian Birth Statistics

Failure of neural tube closure either incorrectly or incomplete

- **Dysraphism** is the term often used to describe the defective fusion of the neural folds. The position and degree of failure of fusion will result in either embryonic death or a range of different neural defects. The way (mode) in which the human neural tube fuses has been a source of contention. In humans, fusion appears to initiate at multiple sites but the mode is different from that found in many animal species used in developmental studies.

- severity dependent upon level within the tube and degree of failure
- caudal failure - spina bifida cranial failure - anancephaly

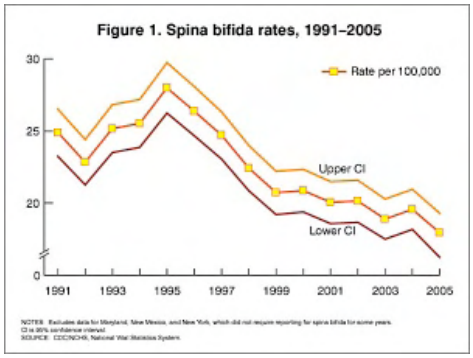


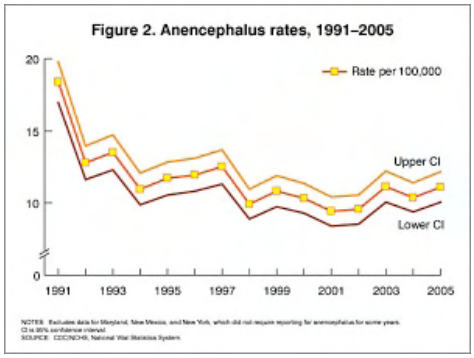
Neural tube defect - Meningomyelocele

Maternal Diet

Found that supplementation of maternal diet with folate reduces incidence of NTDs (More? Folic Acid and Neural Tube Defects (http://embryology.med.unsw.edu.au/Defect/page5e.htm))

- A randomised controlled trial conducted by the Medical Research Council of the United Kingdom demonstrated a 72% reduction in risk of recurrence by periconceptional (ie before and after conception) folic acid supplementation (4mg daily).
- Women who have one infant with a neural tube defect have a significantly increased risk of recurrence (40-50 per thousand compared with 2 per thousand for all births)





In the U.S.A. the Food and Drug Administration in 1996 authorized that all enriched cereal grain products be fortified with folic acid, with optional fortification beginning in March 1996 and mandatory fortification in January 1998. The data in the above graphs show the subsequent changes in anencephaly and spina bifida rate over that period.

Holoprosencephaly

Holoprosencephaly (HPE) is developmental abnormality where the forebrain does not divide into the two separate hemispheres and ventricles.

Critical Periods of Human Development

Exposure to teratogens during these "critical periods" results in specific abnormalities. Critical Periods (http://embryology.med.unsw.edu.au/Medicine/images/hcriticaldev.gif)

- most systems are susceptible during embryonic development (first trimester)
- the earlier the exposure the more severe the effects
- each system has a different critical period
- longest critical periods
  - longest developing systems (neural, genital)
  - complicated developmental origins (sensory systems)

Take the Quiz

1. Ectoderm refers only to the neural plate region of the trilaminar embryo

- ○ true
- ○ false

2. The central nervous system forms in the sequence:

- ○ norochord to neural plate to neural tube
- ○ neural tube to neural plate to neural groove
- ○ neural plate to neural groove to neural tube
- ○ neural plate to neural crest to neural zone

3. The neural plate is narrower at the caudal (tail) end and therefore closes earlier than the broad cranial (head) end.

- true
- false

4. The correct sequence from cranial to caudal of the secondary brain vesicles is:

- prosencephalon, mesencephalon, metencephalon, myelencephalon, rhombencephalon
- telencephalon, diencephalon, metencephalon, mesencephalon, myelencephalon
- telencephalon, diencephalon, mesencephalon, metencephalon, myelencephalon
- prosencephalon, diencephalon, mesencephalon, myelencephalon, metencephalon

Submit

UNSW Embryology Neural Links

- Neural Lecture 5 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture05.htm)
- Neural Notes (http://embryology.med.unsw.edu.au/Notes/neuron.htm) | Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/neuron3.htm) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/neuron4.htm) | Stage 22 Brain (http://embryology.med.unsw.edu.au/Notes/neuron5.htm#high%20power) | Stage 22 Spinal Cord (http://embryology.med.unsw.edu.au/Notes/neuron5a.htm) | Ventricular System (http://embryology.med.unsw.edu.au/Notes/neuron6.htm) | Cerebrospinal Fluid (http://embryology.med.unsw.edu.au/Notes/neuron6a.htm) | Week 10 (http://embryology.med.unsw.edu.au/Notes/neuron4a.htm) | Fetal (http://embryology.med.unsw.edu.au/Notes/neuron8.htm) | Gliogenesis (http://embryology.med.unsw.edu.au/Notes/neuron7.htm) | Pain (http://embryology.med.unsw.edu.au/Notes/neuron_pain.htm) | Molecular (http://embryology.med.unsw.edu.au/Notes/neuron11.htm)
- Abnormalities - Abnormalities (http://embryology.med.unsw.edu.au/Notes/neuron2.htm) | Folic Acid and Neural Tube Defects (http://embryology.med.unsw.edu.au/Defect/page5e.htm) | Critical Periods (http://embryology.med.unsw.edu.au/Medicine/images/hcriticaldev.gif)
- Postnatal - Postnatal Neural (http://embryology.med.unsw.edu.au/Child/page7.htm) | Neural Assessment (http://embryology.med.unsw.edu.au/Child/page7a.htm)
- Neural Crest Notes (http://embryology.med.unsw.edu.au/Notes/ncrest.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/ncrest2.htm) Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/ncrest3.htm) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/ncrest4.htm) | Stage 22 high power (http://embryology.med.unsw.edu.au/Notes/ncrest5.htm) | Generation (http://embryology.med.unsw.edu.au/Notes/ncrest6.htm) | Migration (http://embryology.med.unsw.edu.au/Notes/ncrest7.htm) | Peripheral Ganglia (http://embryology.med.unsw.edu.au/Notes/ncrest8.htm) | GIT Enteric (http://embryology.med.unsw.edu.au/Notes/ncrest9.htm) | Heart (http://embryology.med.unsw.edu.au/Notes/ncrest12.htm) | Molecular (http://embryology.med.unsw.edu.au/Notes/ncrest10.htm) | Web Links (http://embryology.med.unsw.edu.au/Notes/ncrestlink.htm)
- Stages - scanning electron micrographs (http://embryology.med.unsw.edu.au/wwwhuman/Stages/Stagesem.htmlCarnegie)
- System Notes (http://embryology.med.unsw.edu.au/sysnote.htm)
- Development Timeline (http://embryology.med.unsw.edu.au/week/weekbyweek.htm)

Internet Links

- **Embryo Images** Early Cell Populations and Establishment of Body Form (http://www.med.unc.edu/embryo_images/unit-bdyfm/bdyfm_htms/bdyfmtoc.htm) | Nervous System Development (http://www.med.unc.edu/embryo_images/unit-nervous/nerv_htms/nervtoc.htm)
- **Society for Neuroscience** http://web.sfn.org/content/Publications/BrainFacts/index.html Brain Facts (http://web.sfn.org/content/Publications/BrainFacts/index.html)
- **Anatomy of the Human Body** The Neural Groove and Tube (http://www.bartleby.com/107/7.html)
- **Environmental Health Perspectives** Critical Periods of Vulnerability for the Developing Nervous System: Evidence from Humans and Animal Models (http://www.ehponline.org/members/2000/suppl-3/511-533rice/rice-full.html) | PMC: 1637807 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1637807) | PMID: 10852851 (http://www.ncbi.nlm.nih.gov/pubmed/10852851)
- **Journal** Development (http://www.neuraldevelopment.com/Neural)

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Mesoderm Ch15,16: p405-423, 426-430 Body Cavities Ch9: p174-184
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Mesoderm Ch11 p311-339 Body Cavities Ch6 p127-146

Additional Textbooks

- Before We Are Born (5th ed.) Moore and Persaud Ch16,17: p379-397, 399-405
- Essentials of Human Embryology Larson Ch11 p207-228
- Human Embryology Fitzgerald and Fitzgerald Body Cavities Ch5 p29-32, Ch7 p47,48
- Human Embryology and Developmental Biology ?Carlson Ch9,10: p173-193, 209-222 Body Cavities Ch5 p29-32, Ch7 p47,48

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Paraxial Mesoderm: The Somites and Their Derivatives (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3455)
- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 - Figure 21-78. Somite formation in the chick embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3943)

- **Madame Curie Bioscience Database** Chapters taken from the Madame Curie Bioscience Database (formerly, Eurekah Bioscience Database) Eurekah.com and Landes Bioscience and Springer Science+Business Media; c2009 Patterning the Vertebrate Neural Plate by Wnt Signaling (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A16427) | Neural Crest Delamination and Migration (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A55523)

Search

- **Bookshelf** ectoderm (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=ectoderm) | neural plate (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=neural_plate) | neural tube (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=neural_tube) | neural crest (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=neural_crest)

- **Pubmed** ectoderm (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=ectoderm) | neural plate (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=neural_plate)

Reviews

- Temporal dynamics of patterning by morphogen gradients. Kutejova E, Briscoe J, Kicheva A. Curr Opin Genet Dev. 2009 Jul 9. PMID: 19596567 (http://www.ncbi.nlm.nih.gov/pubmed/19596567)

- The Hedgehog, TGF-beta/BMP and Wnt families of morphogens in axon guidance. Charron F, Tessier-Lavigne M. Adv Exp Med Biol. 2007;621:116-33. Review.

PMID: 18269215 (http://www.ncbi.nlm.nih.gov/pubmed/18269215)

- Novel brain wiring functions for classical morphogens: a role as graded positional cues in axon guidance. Charron F, Tessier-Lavigne M. Development. 2005 May;132(10):2251-62. Review.

PMID: 15857918 (http://www.ncbi.nlm.nih.gov/pubmed/15857918) | Development Link (http://dev.biologists.org/cgi/content/full/132/10/2251)

Movies

Neural Plate Neural Tube

Neural Development Terms

Only brief descriptions are given below, more complete definitions can be found in the glossary.

- **3DMRI** Three-dimensional magnetic resonance imaging. A new technique that allows 3D analysis of embryonic structures. (More? Prenatal Diagnosis - Magnetic Resonance Imaging (http://embryology.med.unsw.edu.au/Defect/MRI.htm))
- **3rd ventricle** a fluid-filled space formed from neural tube lumen, located within the diencephalon (from the primary vesicle prosencephalon, forebrain).
- **4th ventricle** a fluid-filled space formed from neural tube lumen, located within the rhombencephalon (from the primary vesicle, hindbrain).
- **adenohypophysis** (anterior pituitary) = 3 parts pars distalis, pars intermedia, pars tuberalis.
- **alar plate** afferent, dorsal horns
- **anlage** (German = primordium, structure or cells which will form a future structure.
- **arachnoid** - (G.) spider web-like
- **basal ganglia** - (basal nuclei) neural structure derived from the secondary vesicle telencephalon (endbrain) structure from the earlier primary vesicle prosencephalon (forebrain)
- **basal plate** efferent, ventral horns
- **brachial plexus** mixed spinal nerves innervating the upper limb form a complex meshwork (crossing).
- **brain** general term for the central nervous system formed from 3 primary vesicles.
- **buccopharyngeal membrane** (=oral membrane) at cranial (mouth) end of gastrointestinal tract (GIT) where surface ectoderm and GIT endoderm meet. (see also [#cloacal membrane cloacal membrane])
- **cauda equina** - (=horse's tail) caudal extension of the mature spinal cord.
- **central canal** lumen, cavity of neural tube within the spinal cord. Space is continuous with ventricular system of the brain.
- **cerebral aqueduct** ventricular cavity within the mesencephalon.
- **cervical flexure** most caudal brain flexure (of 3) between spinal cord and rhompencephalon. (sc-^V^)
- **choroid plexus** specialized vascular plexus responsible for secreting ventricular fluid that with further additions becomes cerebrospinal fluid (CSF).
- **cloacal membrane** at caudal (anal) end of gastrointestinal tract (GIT) where surface ectoderm and GIT endoderm meet forms the openings for GIT, urinary, reproductive tracts. (see also buccopharyngeal membrane)
- **cortex** - CNS structure derived from the secondary vesicle telencephalon (endbrain) from the earlier primary vesicle prosencephalon (forebrain).
- **cortical plate** outer neural tube region which post-mitotic neuroblasts migrate too along radial glia to form adult cortical layers.
- **cranial flexure** (=midbrain flexure) most cranial brain flexure (of 3) between mesencephalon and prosencephalon. (sc-^V^)
- **diencephalon** the caudal portion of forebrain after it divides into 2 parts in the 5 secondary vesicle brain (week 5). (cavity- 3rd ventricle) Forms the thalmus and other nuclei in the adult brain. (sc-My-Met-Mes-**Di**-Tel)
- **dorsal root ganglia** (=spinal ganglia) sensory ganglia derived from the neural crest lying laterally paired and dorsally to the spinal cord (in the embryo found ventral to the spinal cord). Connects centrally with the dorsal horn of the spinal cord.
- **dura mater**- "tough" (Latin, *mater* = mother)
- **ectoderm** the germ layer which form the nervous system from the neural tube and neural crest.
- **ependyma** epithelia of remnant cells after neurons and glia have been generated and left the ventricular zone
- **floorplate** early forming thin region of neural tube closest to the notochord.
- **ganglia** (pl. of ganglion) specialized neural cluster.
- **glia** supporting, non-neuronal cells of the nervous system. Generated from neuroepithelial stem cells in ventricular zone of neural tube. Form astrocytes, oligodendrocytes.
- **grey matter** neural regions containing cell bodies (somas) of neurons. In the brain it is the outer layer, in the spinal cord it is inner layer. (see white matter white matter)
- **growth factor** usually a protein or peptide that will bind a cell membrane receptor and then activates an intracellular signaling pathway. The function of the pathway will be to alter the cell directly or indirectly by changing gene expression. (eg shh)
- **hox** (=**h**omeob**ox**) family of transcription factors that bind DNA and activate gene expression. Expression of different Hox genes along neural tube defines rostral-caudal axis and segmental levels.
- **hydrocephalus** abnormality as the result of an imbalance between the rate at which the CSF is being formed and the rate at which the CSF is passing through the arachnoidal villi back into the blood (hydrocephalus rate is a function of the degree of imbalance in these two). Very small imbalance exhibit subtle, if any, symptoms. Large imbalances will have rapidly evolving symptoms of unmistakable import.
- **isthmus**- (G. narrow passage)
- **lamina terminalis** anterior region of brain where cranial neuropore closes.
- **lumbar plexus** mixed spinal nerves innervating the lower limb form a complex meshwork (crossing).
- **mantle layer** layer of cells generated by first neuroblasts migrating from the ventricular zone of the neural tube. Layers are rearranged during development of the brain and spinal cord. (Ven-**Man**-Mar-CP)
- **marginal zone** layer of processes from neuroblasts in mantle layer. (Ven-Man-**Mar**-CP)
- **mater** (Latin, *mater* = mother)

- **meninges** mesenchyme surrounding neural tube forms 3 layer (Dura-, pia-, arachnoid- mater) connective tissue sheath of nervous system. (D-P-A-cns)
- **mesencephalon** (=midbrain), the middle portion of the 3 primary vesicle brain (week 4). (sc-R-**M**-P)
- **metencephalon** the cranial portion of hindbrain after it divides into 2 parts in the 5 secondary vesicle brain (week 5). Forms the pons and cerebellum in the adult brain. (sc-My-**Met**-Mes-Di-Tel)
- **myelencephalon** the caudal portion of hindbrain after it divides into 2 parts in the 5 secondary vesicle brain (week 5). Forms the medulla in the adult brain. (sc-**My**-Met-Mes-Di-Tel)
- **neural tube** neural plate region of ectoderm pinched off to form hollow ectodermal tube above notochord in mesoderm.
- **neural tube defect** (NTD) any developmental abnormality that affects neural tube development. Commonly failure of neural tube closure.
- **neuroblast** undifferentiated neuron found in ventricular layer of neural tube.
- **neurohypophysis** (=posterior pituitary=pas nervosa)
- **neuron** The cellur "unit" of the nervous system, transmitting signals between neurons and other cells. The post-mitotic cells generated from neuroepithelial stem cells (neuroblasts) in ventricular zone of neural tube.
- **neuropore** opening at either end of neural tube: cranial=rostral=anterior, caudal=posterior. The cranial neuropore closes (day 25) approx. 2 days (human) before caudal.
- **notochord** rod of cells lying in mesoderm layer ventral to the neural tube, induces neural tube and secretes sonic hedgehog which "ventralizes" the neural tube.
- **olfactory bulb** (=cranial nerve I, CN I) bipolar neurons from nasal epithelium project axons through cribiform palate into olfactory bulb of the brain.
- optic cup-
- **optic nerve** (=cranial nerve II, CN II) retinal ganglion neurons project from the retina as a tract into the brain (at the level of the diencephalon).
- **otocyst** (=otic vesicle) sensory [#placode placode] which sinks into mesoderm to form spherical vesicle (stage 13/14 embryo) that will form components of the inner ear.
- **pars** (L. part of)
- **pharyngeal arches** (=branchial arches, Gk. gill) form structures of the head. Six arches form but only 4 form any structures. Each arch has a pouch, membrane and cleft.
- **pharynx** uppermost end of GIT, beginning at the buccopharyngeal membrane and at the level of the pharyngeal arches.
- pia mater-
- **placode** specialized regions of ectoderm which form components of the sensory apparatus.
- **pontine flexure** middle brain flexure (of 3) between cervical and cranial flexure in opposite direction, also generates thin roof of rhombencephalon and divides it into myelencephalon and metencephalon. (sc-^**V**^)
- **prosencephalon** (=forebrain), the most cranial portion of the 3 primary vesicle brain (week 4). (sc-R-M-**P**)
- **Rathke's pouch** a portion of the roof of the pharynx pushes upward towards the floor of the brain forming the anterior pituirary (adenohypophysis, pars distalis, pars tuberalis pars intermedia). Where it meets a portion of the brain pushing downward forming the posterior pituitary (neurohypophysis, pars nervosa). Rathke's pouch eventually looses its connection with the pharynx. (Martin Heinrich Rathke 1973-1860, embryologist and anatomist)
- **rhombencephalon** (=hindbrain), the most caudal portion of the 3 primary vesicle brain (week 4). (sc-**R**-M-P)
- **roofplate** early forming thin region of neural tube closest to the overlying ectoderm.
- **spinal cord** caudal end of neural tube that does not contribute to brain. Note: the process of secondary neuralation contributes the caudal end of the spinal cord.
- **spinal ganglia** (=dorsal root ganglia, drg) sensory ganglia derived from the neural crest lying laterally paired and dorsally to the spinal cord (in the embryo found ventral to the spinal cord). Connects centrally with the dorsal horn of the spinal cord.
- **spinal nerve** mixed nerve (motor and sensory) arising as latera pairs at each vertebral segmental level.
- **sonic hedgehog** (=shh) secreted growth factor that binds patched (ptc) receptor on cell membrane. SHH function is different for different tissues in the embryo. In the nervous system, it is secreted by the notochord, ventralizes the neural tube, inducing the floor plate and motor neurons.
- **sulcus** (L. furrow) groove
- **sulcus limitans** longitudinal lateral groove in neural tube approx. midway between roofplate and floorplate. Groove divides alar (dorsal) and basal (ventral) plate regions.
- **sympathetic ganglia**-
- **telencephalon** the cranial portion of forebrain after it divides into 2 parts in the 5 secondary vesicle brain (week 5). (cavity- lateral ventricles and some of 3rd ventricle) Forms the cerebral hemispheres in the adult brain. (sc-My-Met-Mes-Di-**Tel**)
- **thalamus** (G. *thalamos*= bedchamber) cns nucleus, lateral to 3rd ventricle, paired (pl thalami).
- **transcription factor** a factor (protein or protein with steroid) that binds to DNA to alter gene expression, usually to activate. (eg steroid hormone+receptor, Retinoic acid+Receptor, Hox, Pax, Lim, Nkx-2.2)
- **trigeminal ganglion** (=cranial nerve V, CN V) first arch ganglion, very large and has 3 portions.
- **vagal ganglion-** (=cranial nerve X, CN X) fourth and sixth arch ganglion, innervates the viscera and heart.
- **ventricles** the fluid-filled interconnected cavity system with the brain. Fluid (cerebrospinal fluid, CSF) is generated by the specialized vascular network, the choroid plexus. The ventricles are directly connected to the spinal canal (within the spinal cord).

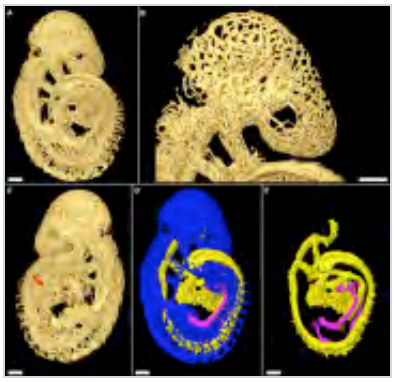
2009 Lecture 7

From Embryology

Contents

Early Vascular Development

Introduction



Mouse embryo (19 somite) vascular distribution

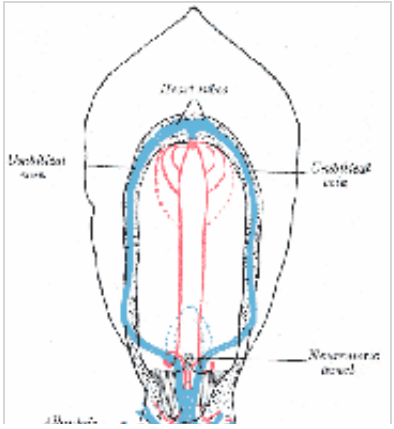
This lecture will introduction to the events in early embryonic development that relate to mesoderm and early cardiovascular development. Most texts will separate heart development from vascular development in order to simplify their descriptions of cardiovascular development, though the two are functionally and embryonically connected. Note that we will be returning later to discuss the late development of the heart and vascular changes.

The complexity of septation, cardiac outflow separation, remodelling of the peripheral vasculature, and the pre- to post-natal changes may also contribute to the relatively large proportion of birth defects associated with this system.

The molecular mechanisms regulating cardiac development are still largely unknown. Development does appear to be an independent mechanism preceding both skeletal and smooth muscle development and using different regulatory mechanisms (not MyoD or myogenin).

- **Lectopia Lecture Audio** Lecture Date: 17-08-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Cardiovascular (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48826)

Lecture objectives



- Understanding of mesoderm development
- Understanding of heart tube formation and early development
- Understanding of early blood vessel and blood development
- Brief understanding of vascular growth and regression
- Brief understanding of vascular growth factors

Textbook references

- Human Embryology (3rd ed.) Larson Chapter 7 p151-188 Heart, Chapter 8 p189-228 Vasculature
- The Developing Human: Clinically Oriented Embryology (6th ed.)

Chapter 14: p304-349

Historic image of early human vascular development

Other textbooks

- Before we Are Born (5th ed.) Moore and Persaud Chapter 12; p241-254
- Essentials of Human Embryology Larson Chapter 7 p97-122 Heart, Chapter 8 p123-146 Vasculature
- Human Embryology Fitzgerald and Fitzgerald Chapter 13-17: p77-111

Recent reviews

- Yutzey KE, Kirby ML. Wherefore heart thou? Embryonic origins of cardiogenic mesoderm. Dev Dyn. 2002 Mar;223(3):307-20. Review. PMID: 11891982 (http://www.ncbi.nlm.nih.gov/pubmed/11891982?dopt=Abstract)
- Three-dimensional reconstruction of gene expression patterns during cardiac development. Soufan AT, Ruijter JM, van den Hoff MJ, de Boer PA, Hagoort J, Moorman AF. Physiol Genomics. 2003 May 13;13(3):187-95. Review. PMID: 12746463 (http://www.ncbi.nlm.nih.gov/pubmed/12746463)
- Moorman A, Webb S, Brown NA, Lamers W, Anderson RH. Development of the heart: (1) formation of the cardiac chambers and arterial trunks. Heart. 2003 Jul;89(7):806-14. PMID: 12807866 (http://www.ncbi.nlm.nih.gov/pubmed/12807866?dopt=Abstract)
- Bruneau BG. Transcriptional regulation of vertebrate cardiac morphogenesis. Circ Res. 2002 Mar 22;90(5):509-19. Review. PMID: 11909814 (http://www.ncbi.nlm.nih.gov/pubmed/11909814?dopt=Abstract)

UNSW Embryology Links

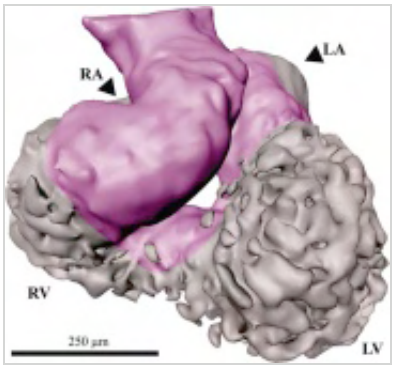
- **Cardiovascular Slides** Cardiovasular Lecture 7 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture07.htm) | Heart Lecture 2008 - 1 slide/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L07Hearts1.pdf) | Heart Lecture 2008 Slides - 4 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L07Hearts4.pdf) | Heart Lecture 2008 Slides - 6 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L07Hearts6.pdf)
- **Cardiovascular Movies** Heart Movies (http://embryology.med.unsw.edu.au/Movies/heart.htm) | Heart Looping (http://embryology.med.unsw.edu.au//Movies/larsen/looping.mov) | Atrial Septation (http://embryology.med.unsw.edu.au//Movies/larsen/atrium.mov) | Realignment (http://embryology.med.unsw.edu.au//Movies/larsen/avc.mov) | Ventricular Septation (http://embryology.med.unsw.edu.au//Movies/larsen/ventricl.mov) | Heart Septation Models (http://embryology.med.unsw.edu.au/Movies/heart.htm#HeartSeptation) | Historic Heart Movie (http://embryology.med.unsw.edu.au/Movies/heart.htm#HistoricHeart) |

- **Cardiovascular Notes** Introduction (http://embryology.med.unsw.edu.au/Notes/heart.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/heart2.htm) | Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/heart3.htm) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/heart4.htm) | Stage 22 Selected Highpower (http://embryology.med.unsw.edu.au/Notes/heart5.htm) | Heart (http://embryology.med.unsw.edu.au/Notes/heart6.htm) | Heart Rate (http://embryology.med.unsw.edu.au/Notes/heart8.htm) | Blood (http://embryology.med.unsw.edu.au/Notes/heart20.htm) Blood Vessels (http://embryology.med.unsw.edu.au/Notes/heart19.htm) | Molecular (http://embryology.med.unsw.edu.au/Notes/heart11.htm) | Lymphatic (http://embryology.med.unsw.edu.au/Notes/heart31.htm) | Text only page (http://embryology.med.unsw.edu.au/Notes/hearttxt.htm) | WWW Links (http://embryology.med.unsw.edu.au/Notes/heartlink.htm) | Postnatal

(http://embryology.med.unsw.edu.au/Child/heart.htm) | History - Harvey (http://embryology.med.unsw.edu.au/history/page2b.htm#Harvey)

Development overview

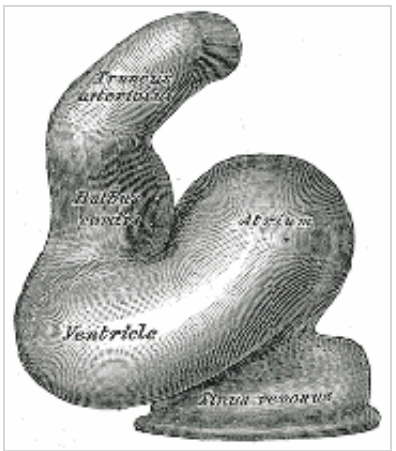
The heart develops from cardiogenic mesoderm that originally lies above the cranial end of the developing neural tube. Enlargement of the cranial neural fold brings this region ventrally to its correct anatomical position. The original paired cardiac tubes fuse, with the "ventricular" primordia initially lying above the "atria". Growth of the cardiac tube flexes it into an "S-shape" tube, rotating the "ventricles" downward and pushing the "atria" upward.



mouse E9.5 heart (stage 10)

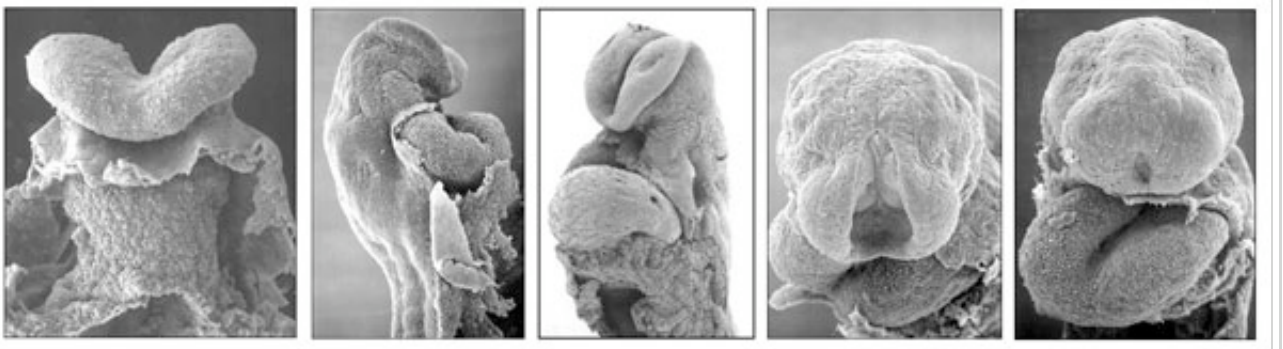
This is then followed by septation, a complex process which converts this simple tube into a four chambered heart and covered in a later lecture and lab. A key part of this process is the separation of cardiac outflow (truncus arteriosus) into a separate pulmonary and aortic arch outflow. During embryonic development there is extensive remodelling of the initially right and left symmetrical cardiovascular system and a contribution from the neural crest to some vessels.

Timecourse



early heart tube

- forms initially in splanchnic mesoderm of prechordal plate region - **cardiogenic region**
  - growth and folding of the embryo moves heart ventrallly and downward into anatomical position
- week 3 begins as paired heart tubes that fuse to form single heart tube
- begins to beat in Humans- day 22-23
- heart tube connects to blood vessels forming in splanchnic and extraembryonic mesoderm


The Human Heart from day 10 to 25 (scanning electron micrograph)

Week 2-3 pair of thin - walled tubes

Week 3 tubes fused, truncus arteriosus outflow, heart contracting

Week 4 heart tube continues to elongate, curving to form S shape

Week 5 Septation starts, atrial and ventricular

Septation continues, atrial septa remains open, foramen ovale

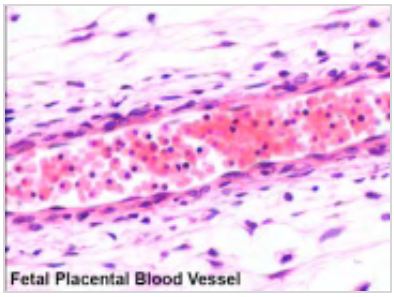
Week 37-38 At birth pressure difference closes foramen ovale leaving a fossa ovalis

Angiogenesis

- blood vessel formation - vasculogenesis
  - also occurs in adult and disease
- begins week 3 in extraembryonic mesoderm and then embryonic splanchnic mesoderm
- yolk sac, connecting stalk and chorion
- growth factors stimulate growth and development - Vascular Endothelial Growth Factor (VEGF) and Placental growth factor (PlGF)
  - Growing blood vessels follow a gradient generated by target tissues/regions of Vascular Endothelial Growth Factor (VEGF) to establish a vascular bed. Recent findings suggest that Notch signaling acts as an inhibitor for this system, preventing sprouting of blood vessels. Notch is a transmembrane receptor protein involved in regulating cell differentiation in many developing systems.
  - PIGF is also a VEGF released from the placental trophoblast cells.
- **angioblasts** form clusters called "blood islands"
- blood islands extend and fuse together to form a primordial vascular network

Blood islands

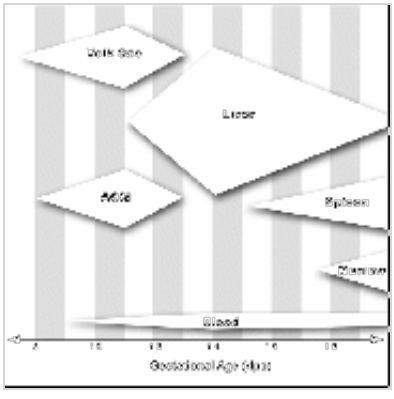
- 2 populations of cells
  - peripheral- form endothelial cells
  - core- form blood cells (haemocytoblasts)
- all vessels (arteries and veins) appear initially the same



fetal blood

Blood formation

- blood formation from stem cells occurs initially in the extraembryonic mesoderm of the yolk sac
- then later (week 5) throughout embryonic mesenchyme
- blood stem cells then migrate into the liver
  - then spleen, bone marrow, lymph nodes



Mouse hematopoietic stem cell location

Red blood cells

The only cells in the blood are nearly entirely fetal red blood cells. These cells differ from adult red blood cells in:

- often remaining nucleated.
- contain fetal haemoglobin - which has different oxygen and carbon dioxide binding characteristics.

Early vascular systems

- one vascular system with 3 components - vitelline, embryonic

(system) and placental
    - each component has own system of artery and vein

Vitelline blood vessels

- (omphalomesenteric) cover entire surface of yolk sac, connect to embryo through yolk stalk
- **Vitelline Arteries** - arises from dorsal aorta, contribute to adult GIT arteries
- **Vitelline Veins** - empties into sinus venosus, contribute to the adult portal system

Embryo blood vessels

- (systemic) will form the most of the cardiovascular system
    - some vessels have neural crest contribution
- Arteries - aortic sac -> aortic arches -> dorsal aorta - umbilical artery
    - dorsal aorta, paired initially and fuses, gives off segmental arteries
- Veins - 3 pairs of veins empty into the sinus venosus of the heart
    - vitelline, umbilical (only left persists), common cardinal veins
    - cardinal veins - anterior, common, posterior

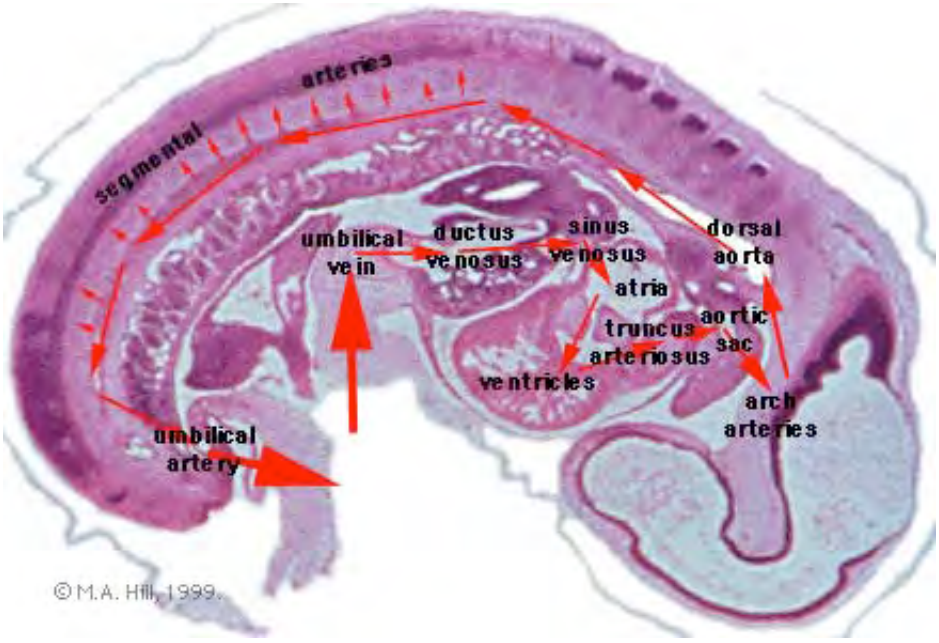
Placental blood vessels

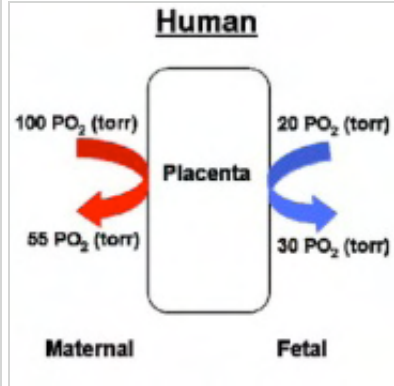
- form initially in the connecting stalk (then umbilical cord) and anastomose in chorioni
- extend maternally - toward the chorionic villi
- extend embryonically - toward the sinus venosus and dorsal aorta

- Arteries - paired and carry deoxygenated blood (from dorsal aorta) and waste products to the placental villi
- Veins - paired initially then only left at end of embryonic period and carry oxygenated blood to the embryo (sinus venosus)

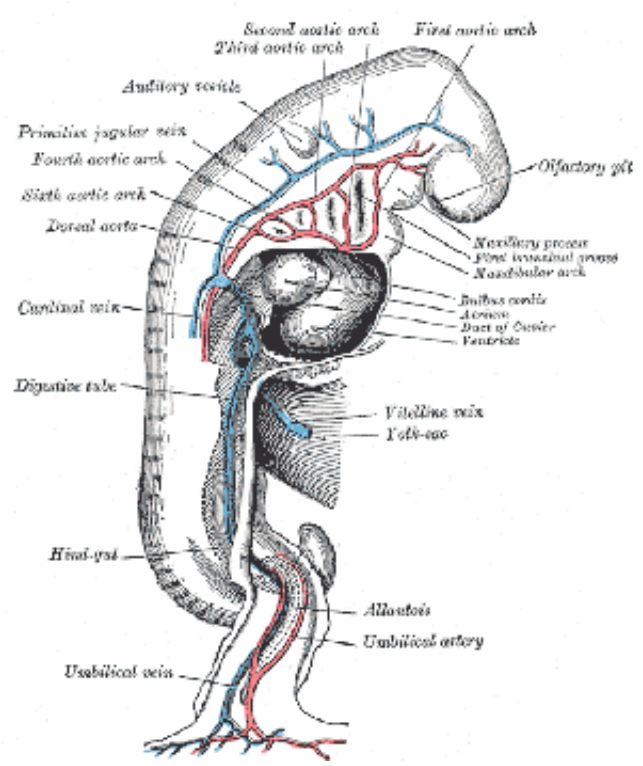
Blood flow through the embryo

High pressure pathway Stage 13/14 sagittal section (http://embryology.med.unsw.edu.au/Notes/heart3.htm#Pig) .

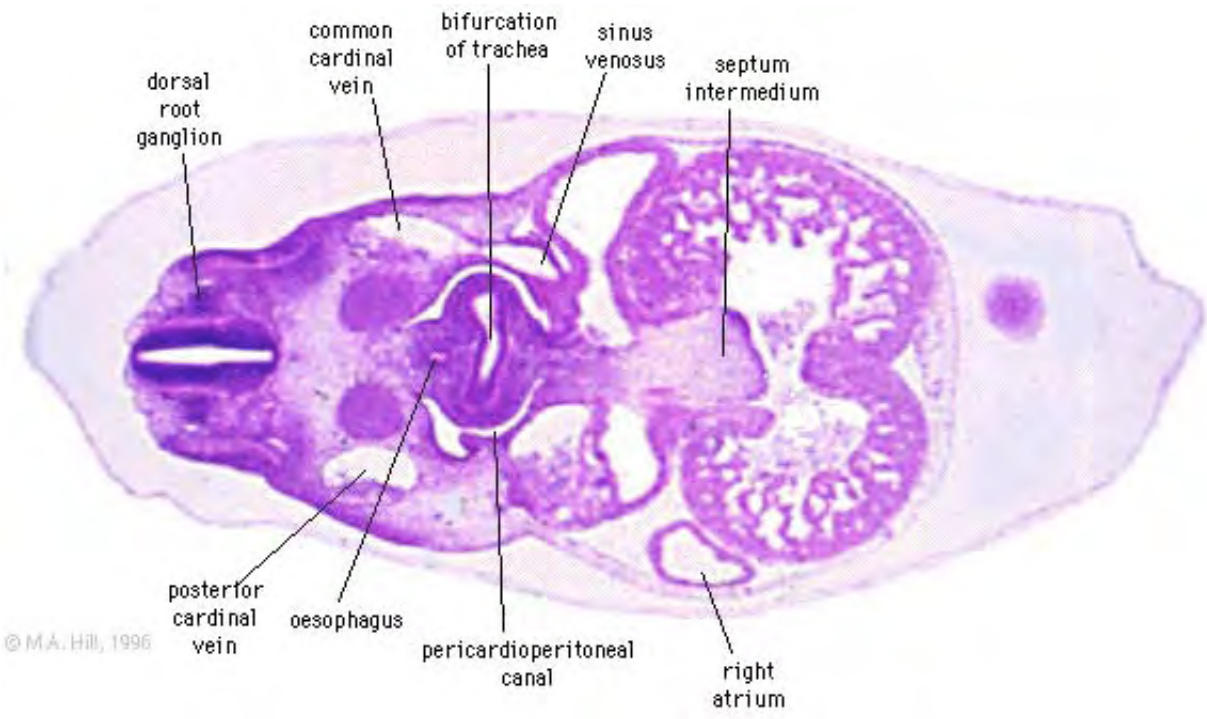




Fetal Oxygen levels



Maternal Blood | -> umbilical vein -> liver -> anastomosis -> sinus venosus -> atria ventricles-> truncus arteriosus -> aortic sac -> aortic arches-> dorsal aorta-> pair of umbilical arteries | Maternal Blood.



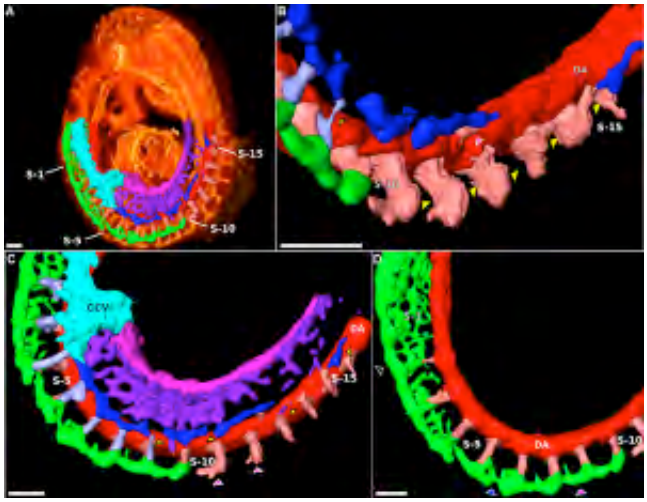
Low pressure pathway Stage 13 (http://embryology.med.unsw.edu.au/Notes/heart3d.htm#venous)

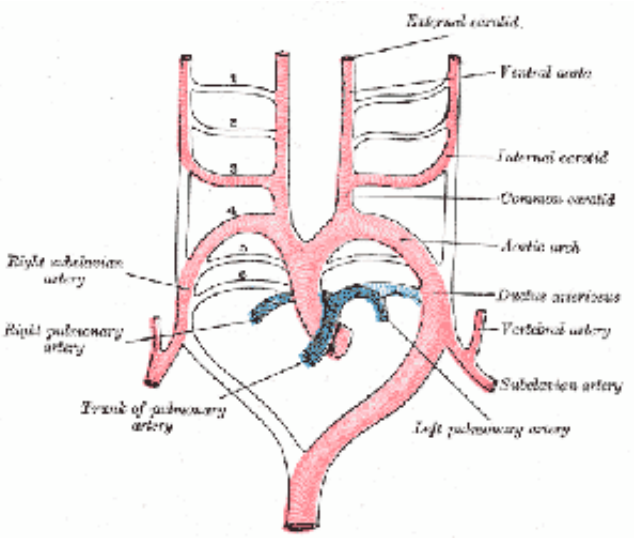
- Head - Large veins lateral to dorsal aortae. These are the superior or anterior cardinal veins. Their function is to drain the head region.
- Body - Large veins lateral to dorsal aortae. These are the inferior or posterior cardinal veins. Their function is to drain the lower part of the embryo.

Blood vessel remodeling

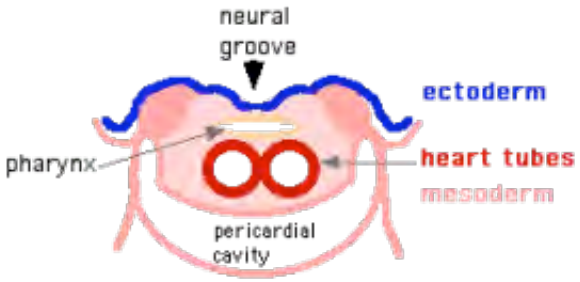
Early vascular development is laterally **symmetrical** (paired left and right). With embryo development this

scheme is extensively remodelled leading to an **asymmetric** adult system in the body.

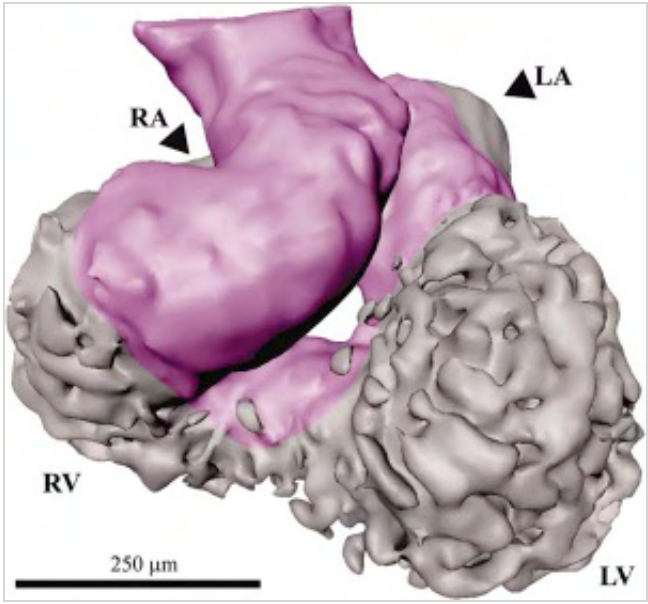




Heart development



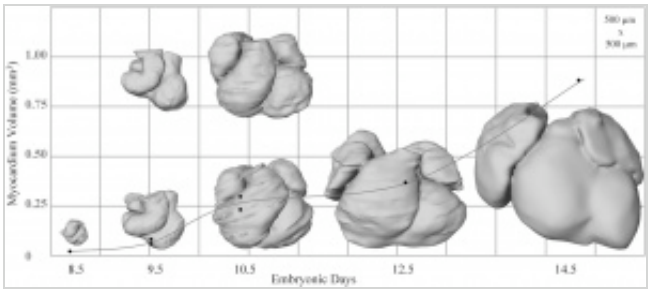
MH - Later development of the heart (septation) will be covered in another lecture.



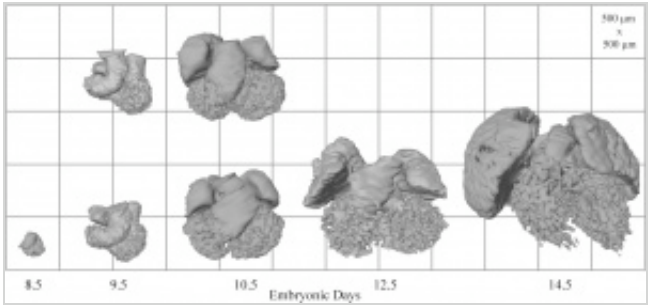
mouse E9.5 heart (stage 10)

Heart looping

Heart Looping



Heart external



Heart internal

(http://embryology.med.unsw.edu.au//Movies/larsen/looping.mov)

Transverse section- Heart is 2 tubes that fuse in the midline anterior to pharynx.

The pericardial cavity can be imagined as the top of the "horseshoe" of the intraembryonic coelom. (where the arms become the pleural cavity and the ends fuse anteriorly to form a single peritoneal cavity).

This view shows the initial positioning of the ventricles above the atria. The ventricles are rotated into their correct anatomical position by the growth of the heart tube, bending into an "S" shape.

Initially...

Cardiac inflow- at the bottom (sinus venosus)

Cardiac outflow- at the top (truncus arteriosus)

Heart neural crest

- The mouse model shows that the heart also has contributions from neural crest E8.5 mouse neural crest (http://dev.biologists.org/cgi/content/full/131/14/3367/FIG1)
  - between the levels of post-otic hindbrain to somite 4, with the most contribution from somite 2 level.

- 7 somite stage - Migration of cardiac neural crest from the neural tube begins. (level post-otic hindbrain and somite 4)
  - Pathways dorsolateral, medial, and between somites.
  - Then through peri-aortic mesenchyme (lateral to pharynx), through pharyngeal arches (3, 4, 6) into the aortic sac.
- 32 somite stage: Colonisation of the outflow tract mesenchyme.

Data from: Chan WY, Cheung CS, Yung KM, Copp AJ. Chan WY, Cheung CS, Yung KM, Copp AJ. Cardiac neural crest of the mouse embryo: axial level of origin, migratory pathway and cell autonomy of the splotch (Sp2H) mutant effect. Development. 2004 Jul;131(14):3367-79. PMID: 15226254 (http://www.ncbi.nlm.nih.gov/pubmed/15226254)

Heart layers

- **pericardium** - covers the heart. Formed by 3 layers consisting of a fibrous pericardium and a double layered serous pericardium (parietal layer and visceral epicardium layer).

- **myocardium** - muscular wall of the heart. Thickest layer formed by spirally arranged cardiac muscle cells.
- **endocardium** - lines the heart. Epithelial tissue lining the inner surface of heart chambers and valves.

Embryonic heart rate

Embryonic Heart Rate (http://embryology.med.unsw.edu.au/Notes/heart8.htm)

- Ultrasonographic measurement of embryonic heart rate (EHR) shows a steady increase from Stage 9-10 (75 beats/minute) to Stage 18 (130 beats/minute) and on to Stage 20, following which a gradual decrease in EHR occurs
- Maximal EHR is reached when morphological development of the embryonic heart is completed.

Take the Quiz

1. Both blood stem cells and the endothelial lining of blood vessels arise from blood islands.

- ○ true
- ○ false

2. The region of the early heart tube that corresponds to the inflow and out flow respectively are:

- ○ inferior vena cava and aortic arch
- ○ portal artery and aorta
- ○ sinus arteriosus and cordus bulbus
- ○ truncus arteriosus and sinus venosus

3. Embryonic red blood cells only differ from adult cells in still having nuclei.

- ○ true
- ○ false

4. The embryo cardinal venous vessels which drain into the sinus venosus are:

- ○ anterior cardinal veins
- ○ common cardinal veins
- ○ inferior cardinal veins
- ○ superior cardinal veins

5. The embryonic heart rate rises throughout development.

- ○ true
- ○ false

Submit

UNSW Embryology Links

- Lecture 9 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture09.htm)

- Cardiovascular Movies Heart Movies (http://embryology.med.unsw.edu.au/Movies/heart.htm) | Heart Looping (http://embryology.med.unsw.edu.au//Movies/larsen/looping.mov) | Atrial Septation (http://embryology.med.unsw.edu.au//Movies/larsen/atrium.mov) | Realignment (http://embryology.med.unsw.edu.au//Movies/larsen/avc.mov) | Ventricular Septation (http://embryology.med.unsw.edu.au//Movies/larsen/ventricl.mov) | Heart Septation Models (http://embryology.med.unsw.edu.au/Movies/heart.htm#HeartSeptation) | Historic Heart Movie (http://embryology.med.unsw.edu.au/Movies/heart.htm#HistoricHeart) |
- Other Cardiac and Vascular Movies Fetal Circulation (Before Birth) (http://embryology.med.unsw.edu.au//Movies/larsen/8-15.mov) | Circulation (After Birth) (http://embryology.med.unsw.edu.au//Movies/larsen/8-15b.mov) | Aortic Branches to Glands (Kidneys only) (http://embryology.med.unsw.edu.au//Movies/larsen/kidney.mov) | Aortic Branches to Glands (Gonads only) (http://embryology.med.unsw.edu.au//Movies/larsen/gonad.mov)
- Cardiovascular Notes Introduction (http://embryology.med.unsw.edu.au/Notes/heart.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/heart2.htm) | Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/heart3.htm) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/heart4.htm) | Stage 22 Selected Highpower (http://embryology.med.unsw.edu.au/Notes/heart5.htm) | Heart (http://embryology.med.unsw.edu.au/Notes/heart6.htm) | Heart Rate (http://embryology.med.unsw.edu.au/Notes/heart8.htm) | Blood (http://embryology.med.unsw.edu.au/Notes/heart20.htm) Blood Vessels (http://embryology.med.unsw.edu.au/Notes/heart19.htm) | Molecular (http://embryology.med.unsw.edu.au/Notes/heart11.htm) | Lymphatic (http://embryology.med.unsw.edu.au/Notes/heart31.htm) | Text only page (http://embryology.med.unsw.edu.au/Notes/hearttxt.htm) | WWW Links (http://embryology.med.unsw.edu.au/Notes/heartlink.htm) | Postnatal (http://embryology.med.unsw.edu.au/Child/heart.htm) | History - Harvey (http://embryology.med.unsw.edu.au/history/page2b.htm#Harvey)
- System Notes (http://embryology.med.unsw.edu.au/sysnote.htm)
- Development Timeline (http://embryology.med.unsw.edu.au/week/weekbyweek.htm)

Internet Links

Embryo Images Unit: Embryo Images Online (http://www.med.unc.edu/embryo_images/) Early Cell Populations (cardiogenic section) | Cardiovascular Development (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardevtoc.htm) | Week 3 Development (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev001.htm) | Week 4 Development (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev007.htmhttp://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev007.htm) | Heart Chambers and Outflow Tract (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev018.htm) | Atrioventricular Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev022.htm) | Outflow Tract Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev028.htm) | Ventricular Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev035.htm) | Atrial Septation (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev036.htm) | Atrial

Walls (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev040.htm) Aortic Arch Vessels (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev041.htm) | Changes at Birth (http://www.med.unc.edu/embryo_images/unit-cardev/cardev_htms/cardev042.htm)

References

Textbooks

- Human Embryology (3rd ed.) Larson Chapter 7 p151-188 Heart, Chapter 8 p189-228 Vasculature
- The Developing Human: Clinically Oriented Embryology (6th ed.) Chapter 14: p304-349

Other textbooks

- Before we Are Born (5th ed.) Moore and Persaud Chapter 12; p241-254
- Essentials of Human Embryology Larson Chapter 7 p97-122 Heart, Chapter 8 p123-146 Vasculature
- Human Embryology Fitzgerald and Fitzgerald Chapter 13-17: p77-111

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 The Heart (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3693#3695) | Figure 15.6. Cascade of heart development} | [http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3698 Figure 15.3. Formation of the chick heart from the splanchnic lateral plate mesoderm (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3702) | Figure 15.4. Fusion of the right and left heart rudiments to form a single cardiac tube (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3699) | Figure 15.5. Specification of the atrium and ventricles occurs even before heart looping (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3701)
- **Molecular Biology of the Cell** 4th ed. Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 - Figure 21-35. The vertebrate body plan as a dorsoventral inversion of the insect body plan (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3860) Figure 22-40. The four classes of muscle cells of a mammal (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.4167)

Reviews

- Three-dimensional reconstruction of gene expression patterns during cardiac development. Soufan AT, Ruijter JM, van den Hoff MJ, de Boer PA, Hagoort J, Moorman AF. Physiol Genomics. 2003 May 13;13(3):187-95. Review. PMID: 12746463 (http://www.ncbi.nlm.nih.gov/pubmed/12746463)
- Moorman A, Webb S, Brown NA, Lamers W, Anderson RH. Development of the heart: (1) formation of the cardiac chambers and arterial trunks. Heart. 2003 Jul;89(7):806-14. PMID: 12807866 (http://www.ncbi.nlm.nih.gov/pubmed/12807866?dopt=Abstract)
- Yutzey KE, Kirby ML. Wherefore heart thou? Embryonic origins of cardiogenic mesoderm. Dev Dyn. 2002 Mar;223(3):307-20. Review. PMID: 11891982 (http://www.ncbi.nlm.nih.gov/pubmed/11891982?dopt=Abstract)
- Bruneau BG. Transcriptional regulation of vertebrate cardiac morphogenesis. Circ Res. 2002 Mar 22;90(5):509-19. Review. PMID: 11909814 (http://www.ncbi.nlm.nih.gov/pubmed/11909814?dopt=Abstract)

Search

- **Bookshelf** heart development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=heart_development) | cardiovascular development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=cardiovascular_development) |

- **Pubmed** heart development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=heart_development) | cardiovascular development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=cardiovascular_development) |

Terms

For more cardiovascular term definitions and links to related topics use the glossary.

angioblast - the stem cells in blood islands generating endothelial cells which will form the walls of both arteries and veins. (More? Blood Vessel)

angiogenesis - the formation of blood vessels also called vasculogenesis in the embryo.

anlage (German, *anlage* = primordium) structure or cells which will form a future more developed or differentiated adult structure.

blood islands - earliest sites of blood vessel and blood cell formation, seen mainly on yolk sac chorion.

cardinal veins - paired main systemic veins of early embryo, anterior, common, posterior.

cardiogenic region - region above prechordal plate in mesoderm where heart tube initially forms.

ectoderm - the layer (of the 3 germ cell layers) which form the nervous system from the neural tube and neural crest and also generates the epithelia covering the embryo.

endoderm - the layer (of the 3 germ cell layers) which form the epithelial lining of the gastrointestinal tract (GIT) and accessory organs of GIT in the embryo.

endocardium - lines the heart. Epithelial tissue lining the inner surface of heart chambers and valves.

endothelial cells - single layer of cells closest to lumen that line blood vessels.

extraembryonic mesoderm - mesoderm lying outside the trilaminar embryonic disc covering the yolk sac, lining the chorionic sac and forming the connecting stalk. Contributes to placental villi development.

haemocytoblasts - stem cells for embryonic blood cell formation.

anastomose - to connect or join by a connection (anastomosis) between tubular structures.

chorionic villi - the finger-like extensions which are the functional region of the placental barrier and maternal/fetal exchange. Develop from week 2 onward as: primary, secondary, tertiary villi.

estrogens - support the maternal endometrium.

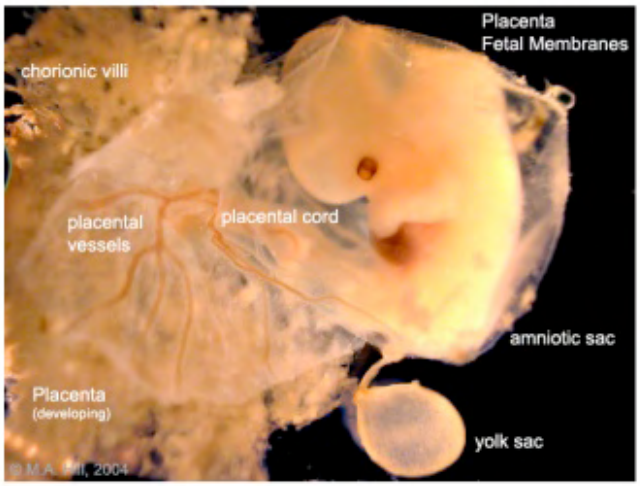
growth factor - usually a protein or peptide that will bind a cell membrane receptor and then activates an intracellular signaling pathway. The function of the pathway will be to alter the cell directly or indirectly by changing gene expression. (eg VEGF, shh)

2009 Lecture 8

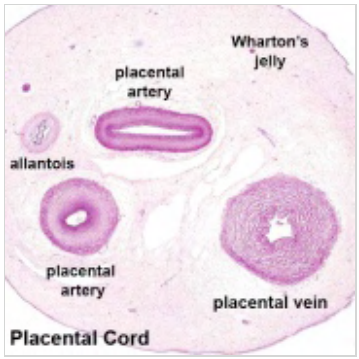
From Embryology

Contents

Introduction



This lecture is an introduction to the development and functions of the placenta.



Placental cord cross-section

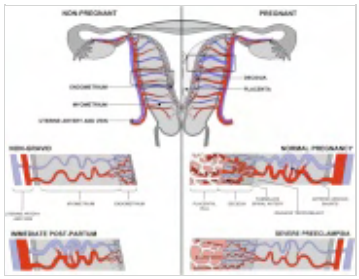
The placenta (Greek, *plakuos* = flat cake) named on the basis of this organs appearance. The placenta a mateno-fetal organ which begins developing at implantation of the blastocyst and is delivered with the fetus at birth. Only recently have we begun to understand the many different functions this organ carries out in addition to its role in embryonic nutrition. This lecture follows on the concepts of cardiovascular development covered in the previous lecture.

The placenta and placental blood at birth has recently been seen as a new source for stem cells in bone marrow replacement therapy in many diseases. (More? Stem Cells - Cord Blood (http://embryology.med.unsw.edu.au/Notes/stemcell4.htm))

- **Lectopia Lecture Audio** Lecture Date: 18-08-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Placenta (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48838)

Lecture Objectives

- Understanding of placental villi development
- Understanding of placental structure
- Understanding of placental functions
- Brief understanding of placental abnormalities


Uterine and placental vasculature

Textbook References

- **Human Embryology** Larson Ch7 p151-188 Heart, Ch8 p189-228 Vasculature
- The Developing Human: Clinically Oriented Embryology (6th ed.) Moore and Persaud Ch14: p304-349

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- Essentials of Human Embryology Larson Ch7 p97-122 Heart, Ch8 p123-146 Vasculature
- Human Embryology Fitzgerald and Fitzgerald Ch13-17: p77-111

UNSW Embryology Links

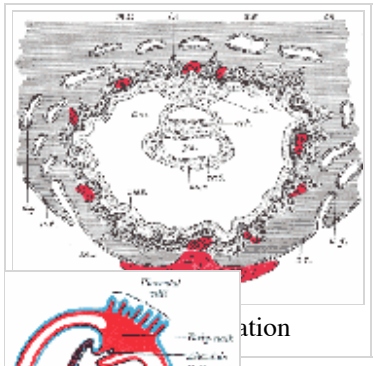
- **Placenta Slides** Placenta Lecture 8 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture08.htm) | Placenta Lecture 2008 - 1 slide/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L8Placentas1.pdf) | Placenta Lecture 2008 Slides - 4 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L8Placentas4.pdf) | Placenta Lecture 2008 Slides - 6 slides/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L8Placentas6.pdf)
- **Placenta Movies** Heart Movies (http://embryology.med.unsw.edu.au/Movies/heart.htm) | Heart Looping (http://embryology.med.unsw.edu.au//Movies/larsen/looping.mov) | Atrial Septation (http://embryology.med.unsw.edu.au//Movies/larsen/atrium.mov) | Realignment (http://embryology.med.unsw.edu.au//Movies/larsen/avc.mov) | Ventricular Septation (http://embryology.med.unsw.edu.au//Movies/larsen/ventricl.mov) | Heart Septation Models (http://embryology.med.unsw.edu.au/Movies/heart.htm#HeartSeptation) | Historic Heart Movie (http://embryology.med.unsw.edu.au/Movies/heart.htm#HistoricHeart) |

- **Placenta Notes** Introduction (http://embryology.med.unsw.edu.au/Notes/placenta.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/placenta2.htm) | Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/placenta3.htm) | Human (Stage22) (http://embryology.med.unsw.edu.au/Notes/placenta4.htm) | Histology (http://embryology.med.unsw.edu.au/Notes/placenta5.htm) | Villi Development (http://embryology.med.unsw.edu.au/Notes/placenta7.htm) | Maternal Decidua (http://embryology.med.unsw.edu.au/Notes/placenta8.htm) | Vascular Beds (http://embryology.med.unsw.edu.au/Notes/placenta6.htm) | Molecular (http://embryology.med.unsw.edu.au/Notes/placenta11.htm) | Postnatal (http://embryology.med.unsw.edu.au/Child/heart.htm) | Endocrine Placenta (http://embryology.med.unsw.edu.au/Notes/endocrine14.htm)

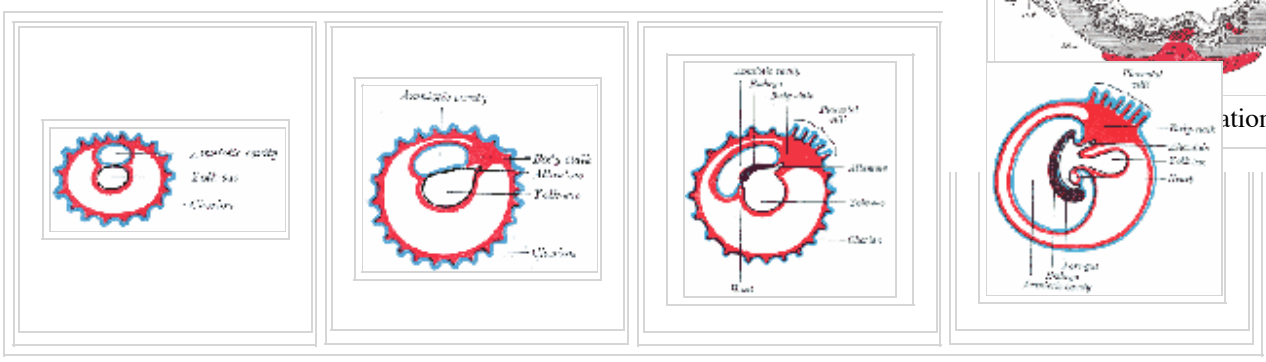
- System Notes (http://embryology.med.unsw.edu.au/sysnote.htm) | Development Timeline (http://embryology.med.unsw.edu.au/week/weekbyweek.htm)
- Virtual Microscopy fetal-membranes (http://vslide2.med.unsw.edu.au/fetal-membranes.html)

Nutrition

- **Histiotrophic** nutrition describes early placental development and the form of intital transfer of nutrition from maternal to embryo.
- **Hemotrophic** nutrition describes the later blood-borne nutrition.

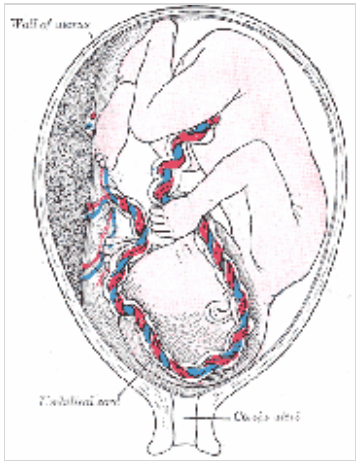


Fetal Membranes



Placenta at Birth

- **Placenta** (Greek, *plakuos* = flat cake)
- embryonic/maternal organ
- villous chorion/decidua basalis
- continuous with amniotic and chorionic sacks



Fetus in utero, between fifth and sixth months

Dimensions

- at birth - discoid up to 20cm diameter and 3 cm thick (term) and weighs 500-600 gm
- Shapes - accessory placenta, bidiscoid, diffuse, horseshoe
- maternal and embryonic surface, both delivered at parturition
  - retention may cause uterine hemorrhage

Maternal Surface

- Cotyledons - form cobblestone appearance, originally placental septa formed grooves
- covered with maternal decidua basalis

Fetal Surface

- umbilical cord attachment - cord 1-2 cm diameter, 30-90cm long
- covered with amniotic membrane and attached to chorionic plate
- umbilical vessels branch into chorionic vessels which anastomose

Placental Classification

Classification of placenta is on the basis of histological (microscopic) structural organization and layers between fetal and maternal circulation, giving 3 main groups:

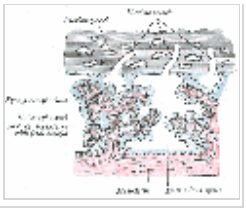
- **Haemochorial** - placenta where the chorion comes in direct contact with maternal blood (human)
- **Endotheliochorial** - maternal endometrial blood vessels are bare to their endothelium and these comes in contact with the chorion. (dogs, cats)
- **Epitheliochorial** - maternal epithelium of the uterus comes in contact with the chorion.considered as primitive (pigs, cows)

The presence of these three differing types of placenta have also been used to describe the pattern mammalian evolution. See also Placental Layers

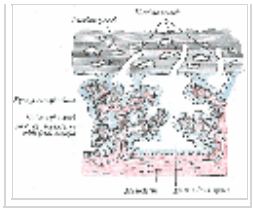
Placental Types

- Discoid in humans, mice, insectivores, rabbits, rats, and monkeys.
- Zonary in dogs, cats, bears and seals.
- Cotyledenary in cows, deer, goat, and giraffe.
- Diffuse in horses, pigs, camels, lemurs, opossums, kangaroos, and whales

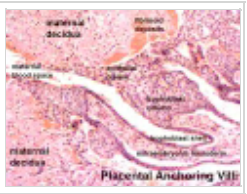
Chorionic Villi



Primary chorionic villi



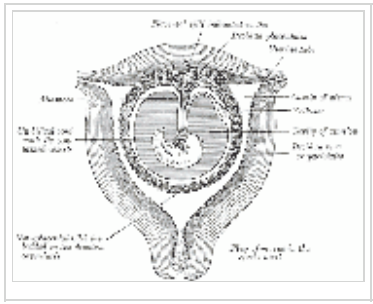
Secondary chorionic villi



Placenta anchoring villi

- **primary villi** - week 2, first stage of chorionic villi development, trophoblastic shell cells (syncitiotrophoblasts and cytotrophoblasts) form finger-like extensions into maternal decidua.
- **secondary villi** - week 3, second stage of chorionic villi development, extraembryonic mesoderm grows into villi, covers entire surface of chorionic sac.
- **tertiary villi** third stage of chorionic villi development, mesenchyme differentiates into blood vessels and cells, forms arteriocapillary network, fuse with placental vessels, developing in connecting stalk
- **stem villi** - or anchoring villi, cytotrophoblast cells attached to maternal tissue.
- **branched villi** - or terminal villi, grow from sides of stem villi, region of main exchange, surrounded by maternal blood in intervillous spaces.

Chorionoic Villi Location



- originally cover entire chorionic surface and become restricted to decidua basalis region forming 2 regions
- Frondosum - "leafy" where villi are mainly located
- Capsularis - smooth chorion, where villi are absent or not abundant

Chorionoic Villi Trimester Development

Trimester 1 and 2

- In the first two trimesters immature intermediate villi, developmental steps towards the stem villi.

Trimester 3

- Mature intermediate villi develop during the last trimester, produce numerous terminal villi.
- Terminal villi are not active outgrowths caused by proliferation of the trophoblast, but rather passive protrusions induced by capillary coiling due to excessive longitudinal growth of the fetal capillaries within the mature intermediate villi.
- The arrangement of the capillary bed in the terminal villi can vary from simple U-like loops to a richly branched network due to capillary elongation and sprouting.

(Data from PMID: 2327595 (http://www.ncbi.nlm.nih.gov/pubmed/11045879))

Placental Function

- 4 layers separate maternal and fetal blood: syncitiotrophoblast, cytotrophoblast, villi connective tissue and fetal capillary endothelium
- 3 main functions: metabolism, transport and endocrine

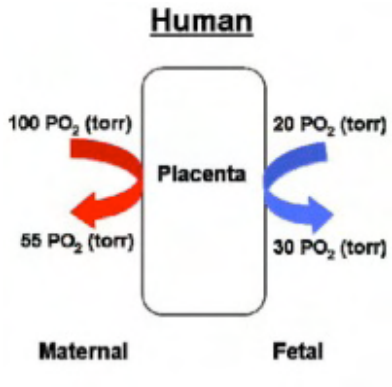
Placental Metabolism

Synthesizes: glycogen, cholesterol, fatty acids

- provides nutrient and energy

Placental Transport

gases and nutrition



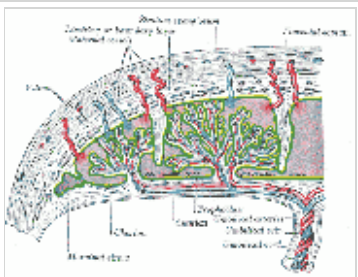
- oxygen, carbon dioxide, carbon monoxide
- water, glucose, vitamins
- hormones, mainly steroid not protein
- electrolytes
- maternal antibodies
- waste products - urea, uric acid, bilirubin
- drugs and their metabolites (fetal drug addiction)
- infectious agents (cytomegalovirus, rubella, measles, microorganisms)

Placental Endocrine

- Human chorionic gonadotrophin (hCG) - like leutenizing hormone, supports corpus luteum
- Human chorionic somatommotropin (hCS) (or placental lactogen) - hormone level increases in maternal blood through pregnancy, decreases maternal insulin sensitivity (raising maternal blood glucose levels and decreasing maternal glucose utilization) aiding fetal nutrition ("anti-insulin" function)
- Human chorionic thyrotropin (hCT) - Peptide placental hormone, similar to anterior pituitary released thyroid stimulating hormone (TSH), which along with human chorionic gonadotrophin (hCG) is thought to act on maternal thyroid. There is little recent research published on this hormone, its level and activities.
- Human chorionic corticotropin (hCACTH) - placental hormone thought to have corticotropin (ACTH)-like activity, increasing maternal cortisol levels.
- Steroid Hormones
  - progestins - progesterone, support of the endometrium and suppress uterine smooth muscle contractility.
  - estrogens - estriol, stimulate growth of the myometrium and mammary gland development.
  - both hormones support maternal endometrium
- Relaxin - Humans high levels early in pregnancy than at birth promotes angiogenesis probably plays a role in development of the uterus/ placenta than in the birth process

Placental Blood vessels

- form initially in the connecting stalk (then umbilical cord) anastomose in chorioni
  - extend maternally toward chorionic villi
  - extend embryonically to the sinus venosus and dorsal aorta

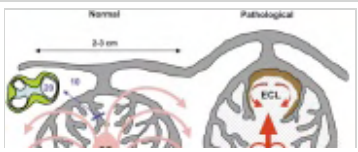


Scheme of placental circulation

Arteries - paired, carry deoxygenated blood (from dorsal aorta) and waste products to the placental villi

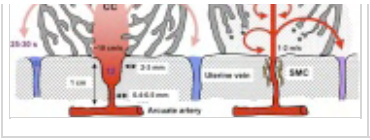
Veins - paired initially then only left at end of embryonic period, carry oxygenated blood to the embryo (sinus venosus) **Parturition (Childbirth) Overview**

Fetal Placenta



Trophoblast cells are the major source of placental hormones.

Placental growth hormone (PGH) is mainly expressed in the syncytiotrophoblast cells (PGH differs from pituitary derived growth hormone by 13 amino acids). extravillous cytotrophoblast - arise from anchoring villi invade the uterine spiral arteries, generating fibrinoid material and endovascular trophoblastic cells. syncytiotrophoblast



Fetal Blood Vessels At least 2 phases of development during pregnancy driven by vascular endothelial growth factor (VEGF):

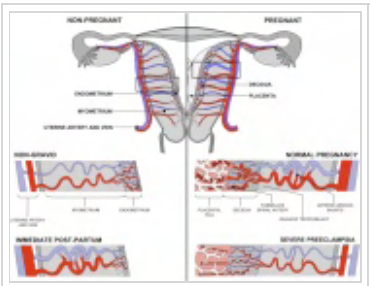
1. Initially cytotrophoblasts are the cellular stimulus to vasculogenesis and angiogenesis.
2. Later Hofbauer (lacental villi macrophages of mesenchymal origin) and stromal cells take over the stimulation of blood vessel development.

Placenta Human chorionic gonadotrophin (hCG) After implantation cells within the developing placenta (syncitiotrophoblasts) synthesize and secrete Human chorionic gonadotrophin (hCG) into the maternal bloodstream. The main function of serum hCG is to maintain the corpus luteum in the maternal ovary and therefore maintain the early pregnancy, that is block the menstrual cycle. Later the placenta itself supports the pregnancy.

Maternal Placenta

Fibrinoid - said to exist as 2 forms of extracellular matrix:

1. Fibrin-type fibrinoid is a maternal blood-clot product which replaces degenerative syncytiotrophoblast
2. Matrix-type fibrinoid is secreted by invasive extravillous trophoblast cells.

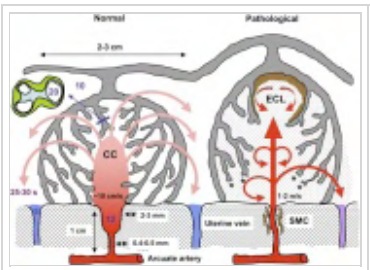


Uterine and placental vasculature

Fibrinoid layer (Nitabuch's layer) is thought to act to prevent excessively deep implantation.

Decidualization - process of endometrial stromal cells (fibroblast-like) change in morphology (polygonal cells) and protein expression and secretion (specific decidual proteins: prolactin, insulin-like growth factor binding protein-1, tissue factor, interleukin-15, and VEGF).

1. Estrogen and progesterone - receptive phase, luminal and glandular epithelial cells change in preparation for blastocyst adplantation.
2. Human Chorionic gonadotropin - luminal epithelium endoreplication leading to epithelial plaque formation.
3. Human Chorionic gonadotropin - trophoblast invasion and decidualization of human stromal fibroblasts.



Placenta spiral artery conversion

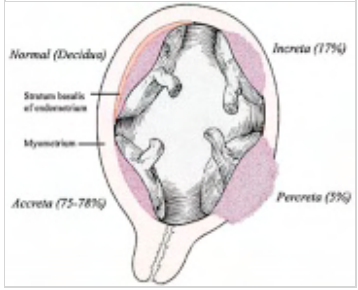
Artery Dilatation - due to extravillous trophoblast cells invading uterine wall and maternal spiral arteries replacing both smooth muscle with fibrinoid material and part of vessel endothelium. There is also a proliferation of maternal blood vessels.

Other changes

- Endoreplication - rounds of nuclear DNA replication without intervening cell or nuclear division (mitosis).
- Cytokines - of maternal origin also act on placental development.
- Natural Killer (NK) cells - 30% of all the decidual cells towards the end of the first trimester of pregnancy. These lymphocytes are present in the maternal decidua in large numbers (70%, normal circulating blood lymphocytes 15%) close to the extravillous trophoblast cells. Have a cytolytic potential against virus-infected and tumor-transformed cells.

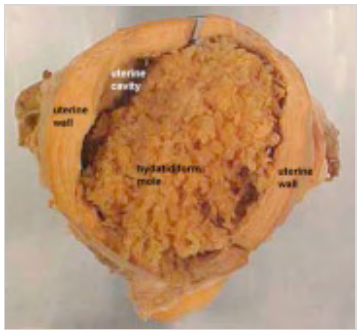
Placental Abnormalities

- **Placenta Accreta** - abnormal adherence, with absence of decidua basalis. The incidence of placenta accreta also significantly increases in women with previous cesarean section compared to those without a prior surgical delivery.
- **Placenta Increta** - occurs when the placenta attaches deep into the uterine wall and penetrates into the uterine muscle, but does not penetrate the uterine serosa. Placenta increta accounts for approximately 15-17% of all cases.
- **Placenta Percreta** - placental villi penetrate myometrium and through to uterine serosa.
- **Placenta Previa** - In this placenatal abnormality, the placenta overlies internal os of uterus, essentially covering the birth canal. This condition occurs in approximately 1 in 200 to 250 pregnancies. In the third trimester and at term, abnormal bleeding can require cesarian delivery and can also lead to Abruptio Placenta. Ultrasound screening programs during 1st and early 2nd trimester pregnancies now include placental localization. Diagnosis can also be made by transvaginal ultrasound.
- **Vasa Previa** - (vasa praevia) placental abnormality where the fetal vessels lie within the membranes close too or crossing the inner cervical os (opening). This occurs normally in 1:2500-5000 pregnancies and leads to complications similar too those for Placenta Previa.Type II is defined as the condition where the fetal vessels are found crossing over the internal os connecting either a bilobed placenta or a succenturiate lobe with the main placental mass. Some recent evidence of successful in utero laser ablation of type II vasa previa at 22.5 weeks of gestation.
- **Abruptio Placenta** - a retroplacental blood clot formation, abnormal hemorrhage prior to delivery.
- **Chronic Intervillositis** - (massive chronicintervillositis, chronic histiocytic intervillositis) Rare placental abnormality and pathology defined by inflammatory placental lesions, mainly in the intervillous space (IVS), with a maternal infiltrate of mononuclear cells (monocytes, lymphocytes, histiocytes) and intervillous fibrinoid deposition.



Placental abnormalities

Historic model of placenta previa



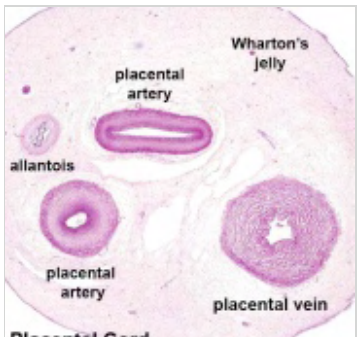
Hydatidiform mole pathology

- **Hydatidiform mole** - placental tumor with no embryo development. Several forms of hydatidiform mole: partial mole, complete mole and persistent gestational trophoblastic tumor. Many of these tumours arise from a haploid sperm fertilizing an egg without a female pronucleus (the alternative form, an embryo without sperm contribution, is called parthenogenesis). The tumour has a "grape-like" placental appearance without enclosed embryo formation. Following a first molar pregnancy, there is approximately a 1% risk of a second molar pregnancy.

Links: Placental Abnormalities (http://embryology.med.unsw.edu.au/Notes/placenta2.htm)

Placental Cord Abnormalities

There are few abnormalities associated with umbilical cord development, other that abnormally short or long cords, which in most cases do not cause difficulties. In some cases though, long cords can wrap around limbs or the fetus neck, which can then restrict blood flow or lead to tissue or nerve damage, and therefore effect develoment.



- **Cord knotting** - can also occur (1%) in most cases these knots have no effect, in some cases of severe knotting this can prevents the passage of placental blood.
- **Cord torsion** - Rare event where even without knot formation can

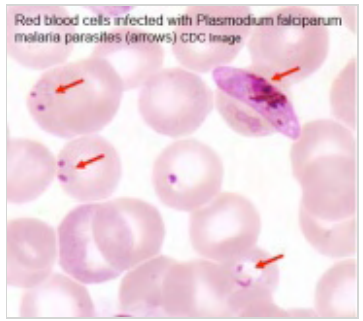
also affect placental blood flow, even leading to fetal demise.

Placental cord cross-section

Links: Placental Abnormalities (http://embryology.med.unsw.edu.au/Notes/placenta2.htm) | WebPath - umbilical cord knot 1 (http://www-medlib.med.utah.edu/WebPath/PLACHTML/PLAC010.html) | WebPath - umbilical cord knot 2 (http://www-medlib.med.utah.edu/WebPath/PLACHTML/PLAC028.html) | WebPath - Pseudoknot of umbilical cord, gross (http://www-medlib.med.utah.edu/WebPath/PLACHTML/PLAC073.html) | WebPath - Torsion of umbilical cord, gross (http://www-medlib.med.utah.edu/WebPath/PLACHTML/PLAC012.html) | WebPath - Torsion of umbilical cord, with fetal demise, gross (http://www-medlib.med.utah.edu/WebPath/PLACHTML/PLAC011.html)

Placental Infections

- Several infective agents may cross into the placenta from the maternal circulation, as well as enter the embry/fetal circulation. The variety of bacterial infections that can occur during pregnancy is as variable as the potential developmental effects, from virtually insignificant to a major developmental, abortive or fatal in outcome.
- Pregnant women have an increased susceptibility to malaria infection. Malarial infection of the placenta by sequestration of the infected red blood cells leading to low birth weight and other effects. There are four types of malaria caused by the protozoan parasite Plasmodium falciparum (main), Plasmodium vivax, Plasmodium ovale, Plasmodium malariae). This condition is common in regions where malaria is endemic with women carrying their first pregnancy (primigravida).



Malaria (plasmodium falciparum)

Placental Pathology

MH - content in this section is not examinable.

- Chronic Villitis - can occur following placental infection leading to maternal inflammation of the villous stroma, often with associated intervillositis. The inflammation can lead to disruption of blood flow and necrotic cell death.
- Massive Chronic Intervillositis (MCI) - maternal blood-filled space is filled with CD68-positive histiocytes and an increase in fibrin, occuring more commonly in the first trimester.
- Meconium Myonecrosis - prolonged meconium exposure leads to toxic death of myocytes of placental vessels (umbilical cord or chorionic plate).
- Neuroblastoma - a fetal malignancy that leads to an enlarged placenta, with tumor cells in the fetal circulation and rarely in the chorionic villi.
- Thrombophilias - (protein C or S deficiency, factor V Leiden, sickle cell disease, antiphospholipid antibody) can generate an increased fibrin/fibrinoid deposition in the maternal or intervillous space, this can trap and kill villi.

Take the Quiz

1. The maternal endometrium response to trophoblast invasion is called the decidual reaction.

- ○ true
- ○ false

2. The human placenta is classified as :

- ○ Endotheliochorial
- ○ Haemochorial

- Epitheliochoria
- Mesoeliochorial

3. Stem villi - or terminal villi, are the region of main exchange, surrounded by maternal blood in intervillous spaces.

- true
- false

4. The 4 cellular layers separating maternal and fetal blood in sequence are:

- spiral artery wall, Nichbaur layer, cytotrophoblast and Hofbaur layer
- syncitiotrophoblast, cytotrophoblast, villi connective tissue and fetal capillary endothelium
- maternal lacuna, trophoblast layer, endothelial and fetal red blood cell
- fetal capillary endothelium, villi connective tissue, cytotrophoblast and syncitiotrophoblast

Submit

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West -

Additional Textbooks

- Before We Are Born (5th ed.) Moore and Persaud
- Essentials of Human Embryology
- Human Embryology Fitzgerald and Fitzgerald
- Human Embryology and Developmental Biology Carlson

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 - Figure 11.30. Human embryo and placenta after 40 days of gestation (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.2627) | Figure 15.11. Transfer of oxygen from the mother to the fetus in human embryos (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3736) | Formation of extraembryonic membranes (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=placenta&rid=dbio.section.2609#2626) | Figure 15.9. Circulatory system of the early avian embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3733)

- **Endocrinology: An Integrated Approach** Nussey, S.S. and Whitehead, S.A. London:Taylor & Francis; c2001

Search

- **Bookshelf** placenta (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=placenta) | placental villi development

(http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=placental_villi_development) |

- **Pubmed** placenta development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=placenta_development) | placenta (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=placenta) | placental villi (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=placental_villi) |

Reviews

- Vogel P. (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=16085037&dopt=Abstract) [See Related Articles (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Display&dopt=pubmed_pubmed&from_uid=16085037&tool=ExternalSearch)] The current molecular phylogeny of Eutherian mammals challenges previous interpretations of placental evolution. Placenta. 2005 Sep-Oct;26(8-9):591-6.
- Cross JC. (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15837063&dopt=Abstract) [See Related Articles (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Display&dopt=pubmed_pubmed&from_uid=15837063&tool=ExternalSearch)] How to make a placenta: mechanisms of trophoblast cell differentiation in mice--a review. Placenta. 2005 Apr;26 Suppl A:S3-9.
- Simmons DG, Cross JC. (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15963972&dopt=Abstract) [See Related Articles (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Display&dopt=pubmed_pubmed&from_uid=15963972&tool=ExternalSearch)] Determinants of trophoblast lineage and cell subtype specification in the mouse placenta. Dev Biol. 2005 Aug 1;284(1):12-24.
- Rama S, Rao AJ. (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14619978&dopt=Abstract) [See Related Articles (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Display&dopt=pubmed_pubmed&from_uid=14619978&tool=ExternalSearch)] Regulation of growth and function of the human placenta. Mol Cell Biochem. 2003 Nov;253(1-2):263-8.
- Evain-Brion D, Malassine A. (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12914725&dopt=Abstract) [See Related Articles (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Display&dopt=pubmed_pubmed&from_uid=12914725&tool=ExternalSearch)] Human placenta as an endocrine organ. Growth Horm IGF Res. 2003 Aug;13 Suppl A:S34-7.

External Links

- Comparative Placentation (http://placentation.ucsd.edu/homefs.html)
- University of Ottawa - Histology - Placenta (http://courseweb.edteched.uottawa.ca/medicine-histology/English/Reproduction/Placenta/Default.htm)
- Virtual Microscopy Histology fetal-membranes (http://vslide2.med.unsw.edu.au/fetal-membranes.html) | female reproductive (http://vslide2.med.unsw.edu.au/female-reproductive.html)

Placenta Development Terms

- **after-birth** - term used to describe the delivery of placenta and placental membranes following birth of the child.
- **allantois** - an endodermal diverticulum from the hindgut which extends from the superior end of the developing bladder into the adjacent placental cord.
- **anastomose** - term used to describe the connection between two tubes. Applied to describe the connection between peripheral blood vessels without an intervening capillary bed.
- **angiogenesis** development of new vessels from already existing vessels, this process is secondary to vasculogenesis which is the initial formation of first blood vessels by differentiation of pluripotent

mesenchymal cells (extraembryonic mesoderm).

- **angioblasts** form clusters or blood islands on surface of yolk sac.
- **capsularis**
- **chorionic sac** fetal membrane that surrounds the developing embryo.
- **cord knotting** umbilical cord knotting occurs in 1%, prevents the passage of placental blood. pseudoknots also occur usually with no effect.
- **cotyledons** maternal side cobblestone appearance, originally placental septa formed grooves is covered with maternal decidua basalis.
- **cytotrophoblast** extraembryonic cells of trophoblastic shell surrounding embryo, contribute to villi and placental membranes.
- **decidua basalis reaction** occurs in maternal endometrium at site of, and following, blastocyst implantation. Seen as a deposition of glycogen and proliferation of blood vessels. (see also decidualization)
- **decidualization** process by which uterine stromal cells differentiate in response to both steroid hormones and embryonic signals into large epitheliod decidual cells. This process is essential for the progress of implantation and establishing fetal-maternal communication.
- **endocrine** function of placenta:
    - Human chorionic gonadotrophin (hCG) like leutenizing hormone, supports corpus luteum
    - Human chorionic somatommotropin (hCS) or placental lactogen, stimulate mammary development
    - Human chorionic thyrotropin (hCT)
    - Human chorionic corticotropin (hCACTH)
    - progesterone and estrogens support maternal endometrium
    - relaxin- role in parturition, softens ligaments
- **fetal drug addiction** occurs when drugs used maternally cross the placental barrier and can establish addiction in the unborn fetus.
- **fetal erythroblastosis** (Haemolytic Disease of the Newborn), an immune problem from fetus Rh+ /maternal Rh-, leakage from fetus causes anti-Rh antibodies, which is then dangerous for a 2nd child.
- **frondosum-**
- **haemocytoblasts** (hemangioblast) stem cells for embryonic blood cell formation, often appearing as a "cluster" or "island".
- **Haemolytic Disease of the Newborn** - see fetal erythroblastosis.
- **hemotrophic nutrition** - Term used to describe in late placental development the transfer of blood-borne nutrition from maternal to embryo/fetus compared to early [#histiotrophic_nutrition histiotrophic nutrition]. (More? Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy. Burton GJ, Watson AL, Hempstock J, Skepper JN, Jauniaux E. J Clin Endocrinol Metab. 2002 Jun;87(6):2954-9. PMID: 12050279 (http://www.ncbi.nlm.nih.gov/pubmed/12050279) | J Clin Endocrinol Metab. (http://jcem.endojournals.org/cgi/content/full/87/6/2954))
- **histiotrophic nutrition** - Term used to describe in early placental development the intital transfer of nutrition from maternal to embryo (histiotrophic nutrition) compared to later blood-borne nutrition ([#hemotrophic_nutrition hemotrophic nutrition]). Histotroph is the nutritional material accumulated in spaces between the maternal and fetal tissues, derived from the maternal endometrium and the uterine glands. This nutritional material is absorbed by phagocytosis initially by blastocyst trophectoderm and then by trophoblast of the placenta. in later placental development nutrition is by the exchange of blood-borne materials between the maternal and fetal circulations, hemotrophic nutrition. (More? Uterine glands provide histiotrophic nutrition for the human fetus during the first trimester of pregnancy. Burton GJ, Watson AL, Hempstock J, Skepper JN, Jauniaux E. J Clin Endocrinol Metab. 2002 Jun;87(6):2954-9. PMID: 12050279 (http://www.ncbi.nlm.nih.gov/pubmed/12050279) | J Clin Endocrinol Metab. (http://jcem.endojournals.org/cgi/content/full/87/6/2954))
- **Hofbauer cells** - placental villi macrophages of mesenchymal origin with potentially additional functions (vasculogenesis/angiogenesis, villi remodeling, regulation of stromal water content) to their macrophage role.
- **Human chorionic gonadotrophin-** (hCG) like leutenizing hormone, supports corpus luteum
- **Human chorionic somatommotropin** - (hCS) or placental lactogen - hormone level increases in maternal blood through pregnancy, decreases maternal insulin sensitivity (raising maternal blood glucose levels and decreasing maternal glucose utilization) aiding fetal nutrition.
- **Human chorionic thyrotropin-** (hCT) placental derived hormone equivilant to thyroid

- **Human chorionic corticotropin-** (hCACTH) placental derived hormone equivilant to corticotropin (ACTH) from the pituitary.
- **methyldopa** - (alpha methyldopa) A central alpha agonist used to lower blood pressure. Used as an antihypertensive drug to lower blood pressure in pre-eclampsia, acting by either a direct or indirect central vasodilatory mechanism. A recent study suggests this drug may have a direct effect on placental and/or endothelial cell function in pre-eclampsia patients, altering angiogenic proteins. Drug commercial brandname (USA) "Aldomet", also available in combination with other drugs: methyldopa and chlorothiazide "Aldochlor", methyldopa and hydrochlorothiazide "Aldoril". (More? Placenta Abnormalities - Pre-eclampsia (http://embryology.med.unsw.edu.au/Notes/placenta2.htm#Pre-eclampsia) | Medline Plus - Methyldopa (http://www.nlm.nih.gov/medlineplus/druginfo/meds/a682242.html) | Effect of antihypertensive therapy with alpha methyldopa on levels of angiogenic factors in pregnancies with hypertensive disorders. Khalil A, Muttukrishna S, Harrington K, Jauniaux E. PLoS ONE. 2008 Jul 23;3(7):e2766. PMID: 18648513 (http://www.ncbi.nlm.nih.gov/pubmed/18648513))
- **maternal antibodies-** antibodies from the mother's immune system that are capable of crossing placental barrier. They can provide immune protection to the embryo, but may also participate in immune disease (fetal erythroblastosis).
- **maternal sinusoids-** placental spaces around chorionic villi that are filled with maternal blood. Closest maternal/fetal exchange site.
- **Nitabuch's layer** (fibrinoid layer) layer formed at maternal/fetal interface during placentation and is thought to act to prevent excessively deep conceptus implantation. Fibrin-type fibrinoid (maternal blood-clot product) and matrix-type fibrinoid (secreted by invasive extravillous trophoblast cells).
- **placenta**- (Gk. plakuos= flat cake) describes its typical mature discoid shape (20cm diameter and 3 cm thick at term,weighs 500-600 gm).
- **placenta accreta-** abnormal, adherence with absence of decidua basalis.
- **placental arteries-** paired, carry deoxygenated blood and waste from the embryo (dorsal aorta->internal iliacs->PA)
- **placental blood**- blood found within the placental vessels. Obviously part of the fetal blood, but can be collected at birth for theraputic use containing blood stem cells (see cord blood banks).
- **placental blood vessels-** form initially in the connecting stalk (then umbilical cord), anastomose in chorioni and extend maternally toward chorionic villi, extend embryonically to the sinus venosus and dorsal aorta.
- **placental layers-** 4 layers separate maternal and fetal blood: syncitiotrophoblast, cytotrophoblast, villi connective tissue, and fetal capillary endothelium.
- **placenta percreta-** abnormal, villi penetrate myometrium.
- **placenta previa-** placenta overlies internal os of uterus, abnormal bleeding, may require cesarian delivery.
- **placental veins-** paired initially then usually only one left at end of embryonic period, carry oxygenated blood to the embryo (sinus venosus)
- **primary villi-** develop week 2, consist of trophoblastic shell cells both syncitiotrophoblasts and cytotrophoblasts. Form finger-like extensions into the maternal endometrium.
- **protein hormone-** usually a protein distributed in the blood that binds to membrane receptors on target cells in different tissues. Do not easliy cross placental barrier.
- **relaxin-** hormone.
- **secondary villi**- develop week 3, extraembryonic mesoderm grows into villi, initially covers entire surface of chorionic sac.
- **sinus venosus-** cavity into which all major embryonic paired veins supply (vitelline, placental, cardinal)
- **syncitiotrophoblast-** extraembryonic cells of trophoblastic shell surrounding embryo, outside the cytotrophoblast layer, involved with implantation of the blastocyst by eroding extracellular matrix surrounding maternal endometrial cells at site of implantation, also contribute to villi. (dark staining, multinucleated)
- **tertiary villi-** develop week 4, mesenchyme within secondary villi differentiates into blood vessels and cells, forms arteriocapillary network, fuse with placental vessels developing in connecting stalk.
- **trophoblast-**
- **umbilical cord-** fetal attachment cord 1-2 cm diameter, 30-90cm long, covered with amniotic attached to chorionic plate, umbilical vessels (artery, vein) branch into chorionic vessels. Vessels anastomose within the placenta.
- **vasculogenesis** formation of first blood vessels by differentiation of pluripotent mesenchymal cells

(extraembryonic mesoderm) followed by angiogenesis which is the development of new vessels from already existing vessels.

- **villi-** initially outgrowth of the trophoblastic shell which involve other tissues with development. Develop in sequence (primary, secondary, tertiary) with mature villi being stem por branched type.
- **virus-** small infectious agent able to cross placental barrier. Can infect embryo and cause developmental abnormalities. (e.g. cytomegalovirus, rubella, measles)
- **vitelline-** Blood vessels cover entire surface of yolk sac and connect to embryo through yolk stalk
  - Arteries- arises from dorsal aorta and contribute to adult GIT arteries.
  - Veins- empties into sinus venosus and contribute to the adult portal system.
- **waste products** products of cellular metabolism and cellular debris, e.g.- urea, uric acid, bilirubin
- **Wharton's jelly** placental cord (umbilical cord) gelatinous connective tissue composed of myofibroblast-like stromal cells, collagen fibers, and proteoglycans. Increases in volume (myxomatous, connective tissue embedded in mucus) at parturition to assist closure of placental blood vessels. Matrix cells from Wharton's jelly have recently been identified as a potential source of stem cells. This placental cord substance is named after Thomas Wharton (1614-1673) an English physician and anatomist who first described it.

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Original Glossary (http://embryology.med.unsw.edu.au/Notes/Index/Index.htm)

Course Content 2009

Embryology Introduction | Cell Division/Fertilization | Cell Division/Fertilization | Week 1&2 Development | Week 3 Development | Lab 2 | Mesoderm Development | Ectoderm, Early Neural, Neural Crest | Lab 3 | Early Vascular Development | **Placenta** | Lab 4 | Endoderm, Early Gastrointestinal | Respiratory Development | Lab 5 | Head Development | Neural Crest Development | Lab 6 | Musculoskeletal Development | Limb Development | Lab 7 | Kidney | Genital | Lab 8 | Sensory - Ear | Integumentary | Lab 9 | Sensory - Eye | Endocrine | Lab 10 | Late Vascular Development | Fetal | Lab 11 | Birth, Postnatal | Revision | Lab 12 | Lecture Audio | Course Timetable

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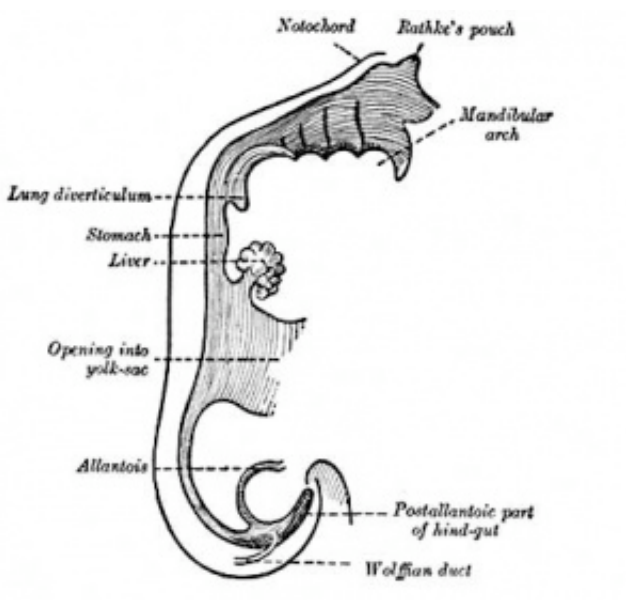
2009 Lecture 9

From Embryology

Contents

Endoderm Development

Introduction



This lecture will cover the early development of the endoderm layer of the trilaminar embryo as it contributes to the lining, glands and organs of the gastrointestinal tract (GIT). Note that we will be returning in the laboratory and later to discuss the gastrointestinal tract, associated organs and physical growth changes.

Gastrulation, or gut formation, was historically the easiest observable feature of frog development.During the 4th week the 3 distinct portions (fore-, mid- and hind-gut) extend the length of the embryo and will contribute different components of the GIT. The large mid-gut is generated by lateral embryonic folding which "pinches off" a pocket of the yolk sac, the 2 compartments continue to communicate through the vitelline duct. On this current page there is a brief developmental overview and stage 13/14 embryo overview. The oral cavity (mouth) is formed following breakdown of the buccopharyngeal membrane (=oropharyngeal) and contributed to mainly by the pharynx lying within the pharyngeal arches. The opening of the GIT means that it contains amniotic fluid, which is also swallowed later in development. From the oral cavity the next portion of the foregut is initially a single gastrointestinal (oesophagus) and respiratory (trachea) common tube, the pharynx which lies behind the heart. Note that the respiratory tract will also form from a ventral bud arising at this level.

- **iLecture Audio** Lecture Date: 24-08-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Gastrointestinal Tract (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48827)

Lecture Objectives

- Understanding of germ layer contributions to the early gastrointestinal tract (GIT)
- Understanding of the folding of the GIT
- Understanding of three main GIT embryonic divisions
- Understanding of associated organ development (liver, pancreas, spleen)

- Brief understanding of mechanical changes (rotations) during GIT development
- Brief understanding of gastrointestinal abnormalities

Textbook References

- **Human Embryology** Larson Chapter 9 p229-260
- **The Developing Human: Clinically Oriented Embryology** (6th ed.) Moore and Persaud Chapter 12 p271-302

Additional Textbooks

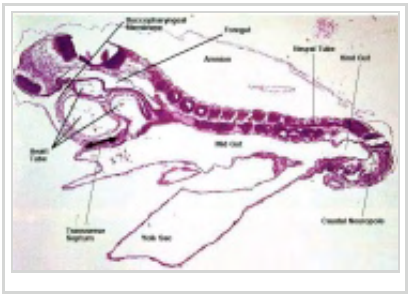
- Before We Are Born (5th ed.) Moore and Persaud Chapter 13 p255-287
- Essentials of Human Embryology Larson Chapter 9 p123-146
- Human Embryology Fitzgerald and Fitzgerald Chapter 19,20 p119-123
- Anatomy of the Human Body 1918 Henry Gray 2. The Digestive Apparatus (http://www.bartleby.com/107/241.html)

Germ Layer Contributions

- **Endoderm** - epithelium and associated glands
- **Mesoderm** (splanchnic) - mesentry, connective tissues, smooth muscle, blood vessels
- **Ectoderm** (neural crest) - enteric nervous system

Both endoderm and mesoderm will contribute to associated organs.

Folding



Folding of the embryonic disc occurs ventrally around the notochord, which forms a rod-like region running rostro-caudally in the midline.

In relation to the notochord:

- **Laterally** (either side of the notochord) lies mesoderm.
- **Rostrally** (above the notochord end) lies the buccopharyngeal membrane, above this again is the mesoderm region forming the heart.
- **Caudally** (below the notochord end) lies the primitive streak (where gastrulation occurred), below this again is the cloacal membrane.
- **Dorsally** (above the notochord) lies the neural tube then ectoderm.
- **Ventrally** (beneath the notochord) lies the mesoderm then endoderm.

The ventral endoderm (shown yellow) has grown to line a space called the yolk sac. Folding of the embryonic disc "pinches off" part of this yolk sac forming the first primative GIT. Movies - Endoderm folding (http://embryology.med.unsw.edu.au/Movies/larsen/yolk.mov) | Folding overview (http://embryology.med.unsw.edu.au/Movies/larsen/exoves.mov)

The cartoon above is a section through the trunk of the trilaminar embryo showing the further development of the 3 layers and the space (coelom) that forms in the mesoderm (only the righhand side is shown).

Within the embryonic disc lateral plate mesoderm a space (coelom) forms, it lies within the embryo and so is called the **intraembryonic coelom**. This single "horseshoe-shaped" space will form the 3 major body cavities: **pericardial** (around the heart), **pleural** (around the lungs) and **peritoneal** (around the GIT and visceral organs).

The mesoderm adjacennt to the endoderm is now called the **splanchnic mesoderm** which forms the connective tissue and muscular wall of the GIT.

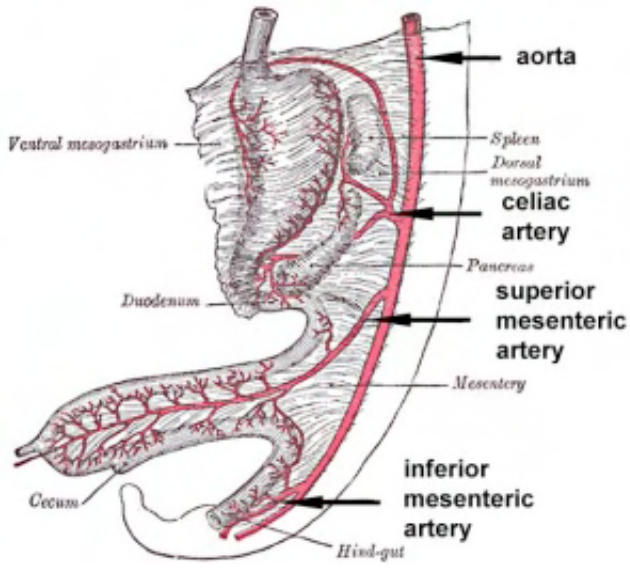
Note intraembryonic coelomic cavity communicates with extraembryonic coelom (space outside the embryo) through portals (holes) initially on lateral margin of embryonic disc.

Folding (http://embryology.med.unsw.edu.au/Medicine/BGDlabGIT_2.htm)

Canalization

Beginning at week 5 endoderm in the GIT wall proliferates to the extent of totally blocking (occluding) by week 6, over the next two weeks this tissue degenerates reforming a hollow gut tube. The process is called recanalization (hollow, then solid, then hollow again), abnormalities in this process can lead to duplications or stenosis. By the end of week 8 the GIT endoderm tube is a tube once more.

3 GIT divisions



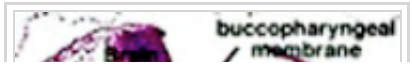
During the 4th week the 3 distinct portions (fore-, mid- and hind-gut) extend the length of the embryo and will contribute different components of the GIT. These 3 divisions are also later defined by the vascular (artery) supply to each of theses divisions.

The large mid-gut is generated by lateral embryonic folding which "pinches off" a pocket of the yolk sac, the 2 compartments continue to communicate through the vitelline duct.

The oral cavity (**mouth**) is formed following breakdown of the buccopharyngeal membrane (oropharyngeal, oral membrane) and contributed to mainly by the pharynx lying within the pharyngeal arches. The opening of the GIT means that it contains amniotic fluid, which is also swallowed later in development.

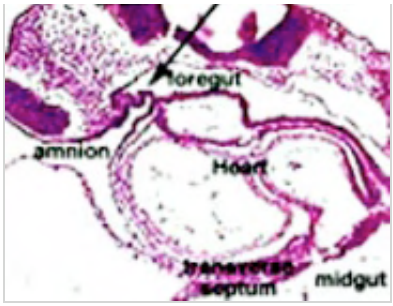
Foregut

From the oral cavity the next portion of the foregut is initially a single gastrointestinal (oesophagus) and respiratory (trachea) common tube, the



pharynx which lies behind the heart. Note that the respiratory tract will form from a ventral bud arising at this level.

- Oral cavity
- Pharynx (esophagus, trachea)
- Respiratory tract
- Stomach

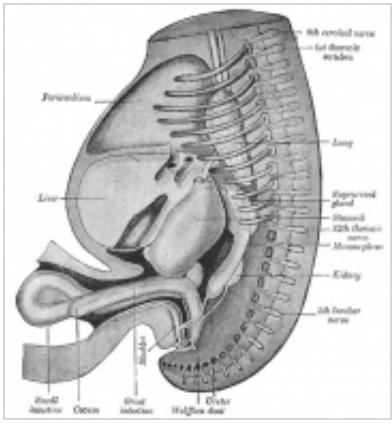


Stage 11 foregut

Midgut

From beneath the stomach the initial portion of the small intestine, the duodenum, and the associated pancreas now lie.

Much of the **midgut is herniated** at the umbilicus external to the abdomen through development. A key step in development is the rotation of this midgut that must occur to place the GIT in the correct abdominal position with its associated mesentry. The GIT itself differentiates to form significantly different structures along its length: oesophagus, stomach, duodenum, jejunum, iliem (small intestine), colon (large intestine). (More? [git13.htm Intestine Development])

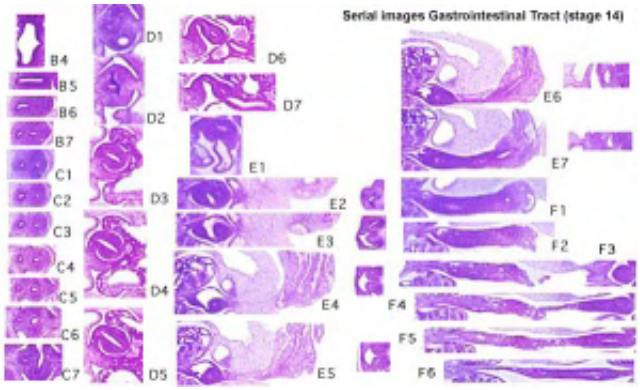

midgut herniation

The **mesentries** of the GIT are generated from the common dorsal mesentry, with the ventral mesentry contributing to the **lesser omentum** and **falciform ligament**.

Hindgut

The distral transverse colon, descending colon, sigmoid colon, rectum and cloaca. The **cloaca** is the common urogenital sinus which will later become partitioned into an anterior urinary and posterior GIT rectal component.

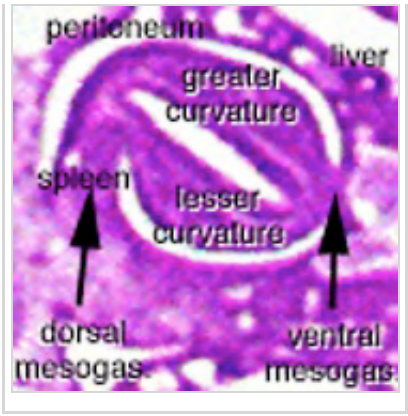
Stage 14



Stomach

During week 4 where the stomach will form the tube begins to dilate

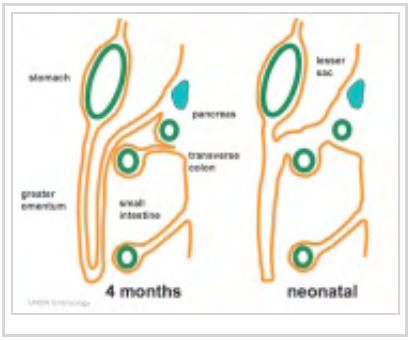
During week 4 where the stomach will form the tube begins to dilate, forming an enlarged lumen in the tube. Dorsal border grows more rapidly than ventral, which establishes the greater curvature of the stomach. A second rotation (of 90 degrees) occurs on the longitudinal axis establishing the adult orientation of the stomach.



stomach notes (http://embryology.med.unsw.edu.au/Notes/git10.htm) | Movie - stomach rotation (http://embryology.med.unsw.edu.au/Movies/larsen/stomrot2.mov)

Greater Omentum

The greater omentum hangs like an apron over the small intestine and transverse colon. It begins attacted to the inferior end of the stomach as a fold of the dorsal mesogastrium which later fuses to form the structure we recognise anatomically. The figure shows a lateral view of this process comparing the early second trimester arrangement with the newborn structure.



Duodenum/Pancreas Rotation

After the stomach the initial portion of the GIT tube is the duodenum which initially lies in the midline within the peritoneal cavity, but then (along with the attached pancreas) undergoes rotation to become a retroperitoneal structure.

The diagram shows this rotation with spinal cord at the top, vertebral body then dorsal aorta then pertioneal wall and cavity.

Midgut Herniation

Gastrointestinal Tract Associated Organs

Liver

The transverse septum (septum transversum) arises at an embryonic junctional site. The junctional region externally is where the ectoderm of the amnion meets the endoderm of the yolk sac. The junctional region internally is where the foregut meets the midgut. The mesenchymal structure of the transverse septum provides a support within which both blood vessels and the liver begin to form.

liver notes (http://embryology.med.unsw.edu.au/Notes/git7.htm)

Spleen

Mesoderm within the dorsal mesogastrium form a long strip of cells adjacent to the forming stomach above the developing pancreas.

The spleen is located on the left side of the abdomen and has a role initially in blood and then immune system development. The spleen's haematopoietic function (blood cell formation) is lost with embryo development and lymphoid precursor cells migrate into the developing organ. Vascularization of the spleen

arises initially by branches from the dorsal aorta.

spleen notes (http://embryology.med.unsw.edu.au/Notes/git8.htm)

Pancreas

At the foregut/midgut junction the septum transversum generates 2 pancreatic buds (dorsal and ventral endoderm) which will fuse to form the pancreas. The dorsal bud arises first and generates most of the pancreas. The ventral bud arises beside the bile duct and forms only part of the head and uncinate process of the pancreas.

pancreas notes (http://embryology.med.unsw.edu.au/Notes/git9.htm)

Gastrointestinal Tract Abnormalities

Lumen Abnormalities

There are several types of abnormalities that impact upon the continuity of the gastrointestinal tract lumen.

- Atresia - interuption of the lumen (esophageal atresia, duodenal atresia, extrahepatic biliary atresia, anorectal atresia)
- Stenosis - narrowing of the lumen (duodenal stenosis, pyloric stenosis).
- Duplication - incomplete recanalization resulting in parallel lumens, this is really a specialized form of stenosis.

Meckel's Diverticulum

This GIT abnormality is a very common and results from improper closure and absorption of the omphalomesenteric duct (vitelline duct) in development. This transient developmental duct connects the yolk to the primitive GIT.

Intestinal Malrotation

Intestinal Malrotation (http://embryology.med.unsw.edu.au/Notes/git2.htm#IntestinalMalrotation)

Intestinal Aganglionosis

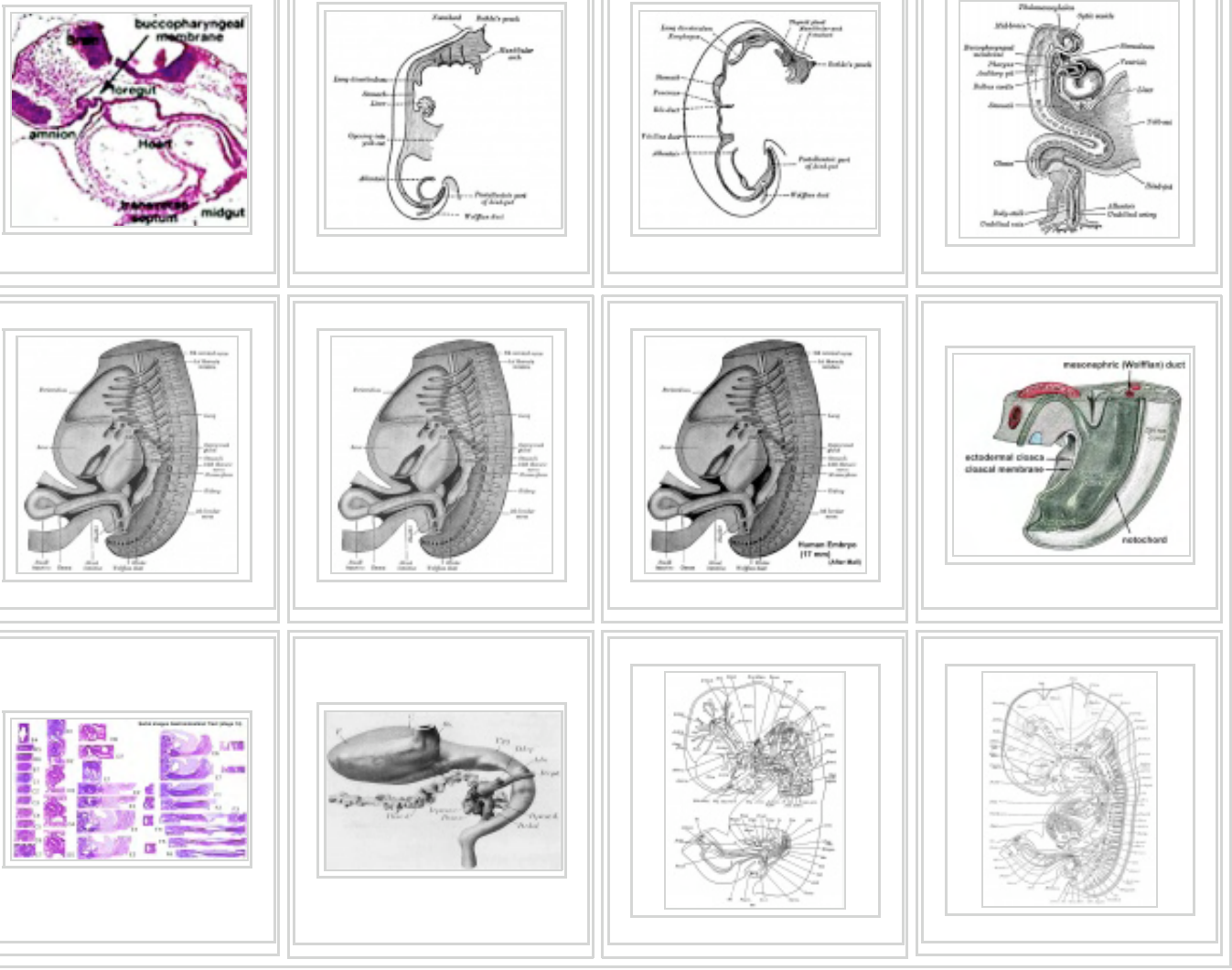
(intestinal aganglionosis, Hirschsprung's disease, aganglionic colon, megacolon, congenital aganglionic megacolon, congenital megacolon) A condition caused by the lack of enteric nervous system (neural ganglia) in the intestinal tract responsible for gastric motility (peristalsis).

MH - will cover again in neural crest lecture.

Gastroschisis

Gastroschisis (omphalocele, paraomphalocele, laparoschisis, abdominoschisis, abdominal hernia) is a congenital abdominal wall defect which results in herniation of fetal abdominal viscera (intestines and/or organs) into the amniotic cavity. Incidence of gastroschisis has been reported at 1.66/10,000, occuring more frequently in young mothers (less than 20 years old). By definition, it is a body wall defect, not a gastrointestinal tract defect, which in turn impacts upon GIT development.

Images



UNSW Embryology Links

- Lecture 9 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture09.htm)
- **Gastrointestinal Tract Notes** Overview of GIT Formation (http://embryology.med.unsw.edu.au/Notes/git6.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/git2.htm) | Overview Stage 13/14 Overview (http://embryology.med.unsw.edu.au/Notes/#Pig) | Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/git3.htm) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/git4.htm) | Selected stage 22 (http://embryology.med.unsw.edu.au/Notes/git5.htm) | Histology (http://embryology.med.unsw.edu.au/Notes/git5a.htm) | Liver (http://embryology.med.unsw.edu.au/Notes/git7.htm) | Gall Bladder (http://embryology.med.unsw.edu.au/Notes/git7a.htm) | Spleen (http://embryology.med.unsw.edu.au/Notes/git8.htm) | Pancreas (http://embryology.med.unsw.edu.au/Notes/git9.htm) | Stomach (http://embryology.med.unsw.edu.au/Notes/git10.htm) | Folding (http://embryology.med.unsw.edu.au/Notes/git12.htm) | Intestine (http://embryology.med.unsw.edu.au/Notes/git13.htm) | Sensory Development - Taste (http://embryology.med.unsw.edu.au/Notes/tongue.htm) | Head and Neck Development - Tongue (http://embryology.med.unsw.edu.au/Notes/head6.htm)
- **Movie links**

    - Endoderm (http://embryology.med.unsw.edu.au/Movies/larsen/9-1.mov) | Endoderm large version (http://embryology.med.unsw.edu.au/Movies/larsen/yolk.mov) Features: gastrointestinal tract, yolk stalk, yolk sac, allantois
    - Stomach Rotation (http://embryology.med.unsw.edu.au/Movies/larsen/stomrot.mov) | Stomach Rotation large version (http://embryology.med.unsw.edu.au/Movies/larsen/stomrot2.mov)
    - Lesser Sac - superior view (http://embryology.med.unsw.edu.au/Movies/larsen/lessersacA.mov) | Lesser Sac - ventrolateral view (http://embryology.med.unsw.edu.au/Movies/larsen/lessersacB.mov)
    - Hindgut (http://embryology.med.unsw.edu.au/Movies/larsen/10-2.mov)
    - Cloaca (http://embryology.med.unsw.edu.au/Movies/larsen/10-9.mov)
    - Formation of Definitive Gut (http://embryology.med.unsw.edu.au/Movies/larsen/Tube.mov)

- System Notes (http://embryology.med.unsw.edu.au/sysnote.htm)
- Development Timeline (http://embryology.med.unsw.edu.au/week/weekbyweek.htm)

Links

- **Embryo Images** by Drs. Kathleen K. Sulik and Peter R. Bream Jr. notes/images sections on Gut Development (http://www.med.unc.edu/embryo_images/unit-digest/digest_htms/digesttoc.htm)
- Anatomy of the Human Body 1918 Henry Gray 2. The Digestive Apparatus (http://www.bartleby.com/107/241.html) | liver (http://www.bartleby.com/107/250.html)

Terms

allantois - An extraembryonic membrane, endoderm in origin extension from the early hindgut, then cloaca into the connecting stalk of placental animals, connected to the superior end of developing bladder. In reptiles and birds, acts as a reservoir for wastes and mediates gas exchange. In mammals is associated/incorporated with connecting stalk/placental cord fetal-maternal interface.

amnion - An extraembryonic membrane]ectoderm and extraembryonic mesoderm in origin and forms the innermost fetal membrane, produces amniotic fluid. This fluid-filled sac initially lies above the trilaminar embryonic disc and with embryoic disc folding this sac is drawn ventrally to enclose (cover) the entire embryo, then fetus. The presence of this membane led to the description of reptiles, bird, and mammals as amniotes.

amniotic fluid - The fluid that fills amniotic cavity totally encloses and cushions the embryo. Amniotic fluid enters both the gastrointestinal and respiratory tract following rupture of the buccopharyngeal membrane. The late fetus swallows amniotic fluid.

buccal - (Latin, *bucca* = cheek) A term used to relate to the mouth (oral cavity).

buccopharyngeal membrane - (oral membrane) (Latin, *bucca* = cheek) A membrane which forms the external upper membrane limit (cranial end) of the early gastrointestinal tract (GIT). This membrane develops during gastrulation by ectoderm and endoderm without a middle (intervening) layer of mesoderm. The membrane lies at the floor of the ventral depression (stomadeum) where the oral cavity will open and will breakdown to form the initial "oral opening" of the gastrointestinal tract. The equivilent membrane at the lower end of the gastrointestinal tract is the cloacal membrane.

cloacal membrane - Forms the external lower membrane limit (caudal end) of the early gastrointestinal tract (GIT). This membrane is formed during gastrulation by ectoderm and endoderm without a middle (intervening) layer of mesoderm. The membrane breaks down to form the initial "anal opening" of the gastrointestinal tract.

coelom - Term used to describe a space. There are extraembryonic and intraembryonic coeloms that form during vertebrate development. The single intraembryonic coelom will form the 3 major body cavities: pleural, pericardial and peritoneal.

foregut - The first of the three part/division (**foregut** - midgut - hindgut) of the early forming gastrointestinal tract. The foregut runs from the buccopharyngeal membrane to the midgut and forms all the tract (esophagus and stomach) from the oral cavity to beneath the stomach. In addition, a ventral bifurcation of the foregut will also form the respiratory tract epithelium.

gastrula - (Greek, *gastrula* = little stomach) A stage of an animal embryo in which the three germ layers have just formed.

gastrulation - The process of differentiation forming a gastrula. Term means literally means "to form a gut" but is more in development, as this process converts the bilaminar embryo (epiblast/hypoblast) into the trilaminar embryo ([E.htm#endoderm endoderm]/mesoderm/ectoderm) establishing the 3 germ layers that will form all the future tissues of the entire embryo. This process also establishes the the initial body axes.

hindgut - The last of the three part/division foregut - midgut - **hindgut**) of the early forming gastrointestinal tract. The hindgut forms all the tract from the distral transverse colon to the cloacal membrane and extends into the connecting stalk (placental cord) as the allantois. In addition, a ventral of the hindgut will also form the urinary tract (bladder, urethra) epithelium.

intraembryonic coelom - The "horseshoe-shaped" space (cavity) that forms initially in the third week of development in the lateral plate mesoderm that will eventually form the 3 main body cavities: pericardial, pleural, peritoneal. The intraembryonic coelom communicates transiently with the extraembryonic coelom.

neuralation - The general term used to describe the early formation of the nervous system. It is often used to describe the early events of differentiation of the central ectoderm region to form the neural plate, then neural groove, then neural tube. The nervous system includes the central nervous system (brain and spinal cord) from the neural tube and the peripheral nervous system (peripheral sensory and sympathetic ganglia) from neural crest. In humans, early neuralation begins in week 3 and continues through week 4.

pharynx - uppermost end of gastrointestinal and respiratory tract, in the embryo beginning at the buccopharyngeal membrane and forms a major arched cavity within the phrayngeal arches.

somitogenesis The process of segmentation of the paraxial mesoderm within the trilaminar embryo body to form pairs of somites, or balls of mesoderm. A somite is added either side of the notochord (axial mesoderm) to form a somite pair. The segmentation does not occur in the head region, and begins cranially (head end) and extends caudally (tailward) adding a somite pair at regular time intervals. The process is sequential and therefore used to stage the age of many different species embryos based upon the number visible somite pairs. In humans, the first somite pair appears at day 20 and adds caudally at 1 somite pair/90 minutes until on average 44 pairs eventually form.

splanchnic mesoderm - Gastrointestinal tract (endoderm) associated mesoderm formed by the separation of the lateral plate mesoderm into two separate components by a cavity, the intraembryonic coelom. Splanchnic mesoderm is the embryonic origin of the gastrointestinal tract connective tissue, smooth muscle, blood vessels and contribute to organ development (pancreas, spleen, liver). The intraembryonic coelom will form the three major body cavities including the space surrounding the gut, the peritoneal cavity. The other half of the lateral plate mesoderm (somatic mesoderm) is associated with the ectoderm of the body wall.

stomadeum - (stomadeum) A ventral surface depression on the early embryo head surrounding the

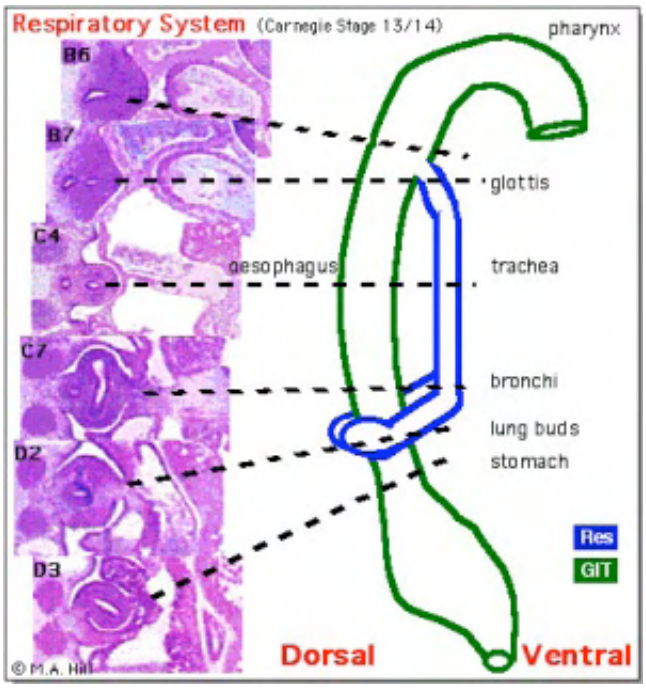
2009 Lecture 10

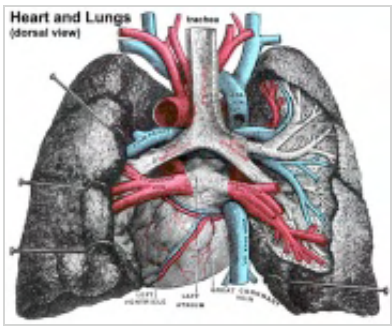
From Embryology

Contents

Respiratory Development

Introduction





adult lungs

The respiratory system does not carry out its physiological function (of gas exchange) until after birth. The respiratory tract, diaphragm and lungs do form early in embryonic development. The respiratory tract is divided anatomically into 2 main parts: 1. upper respiratory tract, consisting of the nose, nasal cavity and the pharynx; 2. lower respiratory tract consisting of the larynx, trachea, bronchi and the lungs.

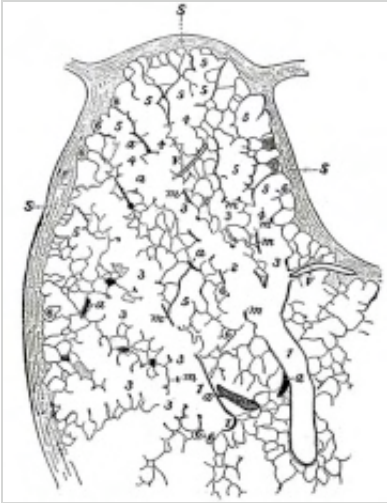
The respiratory "system" usually includes descriptions of not only the functional development of the lungs, but also related musculoskeletal (diaphragm) and vascular (pulmonary) development.

- **iLecture Audio** Lecture Date: 25-08-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Respiration (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48839)

Lecture Objectives

- Understanding of embryonic lung development

- Understanding of embryonic lung development
- Understanding of 4 stages of lung development
- Understanding of diaphragm development
- Brief understanding of respiratory vascular development
- Brief understanding of respiratory abnormalities
- Brief understanding of molecular mechanisms



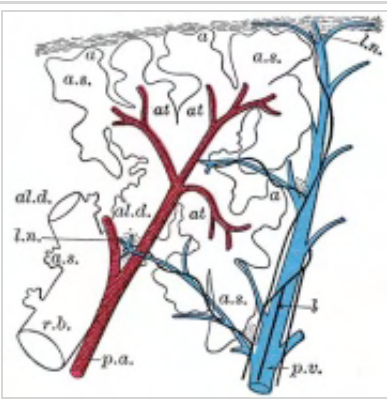
lung structure

Textbook References

- **Human Embryology** Larson Chapter 9 p229-260
- **The Developing Human: Clinically Oriented Embryology** (6th ed.) Moore and Persaud Chapter 12 p271-302

Additional Textbooks

- Before We Are Born (5th ed.) Moore and Persaud Chapter 13 p255-287
- Essentials of Human Embryology Larson Chapter 9 p123-146
- Human Embryology Fitzgerald and Fitzgerald Chapter 19,20 p119-123
- Anatomy of the Human Body 1918 Henry Gray 1. The Respiratory Apparatus (http://www.bartleby.com/107/235.html)



alveoli and blood vessels

Developmental Overview

Week 4 - laryngotracheal groove forms on floor foregut.

Week 5 - left and right lung buds push into the pericardioperitoneal canals (primordia of pleural cavity)

Week 6 - descent of heart and lungs into thorax. Pleuroperitoneal foramen closes.

Week 7 - enlargement of liver stops descent of heart and lungs.

Month 3-6 - lungs appear glandular, end month 6 alveolar cells type 2 appear and begin to secrete surfactant.

Month 7 - respiratory bronchioles proliferate and end in alveolar ducts and sacs.

Lung Development

- week 4 - 5 embryonic
- week 5 - 17 pseudoglandular
- week 16 - 25 canalicular
- week 24 - 40 terminal sac
- late fetal - 8 years alveolar

Germ Layers

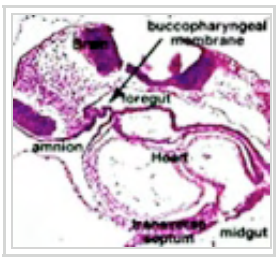
Endoderm and splanchnic mesoderm form majority of conducting and alveoli. Ectoderm will contribute the neural innervation. (this does not cover the origins of the supporting musculoskeletal components)

Foregut development

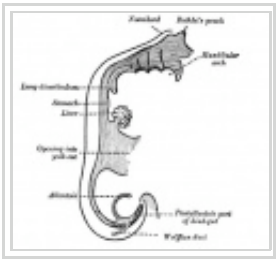
From the oral cavity the next portion of the foregut is initially a single gastrointestinal (oesophagus) and respiratory (trachea) common tube, the pharynx which lies behind the heart. Note that the respiratory tract will form from a ventral bud arising at this level.

- Oral cavity
- Pharynx (esophagus, trachea)
- Respiratory tract
- Stomach

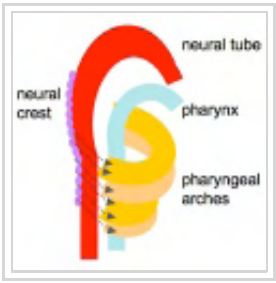
Upper respiratory tract



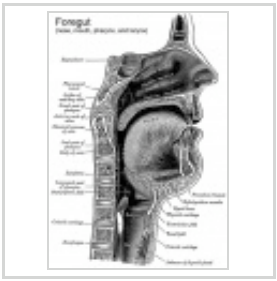
stage 11 foregut



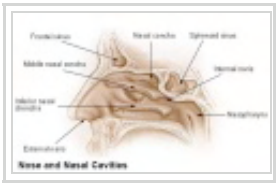
week 4 early respiratory endodermal bud



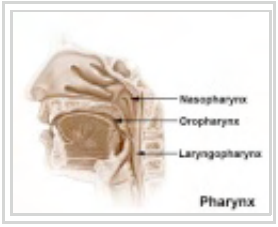
Head arches cartoon



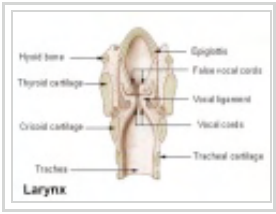
Pharynx



Nasal cavities



Pharynx

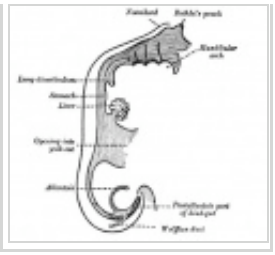


Larynx

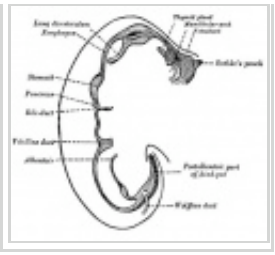
- part of foregut development
- anatomically the nose, nasal cavity and the pharynx
- the pharynx forms a major arched cavity within the pharyngeal arches

MH - pharyngeal arches will be described in head development lecture

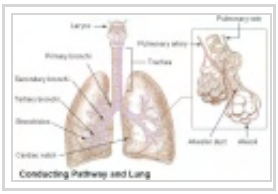
Lower respiratory tract



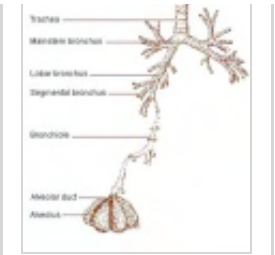
week 4 early respiratory endodermal bud



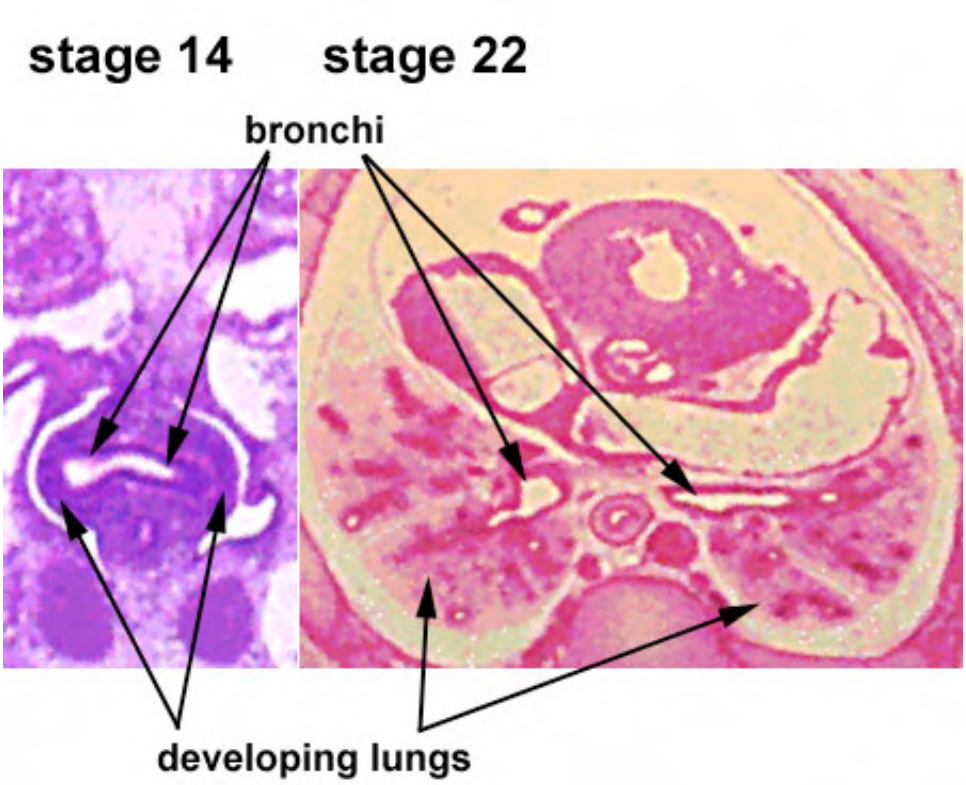
week 4 later ventral endoderm growth



lower respiratory tract



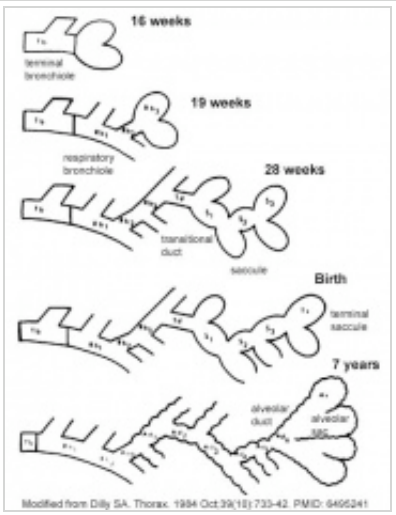
conducting system bronchi to lungs



- The lungs go through an embryonic and 4 distinct histological phases of development

Growth initially of branched "conducting" system of bronchial tree, followed by later development of the "functional units" of the alveoli.

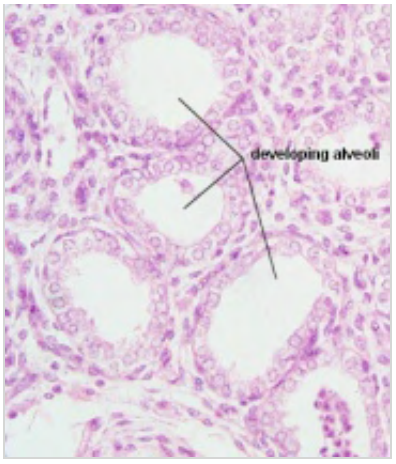
- **embryonic** - week 4 - 5 (stage 14 above)
- **pseudoglandular** - week 5 - 17 (stage 22 above)
- **canalicular** - week 16 - 25
- **terminal sac** - week 24 - 40
- **alveolar** - late fetal - 8 years (Latin, *alveus* = cavity or hollow)



Lung alveoli development cartoon

- in late fetal development respiratory motions and amniotic fliud are thought to have a role in lung maturation.
- Development of this system is not completed until late fetal just before birth.

- Therefore premature babies have difficulties associated with insufficient surfactant (end month 6 alveolar cells type 2 appear and begin to secrete surfactant).



Fetal lung histology

Lung morphogenesis

- lung buds (endoderm epithelial tubes) grow/push into mesenchyme covered with pleural cells (lung border)
- generates a tree-like network by repeated:

1. elongation
2. terminal bifurcation
3. lateral budding

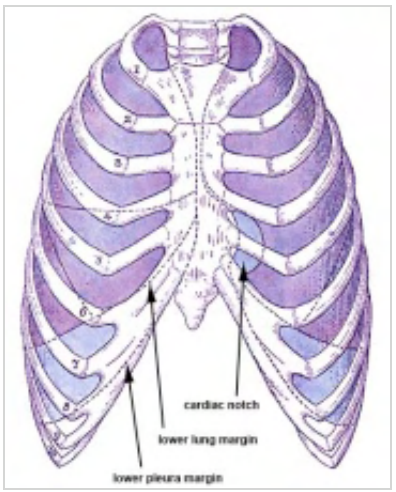
Fetal lung volume

Each lung volume as determined by ultrasound and matched to gestational age (PMID: 16388511)

- 12-13 weeks 0.05 mL
- 19-22 weeks 0.5 mL
- 29-32 weeks 1.9 mL

Pleural Cavity

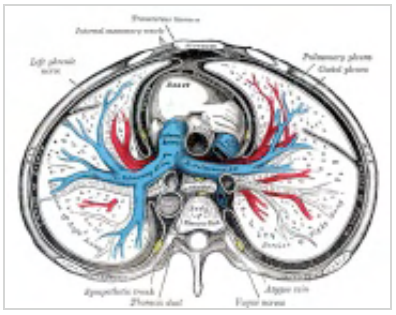
- The anatomical body cavity in which the lungs develop and lie.
- The pleural cavity forms in the lateral plate mesoderm as part of the early single intraembryonic coelom.
- This cavity is initially continuous with pericardial and peritoneal cavities and form initially as two narrow canals
  - later becomes separated by folding (pleuropericardial fold, pleuroperitoneal membrane) and the later formation of the diaphragm



pleura

pleuropericardial fold - (pleuropericardial membrane) An early embryonic fold which restricts the communication between pleural cavity and pericardiac cavity, contains both the cardinal vein and phrenic nerve.

pleuroperitoneal membrane - An early embryonic membrane that forms inferiorly at the septum transversum to separate peritoneal cavity from pleural cavity.


pleura

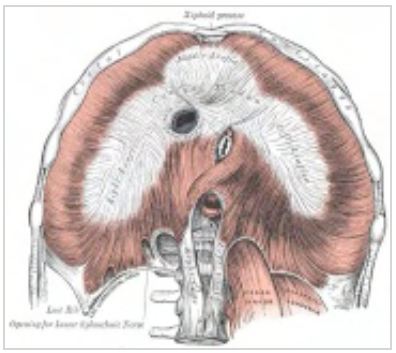
Pleura

- serous membrane covers the surface of the lung and the spaces between the lobes
- arranged as a closed invaginated sac
- two layers (pulmonary, parietal) continuous with each other, the potential space between them is the **pleural cavity**

Diaphragm

Not respiratory tract but musculoskeletal development, there are 5 elements that contribute to the diaphragm

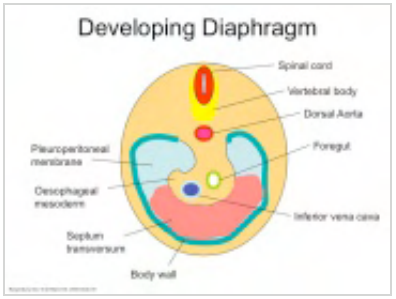
- septum transversum- central tendon
- 3rd to 5th somite- musculature of diaphragm
- ventral pleural sac- connective tissue
- mesentry of oesophagus- connective tissue around oesophasus and IVC
- pleuroperitoneal membranes- connective tissue around central tendon



adult diaphragm

Pulmonary Circulation

- the pulmonary system not "functional" until after birth
- pulmonary arteries - 6th aortic arch arteries
- pulmonary veins - are incorporated into the left atrium wall
- bronchial arteries - branches from dorsal aorta



Components of the diaphragm

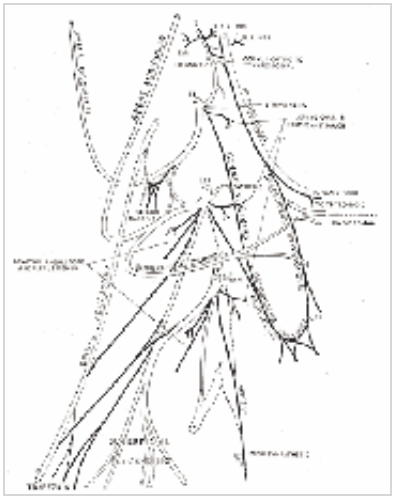
The First Breath

- The respiratory system does not carry out its physiological function (gas exchange) prenatally and remain entirely fluid-filled until birth.
- At birth, fluid in the upper respiratory tract is expired and fluid in the lung aveoli is rapidly absorbed this event has also been called "dewatering of the lung".
    - The lung epithelia has to now rapidly change from its prenatal secretory function to that of fluid absorbtion.

The exchange of lung fluid for air leads to:

- fall in pulmonary vascular resistance
- increase in pulmonary blood flow
- thinning of pulmonary arteries (stretching as lungs increase in size)
- blood fills the alveolar capillaries

In the heart, pressure in the right side of the heart decreases and pressure in the left side of the heart increases (more blood returning from pulmonary).



phrenic nerve

Respiratory Tract Abnormalities

Tracheoesophageal Fistula

(Tracheo-Oesophageal Fistula, Oesophageal Atresia) - Oesophageal Atresia with or without tracheo-oesophageal fistula

Lobar Emphysema (Overinflated Lung)

1. There is an overinflated left upper lobe
2. There is a collapsed lower lobe
3. The left lung is herniating across the mediastinum

Congenital Diaphragmatic Hernia

Failure of the pleuroperitoneal foramen (foramen of Bochdalek) to close allows viscera into thorax. Intestine, stomach or spleen can enter the pleural cavity, compressing the lung.

Azygos Lobe

Common condition (0.5% of population). The right lung upper lobe expands either side of the posterior cardinal. There is also some course variability of the phrenic nerve in the presence of an azygos lobe.

Congenital Laryngeal Webs

Laryngeal abnormality due to embryonic (week 10) incomplete recanalization of the laryngotracheal tube during the fetal period. Rare abnormality occuring mainly at the level of the vocal folds (glottis).

Meconium Aspiration Syndrome

(MAS) Meconium is the gastrointestinal contents that accumulate in the intestines during the fetal period. Fetal stress in the third trimester, prior to/at/ or during parturition can lead to premature meconium discharge into the amniotic fluid and sunsequent ingestion by the fetus and damage to respiratory function. Damage to placental vessels meconium myonecrosis may also occur.

Newborn Respiratory Distress Syndrome

(Hyaline Membrane Disease) medline plus (http://www.nlm.nih.gov/MEDLINEPLUS/ency/article/001563.htm) | eMedicine (http://www.medscape.com/article/976034-overview)

Bronchopulmonary Dysplasia

A chronic lung disease which can occur following premature birth. The definition of bronchopulmonary dysplasia (BPD) has in recent years changed from a severe lung injury and associated repair, to more of a disruption of lung development.

Take the Quiz

1. The lung buds grow into the coelomic cavity in the region:

- ○ pericardial cavity
- ○ pericardio-peritoneal canals
- ○ peritoneal cavity
- ○ amniotic cavity
- ○ septum transversum

2. The lung bud mesenchyme gives rise to the:

- ○ pseudostratified columnar epithelium
- ○ epithelial lining of the alveolar sac

- smooth muscles
- type II cells

3. The adult lung alveoli number is reached by:

- canalicular stage
- terminal sac stage
- alveolar stage
- newborn
- childhood 8 years of age

4. Hyaline membrane disease is mainly associated with:

- oxygen therapy at birth
- type I pneumocyte development
- type II pneumocyte development
- diaphragmatic hernia
- ceasarian delivery

Submit

UNSW Embryology Links

- Lecture 10 2008 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture10.htm)
- **Respiratory Tract Notes** Introduction (http://embryology.med.unsw.edu.au/Notes/respire.htm)
- **Movie links** Endoderm (http://embryology.med.unsw.edu.au/Movies/larsen/9-1.mov)
- System Notes (http://embryology.med.unsw.edu.au/sysnote.htm)
- Development Timeline (http://embryology.med.unsw.edu.au/week/weekbyweek.htm)

Links

- **Embryo Images** by Drs. Kathleen K. Sulik and Peter R. Bream Jr. notes/images sections on respiratory development (http://www.med.unc.edu/embryo_images/unit-digest/digest_htms/digest012a.htm)
- Anatomy of the Human Body 1918 Henry Gray 1. The Respiratory Apparatus (http://www.bartleby.com/107/235.html)

Terms

alveolar - (Latin, *alveus* = cavity or hollow) Term used in relation to the alveoli of the lungs. The final functional sac of the respiratory tree where gas exchange occurs between the alveolar space and the pulmonary capillaries.

alveolar stage - (Latin, *alveus* = cavity or hollow) Term used to describe the final

histological/developmental stage (Pseudoglandular, Fetal Canalicular, Terminal sac, Alveolar) of lung development. This stage occurs from late fetal/neonate. The final functional sac of the respiratory tree exists, where gas exchange occurs between the alveolar space and the pulmonary capillaries.

alveolar duct - respiratory tract that in the adult has alveoli opening into it and has no cuboidal epithelium.

alveoli - (Latin, *alveus* = cavity or hollow) The final functional sac of the respiratory tree where gas exchange occurs between the alveolar space and the pulmonary capillaries.

amnion - An extraembryonic membrane]ectoderm and extraembryonic mesoderm in origin and forms the innermost fetal membrane, produces amniotic fluid. This fluid-filled sac initially lies above the trilaminar embryonic disc and with embryoic disc folding this sac is drawn ventrally to enclose (cover) the entire embryo, then fetus. The presence of this membane led to the description of reptiles, bird, and mammals as amniotes.

amniotic fluid - The fluid that fills amniotic cavity totally encloses and cushions the embryo. Amniotic fluid enters both the gastrointestinal and respiratory tract following rupture of the buccopharyngeal membrane. The late fetus swallows amniotic fluid.

atmospheric pressure - Term describing the pressure of the air outside of the body.

atresia - (Greek, *a* = without + *tresis* = perforation) Term used for anatomical closing or absence of a cavity or opening that should exist. Used as an antomical, pathological and clinical term: esophageal atresia, biliary atresia, duodenal atresia, jejunal atresia, choanal atresia, urethral atresia, bronchial atresia.

buccal - (Latin, *bucca* = cheek) A term used to relate to the mouth (oral cavity).

buccopharyngeal membrane - (oral membrane) (Latin, *bucca* = cheek) A membrane which forms the external upper membrane limit (cranial end) of the early gastrointestinal tract (GIT). This membrane develops during gastrulation by ectoderm and endoderm without a middle (intervening) layer of mesoderm. The membrane lies at the floor of the ventral depression (stomadeum) where the oral cavity will open and will breakdown to form the initial "oral opening" of the gastrointestinal tract. The equivilent membrane at the lower end of the gastrointestinal tract is the cloacal membrane.

canalicular stage - (fetal canalicular, canalicular phase) Term used to describe lung development, after early embryonic the second of the histological/developmental stages (Pseudoglandular, **Fetal Canalicular**, Terminal sac, Alveolar). This stage occurs during the fetal period from week 16 to 24. During this stage there is lung bud mesenchymal angiogenesis and cellular differentiation into different stromal cell types (fibroblasts, myoblasts and chondrocytes).

ciliated pseudostratified columnar epithelium - forms mucous membrane that lines the trachea and the nasal cavity and nasopharynx epithelium.

coelom - Term used to describe a space. There are extraembryonic and intraembryonic coeloms that form during vertebrate development. The single intraembryonic coelom will form the 3 major body cavities: pleural, pericardial and peritoneal.

ductus arteriosus - A vascular shunt between the pulmonary artery and descending aorta, which allows fetal right heart output (most, 88%) to go to systemic circulation. This shunt closes normally at birth.

elastic theory - The hypothesis that lung acinar development during the saccular stage is guided by the preprogrammed location of a surrounding elastic network.

epiglottis - (Greek, *epi* = above, upon) cartilaginous part of the larynx above the [G.htm#glottis glottis], which in infancy directs food into the esophagus and not the trachea. Embryologically develops in the foregut from the hypobranchial eminence. Postnatal anatomical development in humans involves a maturational descent in infancy (4 and 6 months of age). Contains lymphoid tissue (larynx-associated lymphoid tissue, LALT and Bronchus-associated lymphoid tissue, BALT).

expiration - (exhalation) The process of letting air out of the lungs during the breathing cycle. Due to the combination of relaxation of the diaphragm and elastic recoil of tissue decreases the thoracic volume and increases the intraalveolar pressure.

fistula - An abnormal communication between 2 structures (organs, vessels, cavities) that do not normally connect.

foregut - The first of the three part/division (**foregut** - midgut - hindgut) of the early forming gastrointestinal tract. The foregut runs from the buccopharyngeal membrane to the midgut and forms all the tract (esophagus and stomach) from the oral cavity to beneath the stomach. In addition, a ventral bifurcation of the foregut will also form the respiratory tract epithelium.

goblet cells - produce mucus that traps airborne particles and microorganisms, nearby ciliated cells propel the mucus upward, where it is either swallowed or expelled.

hypopharyngeal eminence - (hypobranchial eminence) An early embryonic structure in the developing head. A narrow midline mesodermal (mesenchymal) exension lying within the floor curve of the developing pharynx. Fusion of 3rd pharyngeal arches and precursor of root of tongue. Early developing thyroid cells also migrate into this structure as cords of cells. (More? [../Notes/head.htm Head Notes] | [../Notes/endocrine8.htm Endocrine Development - Thyroid])

hyaline cartilage - type of cartilage located in the tracheal wall to provide support and prevent the trachea from collapsing. Note that the tracheal wall has a region of posterior soft tissue to allow for expansion of the esophagus, which is immediately posterior to the trachea.

inspiration - (inhalation) The process of taking air into the lungs. Due to diaphragm contraction and the thoracic cavity increasing in volume. This decreases the intraalveolar pressure leading to air flows into the lungs.

intraalveolar pressure - Term describing the pressure inside the alveoli of the lungs, which changes during inspiration and expiration.

intrapleural pressure - Term describing the pressure within the pleural cavity.

laryngopharynx - (hypopharynx) The portion of the pharynx that extends from the hyoid bone down to the lower margin of the larynx.

laryngotracheal groove - Early embryonic foregut developmental feature, forms on the anterior (ventral) wall of pharynx and gives rise to larynx, trachea, respiratory tree.

larynx - Site of the the vocal folds in the neck below the division of pharynx into the trachea and the esophagus. Embryologically develops from the foregut with the lining derived from endoderm and the cartilage from pharyngeal arch 4 and 6. Beginning as a simple foregut groove, the [#laryngotracheal_groove laryngotracheal groove] which folds to form the laryngotracheal bud, then the larynx and trachea.

lung bud - The term describing the primordia of lung development. Foregut endoderm branches into the

surrounding visceral mesoderm, forming the trachea, which brances again into the bronchi and thsi process is repeated over and over again through development. Establishing the major respiratory branches first, followed by minor branches, then terminal branches, then immature alveoli which later mature to form teh functional end structures of the lung.

nasopharynx - The portion of the pharynx posterior to the nasal cavity and extends inferiorly to the uvula.

oropharynx - The portion of the pharynx that is posterior to the oral cavity.

paranasal sinuses - Air-filled cavities surrounding the nasal cavity and open into it, which combine in function to: reduce skull weight, produce mucus, and act as resonating chambers affecting voice quality. Located within in the frontal, maxilae, ethmoid, and sphenoid bones with the same name as the bones in which they are located.

parietal pleura - Forms the outer lining of pleural cavity. Mesoderm of the thoracic cavity body wall and derived from epithelia of pericardioperitoneal canals from intraembryonic coelom. The other inner pleural layer is the visceral pleura (splanchnic mesodermal in origin).

pharynx - (throat) Forms the initial segment of the upper respiratory tract divided anatomically into three regions: nasopharynx, oropharynx, and laryngopharynx (hypopharynx). Anatomically extends from the base of the skull to the level of the sixth cervical vertebra.

pleura - A double-layered serous membrane enclosing each lung. Visceral pleura layer is firmly attached to the surface of the lung. Parietal pleura layer lines the wall of the thorax. At the lung hilum, the visceral pleura is continuous with the parietal pleura. The pleural cavity between the visceral and parietal pleurae contains a thin film of serous fluid that is produced by the pleura.

pleural cavity - Anatomical body cavity in which the lungs develop and lie. The pleural cavity forms in the lateral plate mesoderm as part of the early single intraembryonic coelom. This cavity is initially continuous with pericardial and peritoneal cavities and later becomes separated by folding ([#pleuropericardial_fold pleuropericardial fold], [#pleuroperitoneal_membrane pleuroperitoneal membrane]) and the later formation of the diaphragm. The pleural cavities form initially as two narrow canals. Note the single intraembryonic coelom forms all three major body cavities: pericardial, pleural, peritoneal.

pleural fluid - A thin film of serous fluid that is produced by the pleura layers and acts as a lubricant, reducing the friction as the two layers slide against each other, and also helps to hold the two layers together as the lungs inflate and deflate.

pleuropericardial fold - (pleuropericardial membrane) An early embryonic fold which restricts the communication between pleural cavity and pericardiac cavity, contains both the cardinal vein and phrenic nerve.

pleuroperitoneal membrane - An early embryonic membrane that forms inferiorly at the septum transversum to separate peritoneal cavity from pleural cavity. (More? [../Notes/coelom.htm Coelom Notes])

radial alveolar count - The number of alveoli between respiratory bronchioles and the end of the acinus, a measurement used in postnatal lung growth.

respiratory bronchiolus - respiratory tract in the adult which has alveoli opening into it and has part of the wall lined by ciliated epithelium. In the canalicular period it is lined by flattened epithelium, which then becomes a mixture of flattened and cuboidal epithelium during the terminal sac period.

sacculation - A general anatomical term meaning to formed a series of sac-like expansions. In lung

development, the term refers to the process of lung epithelial cell differentiation, vascular remodeling and thinning of the mesenchyme. This process leads to enlargement of the diameter and surface area of the alveolar sacs. Distal epithelial cells form 2 populations: 1. cells flattens, thins, and spreads to form type I cells; 2. cells remain cuboidal, acquire surfactant filled lamellar bodies and differentiate into type II cells.

saccule - respiratory tract that forms a large, thin walled air space lined by flattened epithelium (28 weeks to 2 months after birth).

septum transversum - (transverse septum) A mesodermal region in the early embryo. Identified externally as the junctional site between amnion and yolk sacs, and internally (within the embryo) lying directly beneath the heart and at the foregut/midgut junction. This ventro-dorsal "plate" of mesoderm contributes several structures including: the central tendon of diaphragm and some of the liver. The transverse septum has an important structural role in early embryonic development and is pierced by the gastrointestinal tract.

stenosis - Term used to describe an abnormal narrowing, usually in relation to a tube. For example, blood vessel, gastrointestinal tract or respiratory tract.

stomadeum - (stomadeum) A ventral surface depression on the early embryo head surrounding the buccopharyngeal membrane, which lies at the floor of this depression. This surface depression lies between the maxillary and mandibular components of the first pharyngeal arch.

surfactant - a detergent secreted by Type 2 alveolar cells between alveolar epithelium. Functions to lower surface tension, allowing lungs to remain inflated. Note: In humans, these cells and their secretion develop towards the very end of the third trimester, just before birth. Hence the respiratory difficulties associated with premature births (Newborn Respiratory Distress Syndrome, Hyaline membrane disease). (More? [../Notes/respire2.htm Respiratory Abnormalities] | [../Notes/respire2.htm#hyaline+membrane Newborn Respiratory Distress Syndrome])

terminal bronchiolus - respiratory tract forming the last airway before a respiratory bronchiolus.

terminal sac stage (terminal sac phase) Term used to describe fetallung development (late fetal week 24 to 36) the second last histological/developmental stage (Pseudoglandular, Fetal Canalicular, **Terminal sac**, Alveolar). During this stage branching and growth of the terminal sacs occurs, with cellular differentiation of the type -II pneumonocytes and type - I pneumonocytes. The final functional sac of the respiratory tree occurs at the next neonatal period, where gas exchange occurs between the alveolar space and the pulmonary capillaries.

transitional duct - respiratory tract lined by flattened epithelium, which connects the respiratory bronchiolus to the saccules during the terminal sac period. This structure later forms the alveolar duct.

visceral pleura - Forms the inner lining of pleural cavity, covering and attached to the lungs. Embryonically derived from the splanchnic mesoderm.

Waldereyer's Ring - Term used to describe the pharyngeal, palatine, and lingual tonsils which are located in the pharynx.

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Original Glossary (http://embryology.med.unsw.edu.au/Notes/Index/Index.htm)

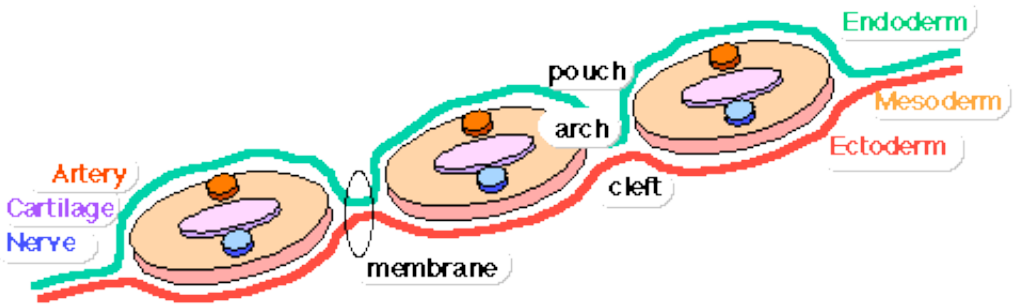
Course Content 2009

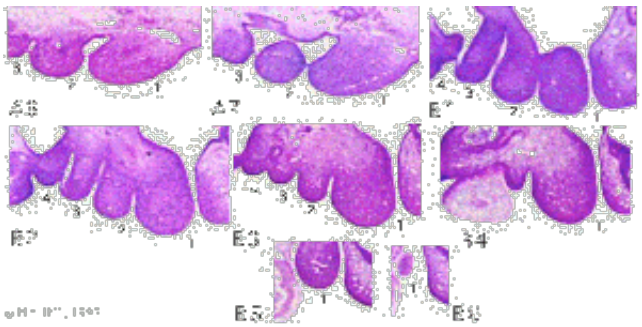
2009 Lecture 11

From Embryology

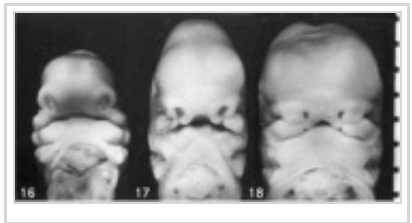
Contents

Head Development





Introduction



The face is the anatomical feature which is truly unique to each human, though the basis of its general development is identical for all humans and similar to that seem for other species. The face has a complex origin arising from a number of head structures and sensitive to a number of teratogens during critical periods of its development. The related structures of upper lip and palate significantly contribute to the majority of face abnormalities.

The head and neck structures are more than just the face, and are derived from pharyngeal arches 1 - 6 with the face forming from arch 1 and 2 and the frontonasal prominence. Each arch contains similar Arch components derived from endoderm, mesoderm, neural crest and ectoderm. These components though will form different structures depending on their arch origin. Because the head contains many different structures also review notes on Special Senses (eye, ear, nose (http://embryology.med.unsw.edu.au/Notes/senses.htm)), Respiratation (pharynx (http://embryology.med.unsw.edu.au/Notes/respire.htm)), Integumentary (Teeth (http://embryology.med.unsw.edu.au/Notes/skin10.htm)), Endocrine (thyroid, pituitary

(http://embryology.med.unsw.edu.au/Notes/endocrine.htm)). Ultrasound - Cleft lip/palate (http://embryology.med.unsw.edu.au/Movies/usoundab/Cleft1.htm)

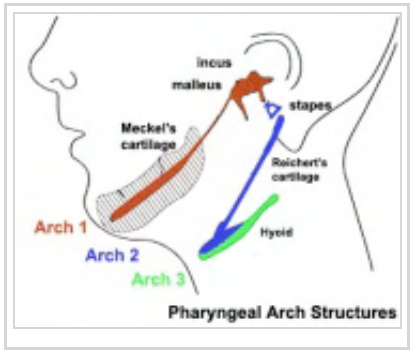
Lectopia Audio: Lecture Date: 31-08-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Head and Neck (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48828)

Lecture Objectives

- List the main structures derived from the pharyngeal arches, pouches and clefts.
- Know the stages and structures involved in the development of the face.
- Predict the results of abnormal development of the face and palate.
- Briefly summarise the development of the tongue.

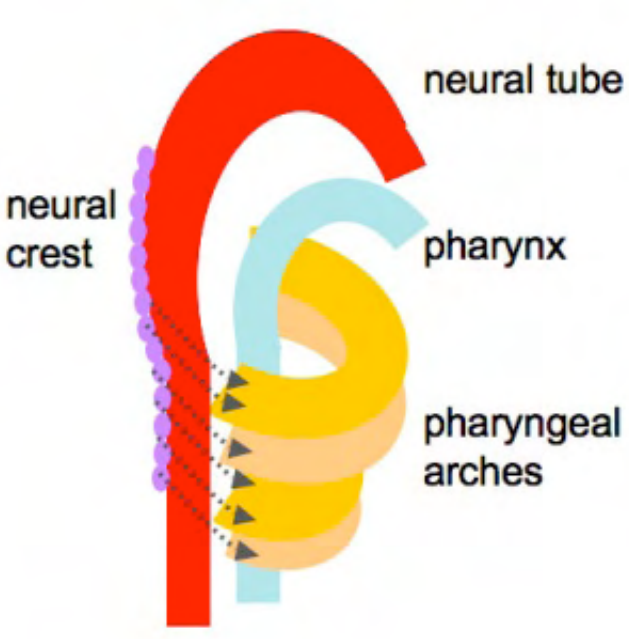
Textbook References

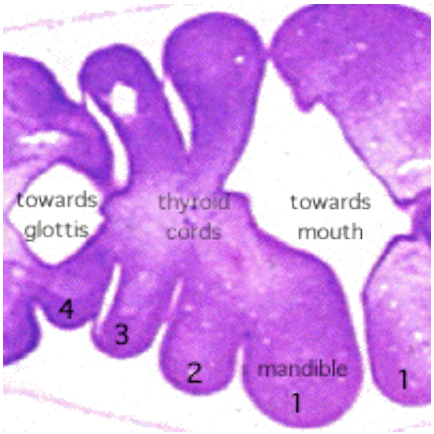
- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter Chapter 10 The Pharyngeal Apparatus pp201 - 240.
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 12 Development of the Head, the Neck, the Eyes, and the Ears pp349 - 418.

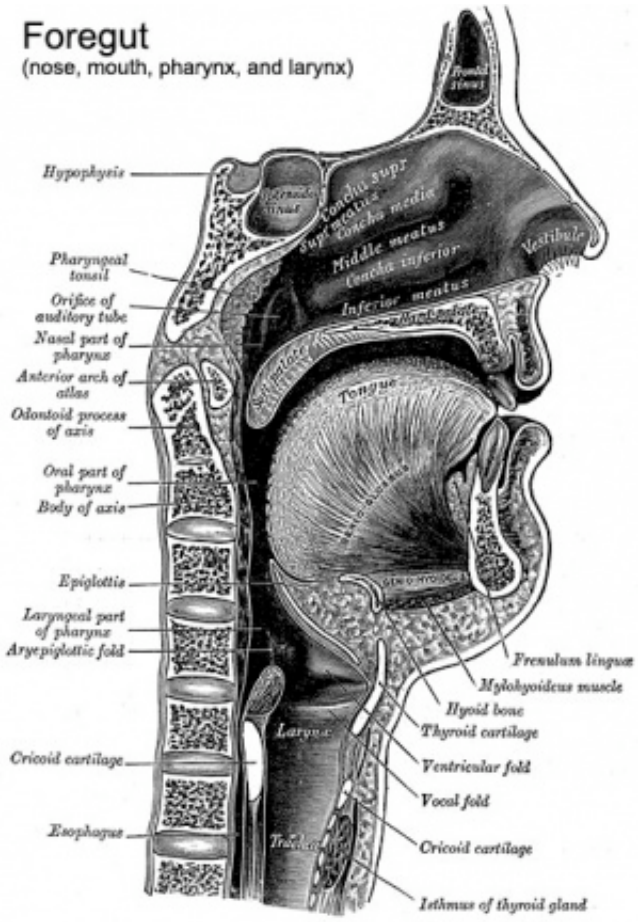


Head and Palate Movies (http://embryology.med.unsw.edu.au/Movies/head.htm)

The Pharynx







The cavity within the pharyngeal arches forms the pharynx.

The pharynx contributes to 2 endocrine organs, in the roof the [endocrine7.htm pituitary] (hypophysis) and the floor the thyroid. The thyroid gland being one of the first endocrine organs to be formed has an important role in embryonic development. The pharynx floor of all arches also contribute to the formation of the [head6.htm tongue].

Pharyngeal Arch Components

Major features to identify for each: **arch**, **pouch**, **groove** and **membrane**. Contribute to the formation of head and neck and in the human appear at the 4th week. The first arch contributes the majority of upper and lower jaw structures.

Early Face and Pharynx

- Pharynx - begins at the buccopharyngeal membrane (oral membrane), apposition of ectoderm with endoderm (no mesoderm between)

Pharyngeal Arch Development

- branchial arch (Gk. branchia= gill)
- arch consists of all 3 trilaminar embryo layers
- ectoderm- outside
- mesoderm- core of mesenchyme
- endoderm- inside

Neural Crest

- Mesenchyme invaded by neural crest generating connective tissue components
- cartilage, bone, ligaments
- arises from midbrain and hindbrain region

Arch Features

Each arch contains: artery, cartilage, nerve, muscular component

Arches and Phanynx Form the face, tongue, lips, jaws, palate, pharynx and neck cranial nerves, sense organ components, glands

- Humans have 5 arches - 1, 2, 3, 4, 6 (Arch 5 does not form or regresses rapidly)
- from in rostro-caudal sequence, Arch 1 to 6 from week 4 onwards
- arch 1 and 2 appear at time of closure of cranial neuropore

- Face - mainly arch 1 and 2
- Neck components - arch 3 and 4 (arch 4 and 6 fuse)

Arch Features

-
    - arch
    - groove
        - externally separates each arch
            - also called a cleft
        - only first pair persist as external auditory meatus
    - pouch
        - internally separates each arch
        - pockets from the pharynx
    - membrane
        - ectoderm and endoderm contact regions
        - only first pair persist as tympanic membrane
- Pharyngeal Arch 1 (Mandibular Arch) has 2 prominances
    - smaller upper- maxillary forms maxilla, zygomatic bone and squamous part of temporal
    - larger lower- mandibular, forms mandible
- Pharyngeal Arch 2 (Hyoid Arch)
    - forms most of hyoid bone
- Arch 3 and 4
    - neck structures

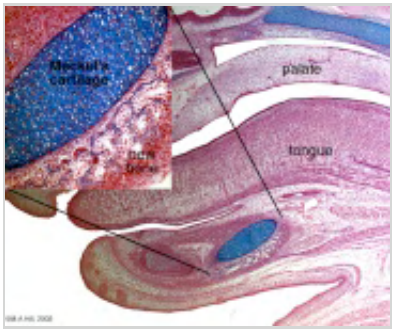
Arch Arteries

- Arch 1 - mainly lost, form part of maxillary artery
- Arch 2 - stapedial arteries
- Arch 3 - common carotid arteries, internal carotid arteries
- Arch 4 - left forms part of aortic arch, right forms part right subclavian artery
- Arch 6 - left forms part of left pulmonary artery , right forms part of right pulmonary artery

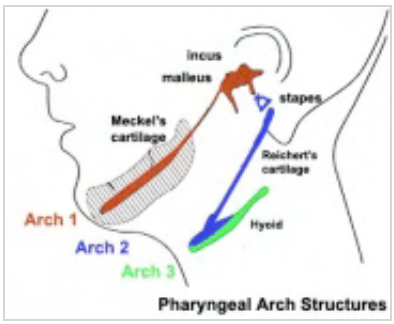
placental vein -> liver -> heart -> truncus arteriosus -> aortic sac -> **arch arteries** -> dorsal aorta -> placental artery

Arch Cartilage

- Arch 1 - Meckel's cartilage, horseshoe shaped
  - dorsal ends form malleus and incus
  - midpart forms ligaments (ant. malleus, sphenomandibular)
  - ventral part forms mandible template
- Arch 2 - Reichert's cartilage
  - dorsal ends form stapes and Temporal bone styloid process
  - ventral part ossifies to form hyoid bone components
  - lesser cornu and superior body
- Arch 3- forms greater cornu and inferior part of hyoid
- Arch 4&6- form laryngeal cartilages, except epiglottis (from hypobranchial eminence)



Meckel's cartilage, first pharyngeal arch



Pharyngeal arch cartilages

Arch Muscle

- Arch 1 - muscles of mastication, mylohyoid, tensor tympanic, ant. belly digastric
- Arch 2 - muscles of facial expression, stapedius, stylohyoid, post. belly digastric
- Arch 3 - stylopharyngeus
- Arch 4&6 - crycothyroid, pharynx constrictors, larynx muscles, oesophagus (st. muscle)

Arch Nerve

- Arch 1 - CN V trigeminal, caudal 2/3 maxillary and mandibular, cranial 1/3 sensory nerve of heaad and neck, mastication motor
- Arch 2 - CN VII facial
- Arch 3 - CN IX glossopharyngeal
- Arch 4&6 - CN X vagus, arch 4- superior laryngeal, arch 6- recurrent laryngeal

Arch Pouches

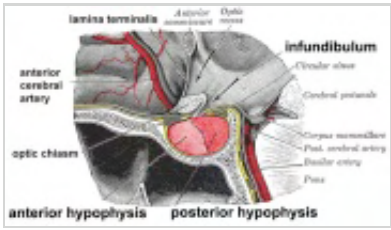
- Arch 1 - elongates to form tubotympanic recess, tympanic cavity, mastoid antrum, eustachian tube
- Arch 2 - forms tonsillar sinus, mostly oblierated by palatine tonsil
- Arch 3 - forms inferior parathyroid and thymus
- Arch 4 - forms superior parathyroid, parafollicular cells of Thyroid

Thyroid Gland

- not a pouch structure
- first endocrine organ to develop day 24
- from floor of pharynx
- descends thyroglossal duct (which closes)
- upper end at foramen cecum

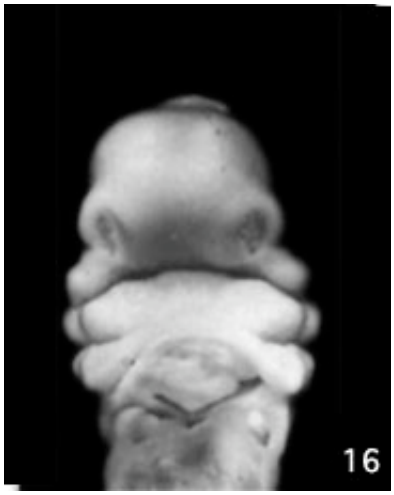
Anterior Pituitary

- not a pouch structure
- boundary epitheilal ectoderm in the roof of the pharynx
- forms a pocket (Rathke's pouch) that comes into contact with the ectoderm of developing brain.
    - Rathke's pouch is named after German embryologist and anatomist Martin Heinrich Rathke (1793 — 1860).



Pituitary

Face Development



Begins week 4 centered around stomodeum, external depression at oral membrane

5 initial primordia from neural crest mesenchyme

single frontonasal prominence (FNP) - forms forehead, nose dorsum and apex
nasal placodes develop later bilateral, pushed medially
paired maxillary prominences - form upper cheek and upper lip
paired mandibular prominences - lower cheek, chin and lower lip

Face Notes (http://embryology.med.unsw.edu.au/Notes/face.htm)

File:Face animation.gif

Head/Skull

- chondrocranium forms base of skull
- in lower vertebrates encases brain
- cranial vault
- calveria
- facial skeleton
- pharyngeal arches

Sensory Placodes

MH - will cover sensory placodes in Senses Lecture.

- During week 4 a series of thickened surface ectodermal patches form in pairs rostro-caudally in the head region.
- Recent research suggests that all sensory placodes may arise from common panplacodal primordium origin around the neural plate, and then differentiate to eventually have different developmental fates.
- These sensory placodes will later contribute key components of each of our special senses (vision, hearing and smell). Other species have a number of additional placodes which form other sensory structures (fish, lateral line receptor). Note that their initial postion on the developing head is significantly different to their final position in the future sensory system

Otic placode

in the stage 13/14 embryo (shown below) the otic placode has sunk from the surface ectoderm to form a hollow epithelial ball, the otocyst, which now lies beneath the surface surrounded by mesenchyme (mesoderm). The epithelia of this ball varies in thickness and has begun to distort, it will eventually form the inner ear membranous labyrinth.

Lens placode

lies on the surface, adjacent to the outpocketing of the nervous system (which will for the retina) and will form the lens.

Nasal placode

has 2 components (medial and lateral) and will form the nose olefactory epithelium.

Head Growth

- continues postnatally - fontanelle allow head distortion on birth and early growth
- bone plates remain unfused to allow growth, puberty growth of face

Skull Overview

Chondrocranium - formed from paraxial mesoderm

- cranial end of vertebral column
- modified vertebral elements
- occipital and cervical sclerotome
- bone preformed in cartilage (endochondrial ossification)

Cranial Vault and Facial Skeleton - formed from neural crest

- muscle is paraxial mesoderm
- somitomeres and occipital somites

Calveria - bone has no cartilage (direct ossification of mesenchyme)

- bones do not fuse, fibrous sutures 1. allow distortion to pass through birth canal 2. allow growth of the brain
- 6 fontanelles, posterior closes at 3 months, anterior closes at 18 months

Palate

The palate has two key stages of development during embryonic and an early fetal involving the fusion of structures (epithelia to mesenchymal).

Embryonic

Primary palate, fusion in the human embryo between stage 17 and 18, from an epithelial seam to the

Phases of Primary Palate Formation

Carnegie stages 17 to 18

(epithelial seam to mesenchymal bridge)

mesenchymal bridge.

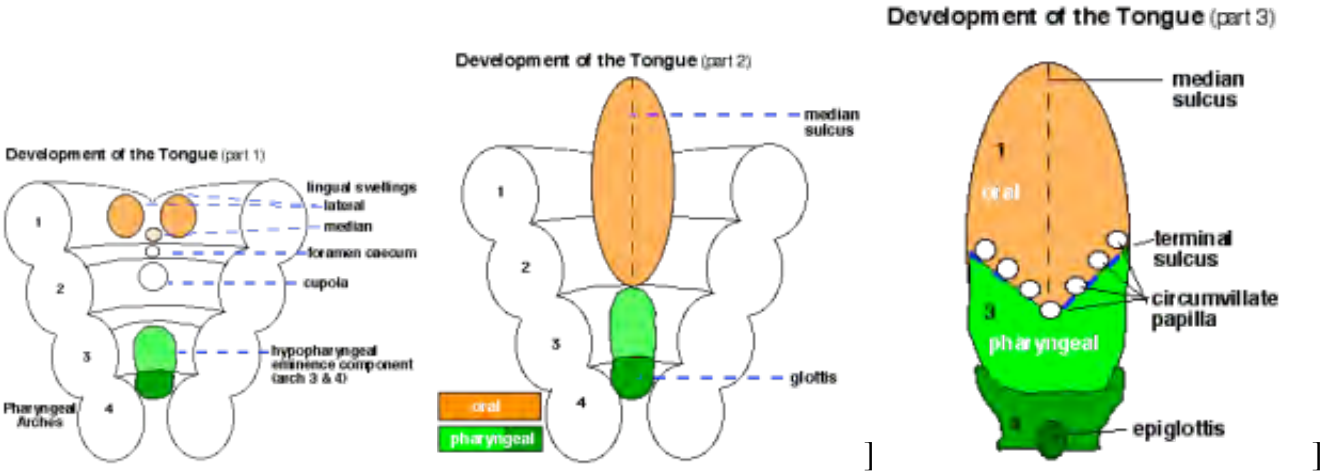
Fetal

Secondary palate, fusion in the human embryo in week 9. This requires the early palatal shelves growth, elevation and fusion during the early embryonic period. The fusion event is to both each other and the primary palate. palatal shelf elevation | secondary palate

Ear Auricles

- form from 6 hillocks (week 5)
- 3 on each of arch 1 and 2

Tongue Development



- Ectoderm of the first arch surrounding the stomodeum forms the epithelium lining the buccal cavity.
- Also the salivary glands, enamel of the teeth, epithelium of the body of the tongue.
    - As the tongue develops "inside" the floor of the oral cavity, it is not readily visible in the external views of the embryonic (Carnegie) stages of development.

- Contributions from all arches, which changes with time
- begins as swelling rostral to foramen cecum, **median tongue bud**

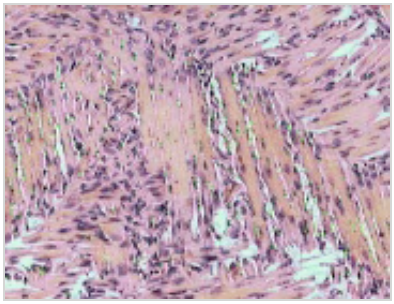
-
    - Arch 1 - oral part of tongue (ant 3/2)

- Arch 2 - initial contribution to surface is lost
- Arch 3 - pharyngeal part of tongue (post 1/3)
- Arch 4 - epiglottis and adjacent regions

tongue development animation | Development of the Tongue (http://embryology.med.unsw.edu.au/Movies/larsen/tongue.mov)

Tongue muscle

- Tongue muscles originate from the somites. Tongue muscles develop before masticatory muscles and is completed by birth.
- Masticatory muscles originate from the somitomeres. These muscles develop late and are not complete even at birth.



tongue muscle

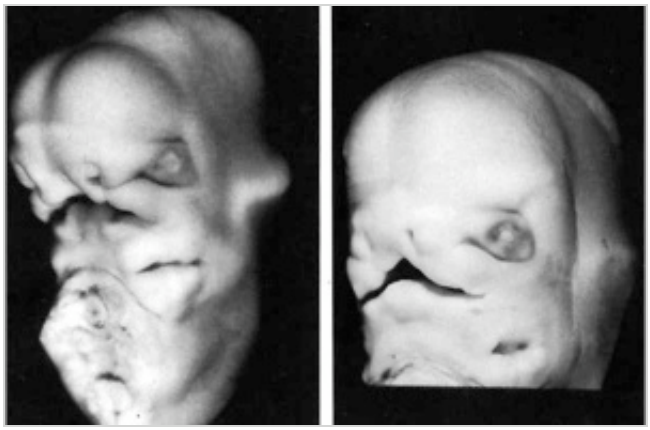
Salivary Glands

- epithelial buds in oral cavity (wk 6-7) extend into mesenchyme
- parotid, submandibular, sublingual

Abnormalities

Cleft Lip and Palate

- 300+ different abnormalities, different cleft forms and extent, upper lip and ant. maxilla, hard and soft palate



Stage 18-19 Cleft Primary Palate

Cleft Palate

- Cleft palate has the International Classification of Diseases code 749.0.
- In Australia the national rate (1982-1992) for this abnormalitity in births was 4.8 - 6/10,000 births, which represented 1,530 infants 5.5% were stillborn and 11.5% liveborn died during neonatal period and slightly more common in twin births than singleton.

Cleft Lip

- The International Classification of Diseases code 749.1 for isolated cleft lip and 749.2 for cleft lip with cleft palate.
- In Australia the national rate (1982-1992) for this abnormalitity was 8.1 - 9.9 /10,000 births. Of 2,465 infants 6.2% were stillborn and 7.8% liveborn died during neonatal period and the rate was similar in singleton and twin births.

First Arch Syndrome

- There are 2 major types of associated first arch syndromes, Treacher Collins (Mandibulofacial dysostosis) and Pierre Robin (Pierre Robin complex or sequence), both result in extensive facial abnormalites.

Treacher Collins Syndrome

Pierre Robin Syndrome

- Hypoplasia of the mandible, cleft palate, eye and ear defects.
- Initial defect is small mandible (micrognathia) resulting in posterior displacement of tongue and a bilateral cleft palate.

DiGeorge Syndrome

- absence of thymus and parathyroid glands, 3rd and 4th pouch do not form
- disturbance of cervical neural crest migration

Cysts

- Many different types

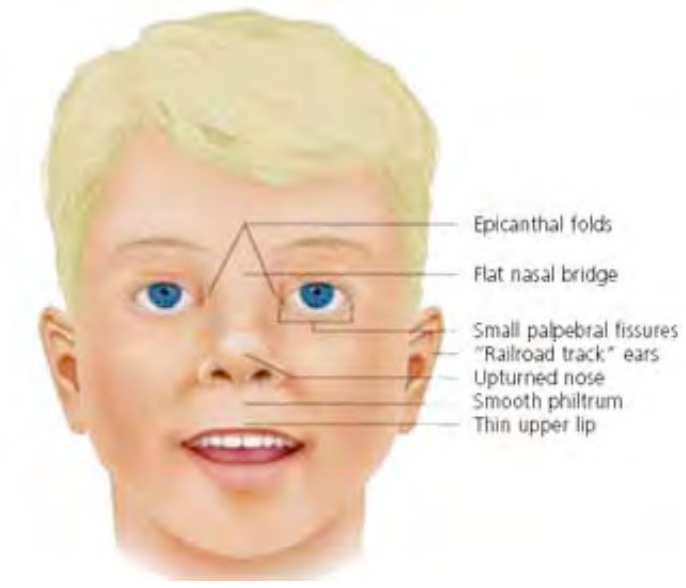
Facial Clefts

- - extremely rare
- Holoprosencephaly
  - shh abnormality

Maternal Effects

- Retinoic Acid - present in skin ointments
- 1988 associated with facial developmental abnormalities

Fetal Alcohol Syndrome



Due to alcohol in early development (week 3+) leading to both facial and neurological abnormalities

lowered ears, small face, mild+ retardation
Microcephaly - leads to small head circumference
Short Palpebral fissure - opening of eye
Epicanthal folds - fold of skin at inside of corner of eye
Flat midface
Low nasal bridge
Indistinct Philtrum - vertical grooves between nose and mouth
Thin upper lip
Micrognathia - small jaw

Exposure of embryos in vitro to ethanol simulates premature differentiation of prechondrogenic mesenchyme of the facial primordia (1999)

Fetal Alcohol Syndrome (http://embryology.med.unsw.edu.au/Defect/page5a.htm)

Molecular Mechanisms

- Recent experiments with human embryos have shown that gene expression in the head region follows that seen in other species embryo models
- Branchial HOX Gene Expression and Human Craniofacial Development
  - Vieille-Grosjean etal. Dev Biol. 1997
- hindbrain segmentation into rhombomeres
- Hox expression regulates segmentation
- retinoic acid may regulate Hox expression
- Neural Crest migrates into arches from specific rhombomere levels

Dlx Expression - dlx are homeobox genes, family of dlx-1 to dlx-7, regulates Anterior-Posterior identity, dlx-1 and -2 regulate arch 1

- paraxial mesoderm unsegmented somitomeres (7)
- follows neural crest migration pathways
- somitomere 3 mesodermal cells (blue) in Arch 1
- SHH - expressed in arches, regulates midface formation
- Pax-3 expressed in placode cells, contribute to the CNV, ophthalmic branch

Structures derived from Arches

Arch	Nerve	Skeletal Structures	Muscles	Ligaments
1 (maxillary/mandibular)	trigeminal (V)	mandible, maxilla, malleus, incus		ant lig of malleus, sphenomandibular ligament
2 (hyoid)	facial (VII)	stapes, styloid process, lesser cornu of hyoid, upper part of body of hyoid bone		stylohyoid ligament
3	glossopharyngeal (IX)	greater cornu of hyoid, lower part of body of hyoid bone		
4 & 6	superior laryngeal and recurrent laryngeal branch of vagus (X)	thyroid, cricoid, arytenoid, corniculate and cuneform cartilages		

Structures derived from Arches

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Skeletal Structures

File:Mandible sm.jpg	mandible
File:Hyoid bone sm.jpg	hyoid
File:Larynx cartilage sm.jpg	

Structures derived from Pouches

Each pouch is lined with endoderm and generates specific structures.

POUCH	Overall Structure	Specific Structures
1	tubotympanic recess	tympanic membrane, tympanic cavity, mastoid antrum, auditory tube
2	intratonsillar cleft	crypts of palatine tonsil, lymphatic nodules of palatine tonsil
3	inferior parathyroid gland, thymus gland	
4	superior parathyroid gland, ultimobranchial body	
5	becomes part of 4th pouch	

Structures derived from Grooves

Only the **first groove** differentiates into an adult structure and forms part of the external acoustic meatus.

Structures derived from Membranes

At the bottom of each groove lies the membrane which is formed from the contact region of ectodermal groove and endodermal pouch. Only the **first membrane** differentiates into an adult structure and forms the tympanic membrane.

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter Chapter 10 The Pharyngeal Apparatus pp201 - 240.
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 12 Development of the Head, the Neck, the Eyes, and the Ears pp349 - 418.

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Figure 1.3. Pharyngeal arches (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.43) | Table 13.2. Some derivatives of the pharyngeal arches (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.table.3135) | The Cranial Neural Crest (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?

&rid=dbio.section.3109#3133)

- **Madame Curie Bioscience Database** Chapters taken from the Madame Curie Bioscience Database (formerly, Eurekah Bioscience Database) Cranial Neural Crest and Development of the Head Skeleton (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A53006) | Neural Crest Cells and the Community of Plan for Craniofacial Development: Historical Debates and Current Perspectives (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=ch2957)

Search

- **Bookshelf** pharyngeal arch (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=pharyngeal_arch) | head development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=head_development) | face development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=face_development)

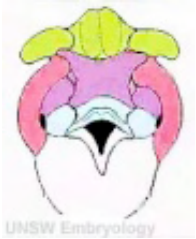
- **Pubmed** pharyngeal arch (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=pharyngeal_arch) | head development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=head_development) | face development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=face_development) |

Movies


Face


Palate 1


Palate 2



Tongue

UNSW Embryology Links

- **Notes:** Head and Neck Development (http://embryology.med.unsw.edu.au/Notes/head.htm) | Head Abmormalities (http://embryology.med.unsw.edu.au/Notes/head2.htm) | Stage 13/14 Head sections (http://embryology.med.unsw.edu.au/Notes/head3.htm) | Stage 22 Human head sections (http://embryology.med.unsw.edu.au/Notes/head4.htm) | Selected Human high power (st22) (http://embryology.med.unsw.edu.au/Notes/head5.htm) | Face (http://embryology.med.unsw.edu.au/Notes/face.htm) | Primary Palate (http://embryology.med.unsw.edu.au/Notes/face6.htm) | Face Abnormalities (http://embryology.med.unsw.edu.au/Notes/face2.htm) | Tongue (http://embryology.med.unsw.edu.au/Notes/head6.htm) | Teeth (http://embryology.med.unsw.edu.au/Notes/skin10.htm) | Skull (http://embryology.med.unsw.edu.au/Notes/skmus8a.htm) | Senses (http://embryology.med.unsw.edu.au/Notes/senses.htm) | Systems (http://embryology.med.unsw.edu.au/wwwpig/system/PigArch.htm) (Pig, pharyngeal) | Head and Neck Sections (http://embryology.med.unsw.edu.au/wwwhuman/LowSet/HeadSet.htm) (Human sets) | Neck (http://embryology.med.unsw.edu.au/wwwhuman/System/HumSysT.htm) (Human sets) | Head Sections (http://embryology.med.unsw.edu.au/wwwpig/lowset/HeadSet.htm) (Pig sets)

- **Movies:** tongue | palate | palatal shelves | Face Stages 16 to 18 | face | Head and Palate Movies

(http://embryology.med.unsw.edu.au/Movies/head.htm) | Development of the Face (http://embryology.med.unsw.edu.au/Movies/larsen/face.mov) (451Kb) | Development of the Tongue (http://embryology.med.unsw.edu.au/Movies/larsen/tongue.mov) (187Kb)| Animations (http://embryology.med.unsw.edu.au/Movies/HumEmb.htm) | Ultrasound - Cleft lip/palate 1 (http://embryology.med.unsw.edu.au/Movies/usoundab/Cleft1.htm) | Ultrasound - Cleft lip/palate 2 (http://embryology.med.unsw.edu.au/Movies/usoundab/Cleft2.htm)

- **Lectures:** BGD Face 2009 (http://embryology.med.unsw.edu.au/Medicine/BGDFace/BGDFace.htm) BGD slides 2007 (http://embryology.med.unsw.edu.au/Lectures/BGDface/BGDface.htm) | {http://embryology.med.unsw.edu.au/Medicine/BGDlabHead.htm BGD Practical 2009] | ANAT2300 Vertebrate Development- Head Development (http://embryology.med.unsw.edu.au/Sections/anat2300/2004/ANAT2300L09.htm) | ANAM1006 Head Development (http://embryology.med.unsw.edu.au/Sections/anam1006/2003/ANAM1006L7.htm) | ANAT1006 Medicine 2002- Head Development (http://embryology.med.unsw.edu.au/Sections/anat1006/lecture1/embryo_01.htm)

External Links

Embryo Images Unit: Embryo Images Online (http://www.med.unc.edu/embryo_images/) | Craniofacial Development (http://www.med.unc.edu/embryo_images/unit-hednk/hednk_htms/hednktoc.htm) | Cell Populations (http://www.med.unc.edu/embryo_images/unit-hednk/hednk_htms/hednk001.htm) | Pharyngeal Arches (http://www.med.unc.edu/embryo_images/unit-hednk/hednk_htms/hednk007.htm) | Tongue (http://www.med.unc.edu/embryo_images/unit-hednk/hednk_htms/hednk024.htm) | Nose and Upper Lip (http://www.med.unc.edu/embryo_images/unit-hednk/hednk_htms/hednk026.htm) | Palate Development (http://www.med.unc.edu/embryo_images/unit-hednk/hednk_htms/hednk033.htm)

Research Labs: tzahor lab (http://www.weizmann.ac.il/Biological_Regulation/tzahor/research.html)

Terms

- anlage- (Ger.) primordium, structure or cells which will form a future structure.
- brain- general term for the central nervous system formed from 3 primary vesicles.
- buccopharyngeal membrane- (=oral membrane) at cranial (mouth) end of gastrointestinal tract (GIT) where surface ectoderm and GIT endoderm meet. (see also [#cloacal membrane cloacal membrane])
- cloacal membrane- at caudal (anal) end of gastrointestinal tract (GIT) where surface ectoderm and GIT endoderm meet forms the openings for GIT, urinary, reproductive tracts. (see also [#buccopharyngeal membrane buccopharyngeal membrane])
- connective tissue-
- dermomyotome- dorsolateral half of each somite that forms the dermis and muscle.
- dorsal root ganglia- (=spinal ganglia) sensory ganglia derived from the neural crest lying laterally paired and dorsally to the spinal cord (in the embryo found ventral to the spinal cord). Connects centrally with the dorsal horn of the spinal cord.
- dura mater-
- ectoderm- the layer (of the 3 germ cell layers) which form the nervous system from the neural tube and neural crest and also generates the epithelia covering the embryo.
- endoderm- the layer (of the 3 germ cell layers) which form the epithelial lining of the gastrointestinal tract (GIT) and accessory organs of GIT in the embryo.
- epiblast- the layer (of the bilaminar embryo) that generates endoderm and mesoderm by migration of cells through the primitive streak. The remaing cells form ectoderm.
- growth factor- usually a protein or peptide that will bind a cell membrane receptor and then activates an intracellular signaling pathway. The function of the pathway will be to alter the cell directly or

2009 Lecture 12

From Embryology

Contents

Neural Crest Development

Introduction

The neural crest are bilaterally paired strips of cells arising in the ectoderm at the margins of the neural tube. These cells migrate to many different locations and differentiate into many cell types within the embryo. This means that many different systems (neural, skin, teeth, head, face, heart, endocrine, gastrointestinal tract) will also have a contribution fron the neural crest cells.

In the body region, neural crest cells also contribute the peripheral nervous system (both neurons and glia) consisting of sensory ganglia (dorsal root ganglia), sympathetic and parasympathetic ganglia and neural plexuses within specific tissues/organs.

In the head region, neural crest cells migrate into the pharyngeal arches (as shown in movie below) forming **ectomesenchyme** contributing tissues which in the body region are typically derived from mesoderm (cartilage, bone, and connective tissue).

General neural development is also covered in Neural Notes.

> **Lectopia Audio** Lecture Date: 01-09-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Neural Crest (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48840)

Lecture Objectives

- Understand the structures derived from ectoderm.
- Understand the formation of neural folds.
- Identify the initial location of neural crest cells in the trilaminar embryo.
- Identify pathways of neural crest migration throughout the embryo.
- To know the major tissues to which neural crest cells contribute.
- To know how abnormalities in development that result from abnormal neural crest cell migration.
- Understand how neural crest cells contribute to the pharyngeal arches and the head structures they form.

Textbook References

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter 4 p61-63 - p71,75, 385, 392 p393-94 (figure showing cell types); Chapter 10 The Pharyngeal Apparatus pp201 - 240,

- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 4 p74-82 - Chapter 5, experimental methods; Chapter 12 Development of the Head, the Neck, the Eyes, and the Ears pp349 - 418

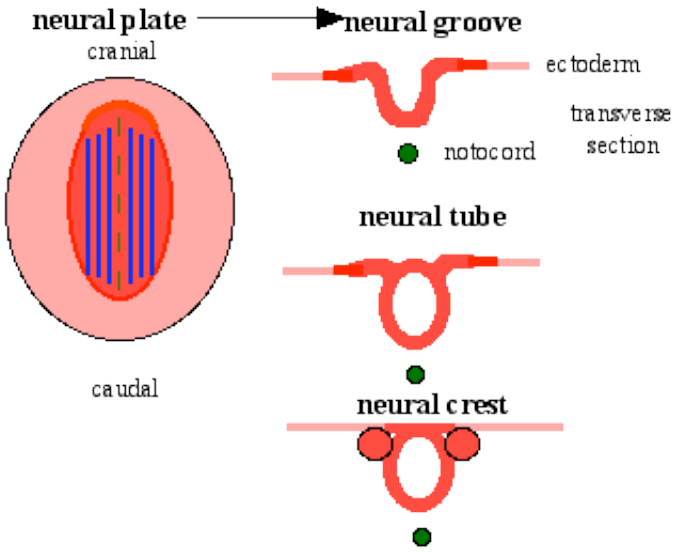
Early Development and Neural Derivatives

- bilaminar embryo- hyoblast
- trilaminar embryo - ectoderm layer
  - neural plate - neural groove - neural tube and neural crest
- cranial expansion of neural tube - central nervous system
- caudal remainder of neural tube - spinal cord

Neural Crest

- dorsal root ganglia
- parasympathetic / sympathetic ganglia.
- ectodermal placodes- components of the special senses
- Sensory placodes - otic placode (otocyst), nasal placode, lens placode

Neural Crest Origin



lateral region of neural plate
dorsal neural fold->tube

Two main embryo regions

Head (CNS) - differentiate slightly earlier, mesencephalic region of neural folds
Body (spinal cord) - lateral edges of fused neural tube

Neural Crest Generation

cranial region - Begins when still neural fold
spinal cord - from day 22 until day 26
after closure of caudal neuropore
rostro-caudal gradient of differentiation

Studies using the chicken model demonstrated that they are not a segregated population. Interactions between the neural plate and epidermis can generate neural crest cells, since juxtaposition of these tissues at early stages results in the formation of neural crest cells at the interface.

At cranial levels, neuroepithelial cells can regulate to generate neural crest cells when the endogenous neural folds are removed, probably via interaction of the remaining neural tube with the epidermis.

Progenitor cells in the neural folds are multipotent, having the ability to form multiple ectodermal derivatives, including epidermal, neural crest, and neural tube cells the neural crest is an induced population that arises by interactions between the neural plate and the epidermis.

The competence of the neural plate to respond to inductive interactions changes as a function of embryonic age.

(Text from: Bronner-Fraser M PNAS 1996 Sep 3;93(18):9352-7)

Neural Crest Derivatives

Neural crest progenitor cells migrate throughout the embryo and give rise to many different adult cells.

This Includes: ganglia cranial, dorsal root, sympathetic trunk, celiac, renal, plexus in GIT, glia, schwann cells, melanocytes (skin), and adrenal medulla (chromaffin cells).

In the head region neural crest also gives rise to a number of connective tissue structures.

Neural Crest - Head

(see also Head Development Notes)

Mesencephalon and caudal Proencephalon

- parasympathetic ganglia CN III
- connective tissue around eye and nerve
- head mesenchyme
- pia and arachnoid mater
- dura from mesoderm

Mesencephalon and Rhombencephalon

- pharayngeal arches
- look at practical notes on neck and head.
- cartilage rudiments (nose, face, middle ear)
- face
- dermis, smooth muscle and fat
- odontoblasts of developing teeth

Rhombencephalon

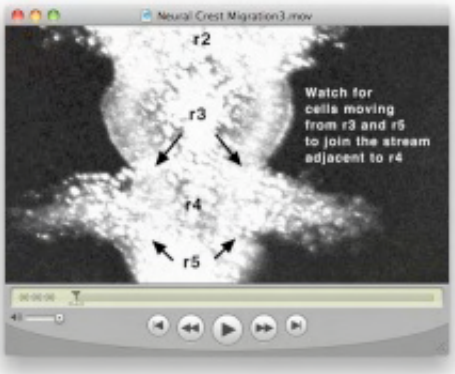
- C cells of thyroid
- cranial nerve ganglia
- neurons and glia
- parasympathetic of VII, IX, X
- sensory ganglia of V, VII, VIII, IX, X

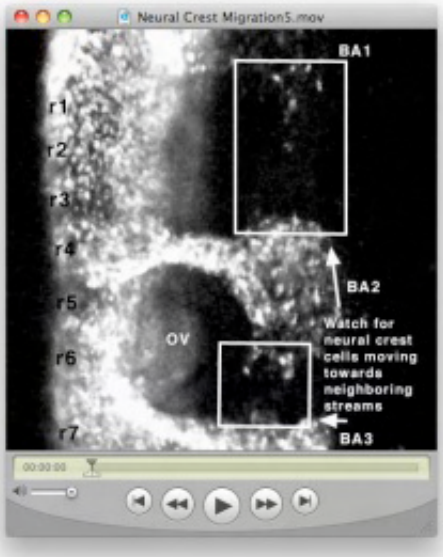
Neural Crest- Spinal Cord

- peripheral nervous system
- dorsal root ganglia (sensory N)
- parasympathetic ganglia
- sympathetic ganglia
- motoneurons in both ganglia
- all associated glia

Neural Crest Migration

Head





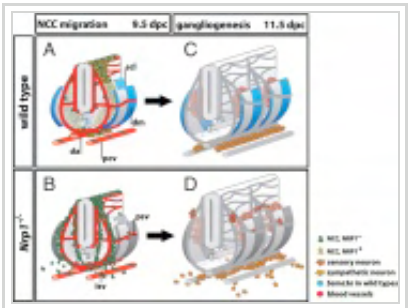
File:Neural Crest Migration7.mov | File:Neural Crest Migration6.mov | Category:Movies

Trunk

Figure 13.2. Neural crest cell migration in the trunk of the chick embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3118)

- Neural crest at the level of the body have two general migration pathways, defined by the position of the somite
  - medial pathway - between the neural tube and the somite
  - lateral pathway - between the somite and the body wall

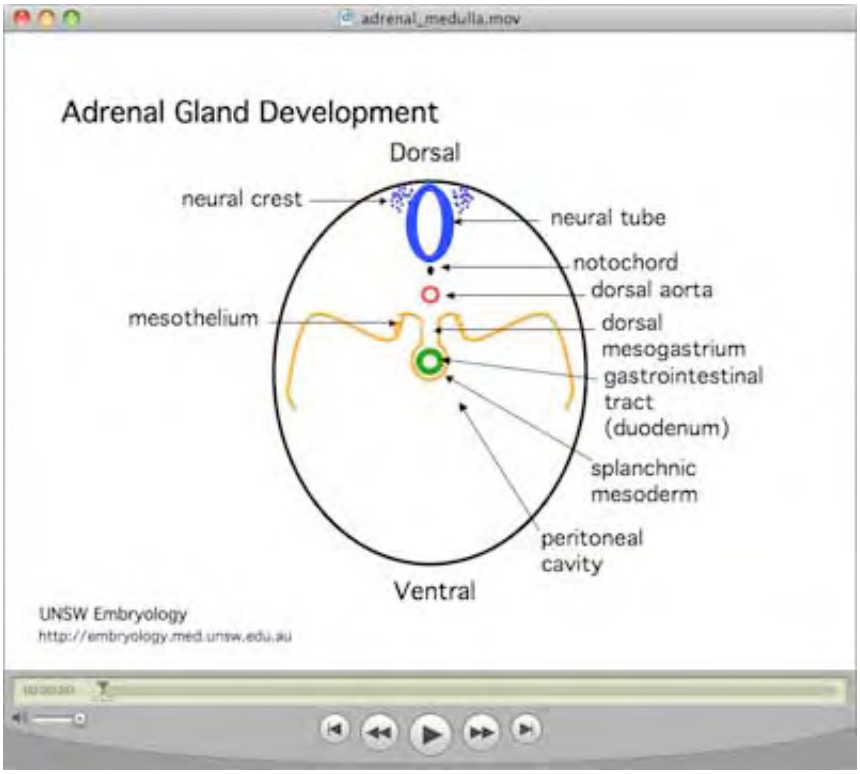
- A recent study of guidance of neural crest cells (NCC) in mice show migrate 3 specific pathways.
  - SEMA3A and its receptor neuropilin 1 (NRP1) - act as repulsive guidance cues
  - migration pathway did not affect specification - differs from the concept of migration pathway specifying the neural crest cell differentiation pathway



Trunk neural crest migration

Neural crest at the level of the head have a different migration pathway.
Figure 13.7. Cranial neural crest cell migration in the mammalian head (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3134)

Sympathetic Ganglia and Adrenal Medulla



Media:Adrenal_medulla.mov

Enteric nervous system

Figure 1. Diagram of an E10 embryo showing the origins of neural crest cells that colonize the developing gastrointestinal tract (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A63004&rendertype=figure&id=A63009)

Historic Migration Experiments

Key early experiments in understanding the pattern of neural crest migration were carried out by LeDouarin in the 1980's (see Development of the peripheral Nervous system from the neural crest, Ann Rev Cell Biol 4 p375) Quail-Chick Chimeras (http://www.sdbonline.org/archive/dbcinema/ledouarin/ledouarin.html) | Figure 1.11. Neural crest cell migration Chimera experiment (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.63)

These transplantation studies in chicken/quail chimeras utilised the different nucleoli appearance of cells to differentiate different species. Thus transplanation and subsequent histological processing allowed identification of the migration path and final destination of transplanted neural crest cells.

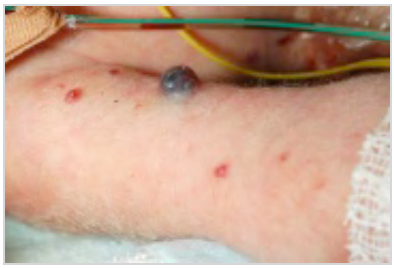
Similar later experiments have now been carried out using the neural crest cells molecularly tagged with (LacZ).

Abnormalities

Neuroblastoma

OMIM - Neuroblastoma

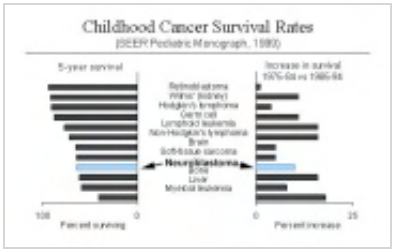
OMIM - Neuroblastoma
(http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=256700)



Neuroblastoma

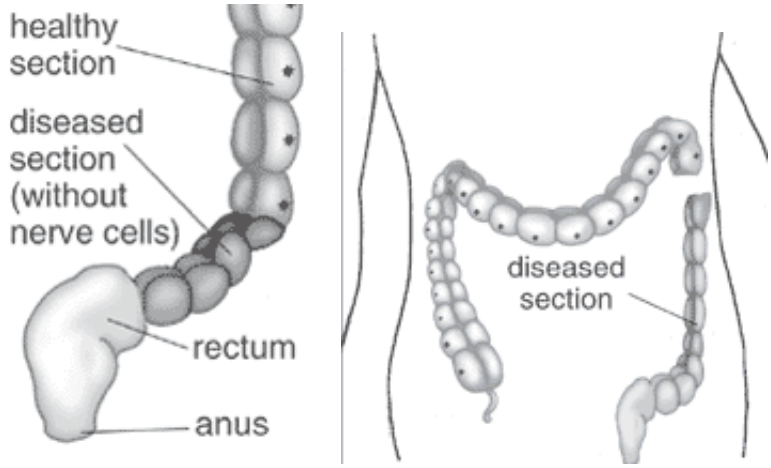
Digeorge Syndrome (DGS)

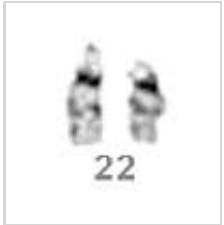
- DiGeorge syndrome is the most frequent microdeletion syndrome in humans caused by a hemizygous deletion (1.5 to 3.0-Mb) of chromosome 22q11.2.
- Velo-cardio-facial syndrome, Hypoplasia of thymus and parathyroids, third and fourth pharyngeal pouch syndrome.
- Abnormalities: cardiovascular, thymic and parathyroid, craniofacial anomalies, renal anomalies, hypocalcemia and immunodeficiency.



Childhood cancer survival rates

Intestinal Aganglionosis

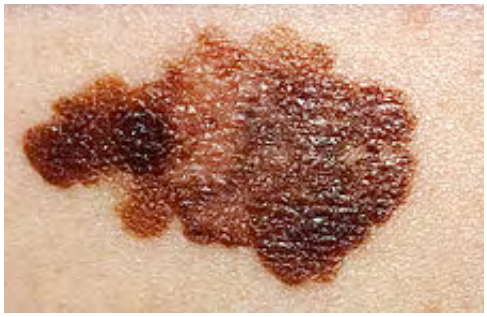




Digeorge chromosome 22

- Intestinal Aganglionosis, Hirschsprung's Disease or Megacolon
- lack of enteric nervous system (neural ganglia) in the intestinal tract responsible for gastric motility (peristalsis).
- severity is dependent upon the amount of the GIT that lacks intrinsic ganglia, due to developmental lack of neural crest migration into those segments.
- first indication in newborns is an absence of the first bowel movement, other symptoms include throwing up and intestinal infections.
- Clinically this is detected by one or more tests (barium enema and x ray, manometry or biopsy) and can currently only be treated by surgery. A temoporary ostomy (Colostomy or Ileostomy) with a stoma is carried out prior to a more permanent pull-through surgery.

Melanoma



- In Australia each year 8,800 people are diagnosed with melanoma, and almost 1000 people die (Data, Cancer Council Australia).
- Two different findings on the reprogramming of melanoma cells, which have a neural crest origin, when transplanted between species into embryos.

Melanoma staging (http://www.melanoma.com/staging.html)

Neurofibromatosis Type 1 (NF1)

- Neurofibromatosis Type 1 (von Recklinghausen) occurs in 1 in 3,000 to 4,000 people with characteristic skin blemishes forming in early childhood.
- Multiple *café-au-lait* spots (flat skin patches darker than the surrounding area) appear in early childhood which increase in both size and number with age.
- tumors can develop along nerves in the skin, brain, and other parts of the body. In the iris of the eye, Lisch nodules (benign growths) also appear

  (French, *café-au-lait* = coffee with milk)

Atlas of Genetics and Cytogenetics in Oncology- Neurofibroma
(http://atlasgeneticsoncology.org/Tumors/NeurofibromaID5098.html)

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter Chapter 10 The Pharyngeal Apparatus pp201 - 240.
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 12 Development of the Head, the Neck, the Eyes, and the Ears pp349 - 418.

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 The Cranial Neural Crest (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3109#3133) | Figure 13.1. Regions of the neural crest (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3111) | Figure 13.7. Cranial neural crest cell migration in the mammalian head (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3134) | Figure 13.2. Neural crest cell migration in the trunk of the chick embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3118) | Figure 13.10. Separation of the truncus arteriosus into the pulmonary artery and aorta (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3138) | Figure 22.23. Chick embryo rhombomere neural crest cells and their musculoskeletal packets (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.5460) | Figure 13.4. Segmental restriction of neural crest cells and motor neurons by the ephrin proteins of the sclerotome (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3127) | Figure 1.3. Pharyngeal arches (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.43) | Table 13.2. Some derivatives of the pharyngeal arches (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.table.3135)

  Neural Crest Experiments: Figure 1.11. Neural crest cell migration Chimera experiment (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.63) | Figure 13.5. Pluripotency of trunk neural crest cells (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.figgrp.3130)

- **Molecular Biology of the Cell** Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 Figure 21-80. The main pathways of neural crest cell migration (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3946) Figure 21-91. Diagram of a 2-day chick embryo, showing the origins of the nervous system (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=mboc4.figgrp.3968) | Figure 19-23. An example of a more complex mechanism by which cells assemble to form a tissue

(http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=neural_crest&rid=mboc4.figgrp.3511)

- **Neuroscience** Purves, Dale; Augustine, George J.; Fitzpatrick, David; Katz, Lawrence C.; LaMantia, Anthony-Samuel; McNamara, James O.; Williams, S. Mark. Sunderland (MA): Sinauer Associates, Inc.; c2001Figure 22.1. Neurulation in the mammalian embryo (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=neurosci.figgrp.1449) | Figure 22.12. Cell signaling during the migration of neural crest cells (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=neurosci.figgrp.1503)
- **Madame Curie Bioscience Database** Chapters taken from the Madame Curie Bioscience Database (formerly, Eurekah Bioscience Database) Cranial Neural Crest and Development of the Head Skeleton (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A53006) | Neural Crest Cells and the Community of Plan for Craniofacial Development: Historical Debates and Current Perspectives (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=ch2957) | Figure 1. Diagram of an E10 embryo showing the origins of neural crest cells that colonize the developing gastrointestinal tract (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=eurekah&part=A63004&rendertype=figure&id=A63009)

- **Basic Neurochemistry: Molecular, Cellular, and Medical Aspects** Siegel, George J.; Agranoff, Bernard W.; Albers, R. Wayne; Fisher, Stephen K.; Uhler, Michael D., editors Philadelphia: Lippincott,Williams & Wilkins; c1999Figure 27-10. Neuropoietic model of neural crest cell lineage (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=bnchm.figgrp.1881) | Figure 27-11. Growth factor control of neural crest lineage decisions (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=neural_crest&rid=bnchm.figgrp.1883) | Figure 27-15. The Schwann cell lineage (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=neural_crest&rid=bnchm.figgrp.1893)

Search

- **Bookshelf** neural crest (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=neural_crest)

- **Pubmed** neural crest (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=neural_crest)

UNSW Embryology Links

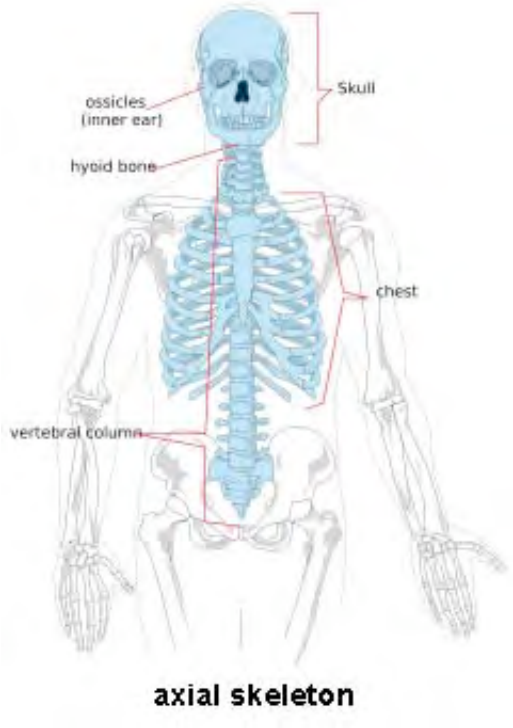
- **Notes:** Introduction (http://embryology.med.unsw.edu.au/Notes/ncrest.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/ncrest2.htm) | Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/ncrest3.htm) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/ncrest4.htm) | Stage 22 high power (http://embryology.med.unsw.edu.au/Notes/ncrest5.htm) | Generation (http://embryology.med.unsw.edu.au/Notes/ncrest6.htm) | Migration (http://embryology.med.unsw.edu.au/Notes/ncrest7.htm) | Peripheral Ganglia (http://embryology.med.unsw.edu.au/Notes/ncrest8.htm) | GIT Enteric (http://embryology.med.unsw.edu.au/Notes/ncrest9.htm) | Heart (http://embryology.med.unsw.edu.au/Notes/ncrest12.htm) Molecular (http://embryology.med.unsw.edu.au/Notes/ncrest10.htm) | Text only (http://embryology.med.unsw.edu.au/Notes/ncresttxt.htm) | Web Links (http://embryology.med.unsw.edu.au/Notes/ncrestlink.htm)
- **Lectures:** ANAT2341 - Embryology 2008 - Lecture 13 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture13.htm)
- **Movies:** Neural Movies (http://embryology.med.unsw.edu.au/Movies/neural.htm#ncrest)

2009 Lecture 13

From Embryology

Contents

Musculoskeletal Development



axial skeleton

Introduction

This lecture is an introduction to the process of musculoskeletal development. In the body, this is mainly about **mesoderm** differentiation beginning with an embryonic connective tissue structure, the **mesenchyme**. In the head, this is a mixture of mesoderm and neural crest differentiation, from mesenchyme and ectomesenchyme respectively. The lecture will cover mainly cartilage and bone, as muscle will be covered in the limb lecture and in this week's laboratory.

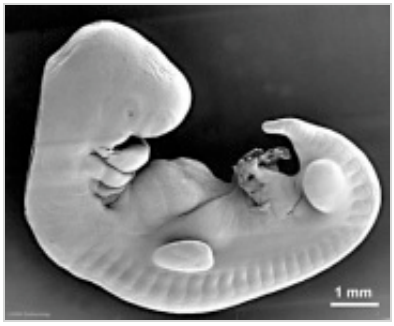
Note that genes that control skeleton patterning and cell differentiation are different.

Lectopia Audio Lecture Date: 14-09-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Musculoskeletal (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48829)

2008 Lecture (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture16.htm)

Lecture Objectives

- Understanding of mesoderm and neural crest development.
- Understanding of connective tissue development.
- Understanding of muscle, cartilage and bone development.
- Understanding of the two forms of bone development.
- Brief understanding of bone molecular development.
- Brief understanding of other bone roles.
- Brief understanding of bone abnormalities.



Embryo stage 14 SEM

Textbook References

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter 15 the skeletal system

- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 11 Limb Dev (bone not well covered in this textbook)

- Before we Are Born (5th ed.) Moore and Persaud Ch16,17: p379-397, 399-405
- Essentials of Human Embryology Larson Ch11 p207-228

Australia

Health expenditure for arthritis and musculoskeletal conditions, 2004-05 (http://www.aihw.gov.au/publications/index.cfm/title/10699)

> "Arthritis and musculoskeletal conditions affect more than 6 million Australians. In 2004-05, direct health expenditure on these conditions amounted to $4.0 billion or 7.5% of total allocated health expenditure in Australia."

Connective Tissue Development

Stage 1 - migrate to site of skeletogenesis

Stage 2 - associate with an epithelium

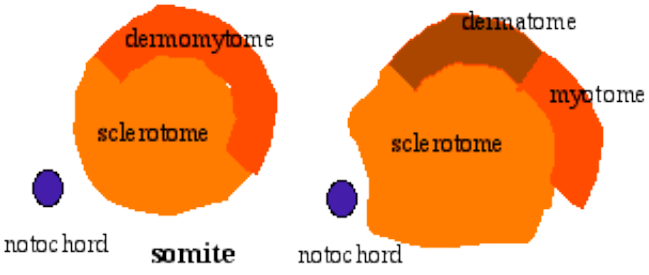
Stage 3 - Cell Condensation - mesenchymal dispersed cell population, gathers together to differentiate

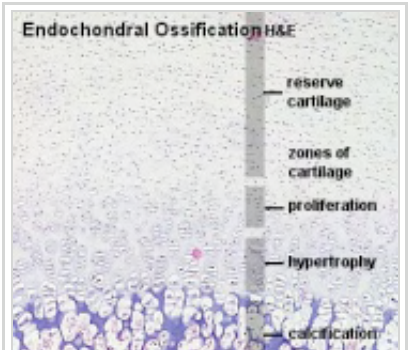
Stage 4 - Overt Differentiation - chrondroblast, osteoblast, myoblast

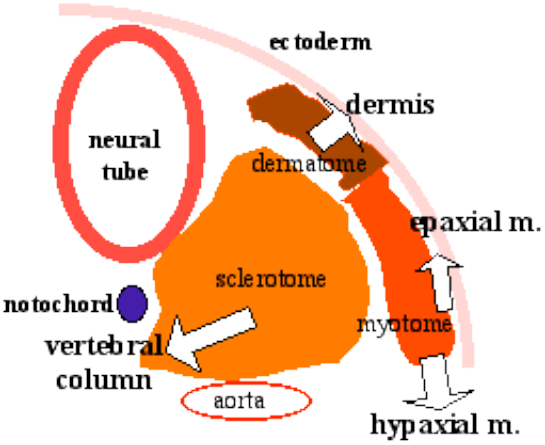
Cartilage

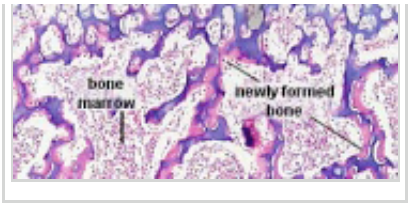
Histology - Cartilage (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Cartilage/Cartil.htm)

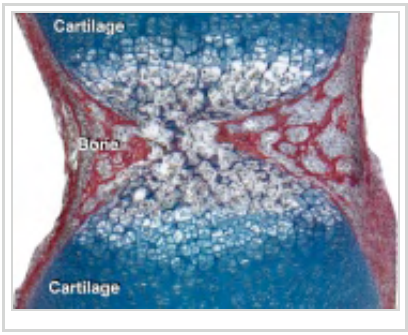
Sclerotome





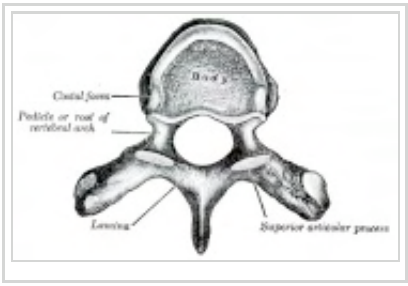


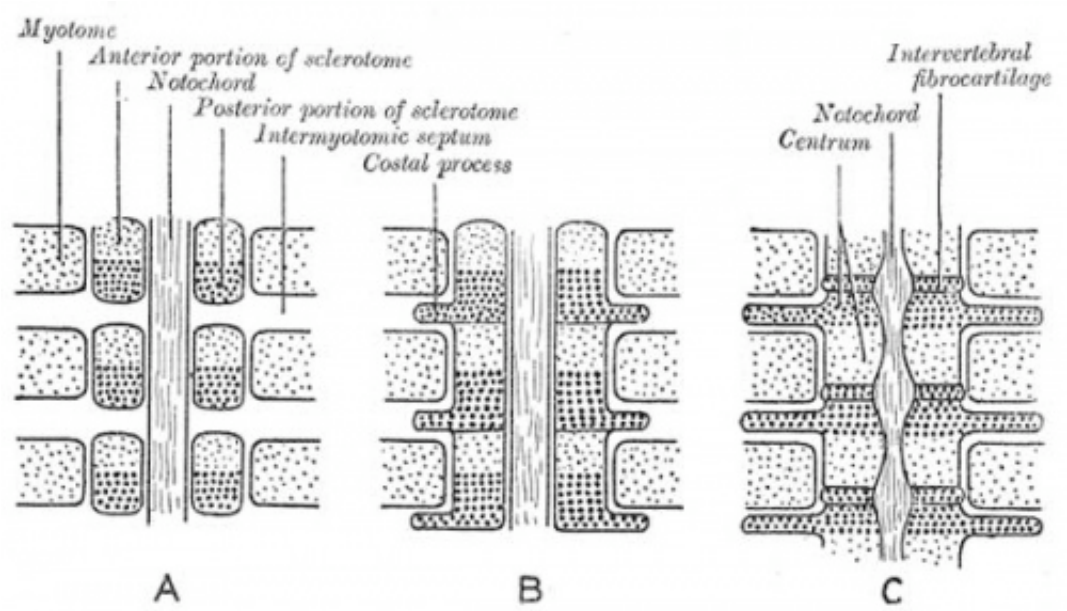




Vertebra

- Vertebral column formation - week 4, somite sclerotome surrounds notochord.
  - notochord (and floorplate) induces sclerotome migration and vertebral body cartilages.
  - neural tube induces vertebral arches.
- Scleretome has 2 components
  - upper loose (pathway for artery and nerve) and lower compact





Vertebra (http://embryology.med.unsw.edu.au/Movies/mesoderm/vertabra3.mov)

- Vertebral segmentation is shifted 1/2 somite caudally - by fusion cephalic compact with caudal loose to form vertebra from 2 sclerotomes.
  - Caudal dense region also forms neural arch.

Adult vertebral column

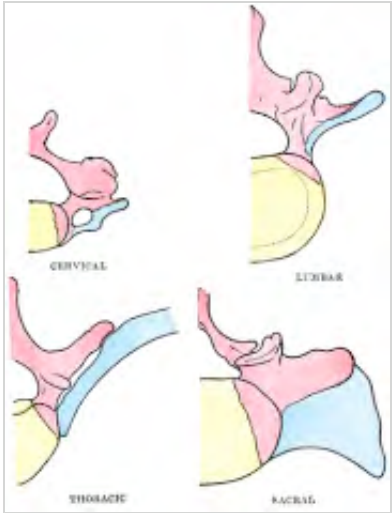
- 33 total - 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 5 coccygeal

Intervertebral Disc

- Structure - annulus and nucleus pulposus
- dense region of sclerotome.
- notochord initially contributes to nucleus pulposus of each disc, contribution replaced and lost postnatally.

Ribs

- dense region of sclerotome contributes costal processes (thoracic region).
    - chondrification commences day 45 and rib cage is cartilage by end of embryonic period.



vertebra origin: body, arch, and costal process

Sternum

- mesenchyme from ventral body wall (manubrium, body, ziphoid).
- sternal cartilage "bars" fuse with costal processes and developing clavicles by end of embryonic period.

Cartilage growth

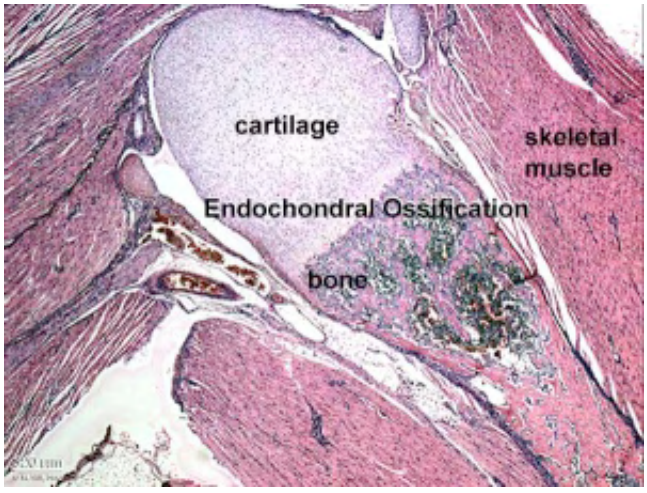
Histology - Cartilage (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Cartilage/Cartil.htm)

- Interstitial growth - occurs mainly in immature cartilage.
  Chondroblasts in existing cartilage divide and form small groups of cells (isogenous groups) which produce matrix to become separated from each other by a thin partition of matrix.
- Appositional growth - occurs also in mature cartilage. Mesenchymal cells surrounding the cartilage in the deep part of the perichondrium (or the chondrogenic layer) differentiate into chondroblasts.

Hypertrophic Chondrocytes

- secrete VEGF, promoting vascular invasion
- hypertrophic calcified cartilage becomes resorbed, by recruited chondroclasts/osteoclasts via MMP9

Bone

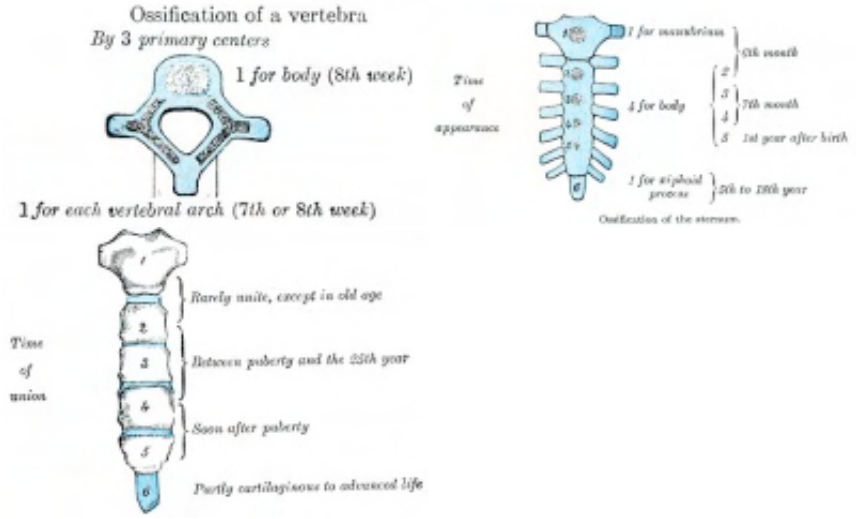


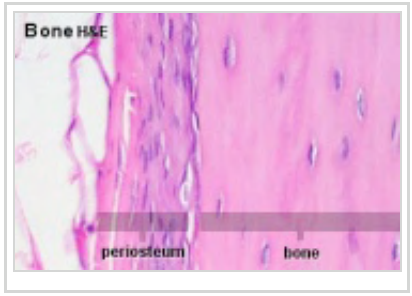
Two major systems of bones: the axial skeleton and the appendicular skeleton.
axial skeleton - 80 bones (skull, ribs, and sternum)
appendicular skeleton - 126 bones (shoulders, pelvis, and limbs)

Two main forms of bone formation: Endochondral and Intramembranous. Ossification process continues postnatally through puberty until mid 20s.

Histology - Bone

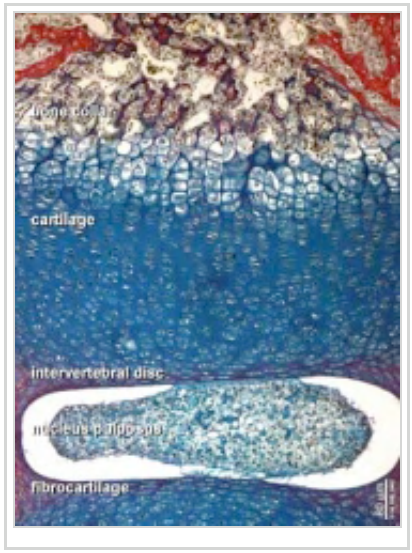
(http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Bone/Bone.htm)



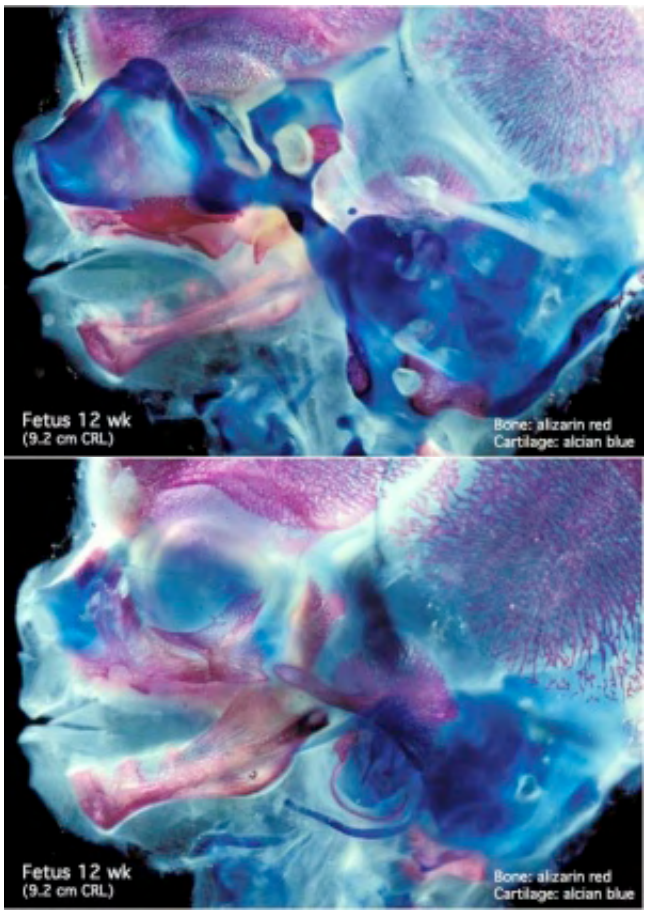


Endochondral Ossification

- Majority of skeleton formed by this process (vertebra, limb long bones)
- Osteoblasts derived from the bone collar replace cartilage matrix with a matrix rich in type I collagen leading to bone formation
- Ossification centres (primary and secondary)
- Early ossification occurs at ends of long bone

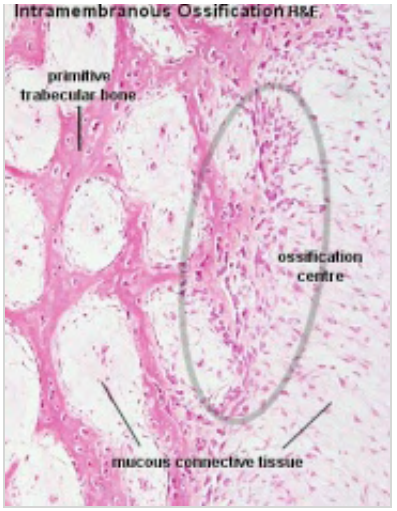


Intramembranous Ossification



- Specialized form of ossification from a mesenchymal membrane.

(skull, clavicle)

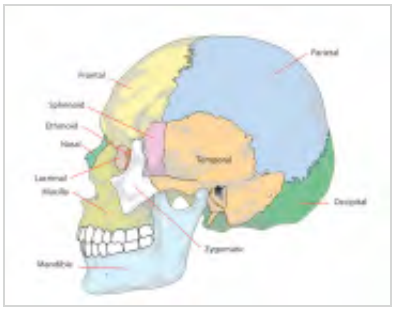


Skull

The Skull is a unique skeletal structure in several ways: embryonic cellular origin (neural crest), form of ossification (intramembranous and endochondrial) and flexibility (fibrous sutures). Musculoskeletal Development - Skull Development (http://embryology.med.unsw.edu.au/Notes/skmus8a.htm)

The bones enclosing the brain have large flexible fibrous joints (sutures) which allow firstly the head to compress and pass through the birth canal and secondly to postnatally expand for brain growth.

These sutures gradually fuse at different times postnatally, firstly the metopic suture in infancy and the others much later. Abnormal fusion (synostosis) of any of the sutures will lead to a number of different skull defects.

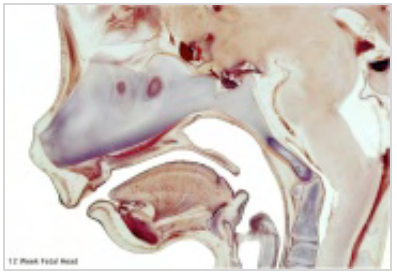


skull bones

Osteogenesis

- Formation of mature osteoblasts - the mesenchymal stem cells initially form preosteoblasts that then differentiate.
- osteogenesis is inhibited by - Wnt signaling pathway antagonists (DKK-1, sclerostin, and SFRP1) and serotonin.

University of Bristol - ossification (http://www.e-radiography.net/articles/ossification/ossification.htm)



12 week fetal head

Cells

- Osteoprogenitor cell - periosteum and endosteum
- Osteoblast - Secrete bone matrix, differentiate into osteocytes
- Osteocyte - Mature bone cell, Embedded in matrix, matrix calcifies soon after deposition

Osteoclastogenesis

- Formation of mature osteoclasts - the osteoblasts regulate this process through the production of RANKL (Receptor Activator for Nuclear Factor ϰ B Ligand) by pre-osteoblast cells.

Osteoclast origin- fusion of monocytes or macrophages, Blood macrophage precursor, Attach to bone matrix

Lysosomes - released into space between ruffled border and bone matrix, enzymes break down collagen fibres, resorption bays or Howship's lacunae

Muscle

Histology - Muscle (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Muscle/Muscle.htm)

Myogenesis

- Smooth muscle - cells originate from undifferentiated mesenchymal cells. These cells differentiate first into mitotically active cells, myoblasts, which contain a few myofilaments. Myoblasts give rise to the cells which will differentiate into mature smooth muscle cells.
- Skeletal muscle - cells originate from the paraxial mesoderm. Myoblasts undergo frequent divisions and coalesce with the formation of a multinucleated, syncytial muscle fibre or myotube. The nuclei of the myotube are still located centrally in the muscle fibre. In the course of the synthesis of the myofilaments/myofibrils, the nuclei are gradually displaced to the periphery of the cell.
- Cardiac muscle - cells originate from the prechordal splanchnic mesoderm.

Skeletal Muscle Stages

Myoblast - individual progenitor cells

Myotube - multinucleated, but undifferentiated contractile apparatus (sarcomere)

Myofibre (myofiber, muscle cell) - multinucleated and differentiated sarcomeres

- primary myofibres - first-formed myofibres, act as a structural framework upon which myoblasts proliferate, fuse in linear sequence
- secondary myofibers - second later population of myofibres that form surrounding the primary fibres.

Muscle Fibre Types

- type IIB, IIA, IIX, and I fibres - based only on the myosin ATPase activity.
  - Type I fibres appear red, due to the presence of myoglobin
  - Type II fibres appear white, due to the absence of myoglobin and their glycolytic nature.
- A group of individual myofibres within a muscle will be innervated by a single motor neuron.
- The electrical properties of the motor neuron will regulate the contractile properties of all associated myofibres.

MH- you do not need to know the table below in detail, it is provided for information purposes only.

Fibre Type	Type I fibres	Type II a fibres	Type II x fibres	Type II b fibres
Contraction time	Slow	Moderately Fast	Fast	Very fast
Size of motor neuron	Small	Medium	Large	Very large
Resistance to fatigue	High	Fairly high	Intermediate	Low
Activity Used for	Aerobic	Long-term anaerobic	Short-term anaerobic	Short-term anaerobic
Maximum duration of use	Hours	<30 minutes	<5 minutes	<1 minute
Power produced	Low	Medium	High	Very high
Mitochondrial density	High	High	Medium	Low
Capillary density	High	Intermediate	Low	Low
Oxidative capacity	High	High	Intermediate	Low
Glycolytic capacity	Low	High	High	High
Major storage fuel	Triglycerides	Creatine phosphate,	Creatine phosphate,	Creatine phosphate,

Major storage fuel	Triglycerides	glycogen	glycogen	glycogen
Myosin heavy chain, human genes	MYH7	MYH2	MYH1	MYH4

Myotome

This term is used to describe the region of the somite that contributes skeletal muscle to the embryo body. Each somite pair level gives rise to a group of skeletal muscles supplied by a specific segmental spinal nerve. The muscle arises from a specific somite and the spinal nerve arises from a specific level of the spinal cord (identified by vertebral column).

In humans this corresponds to the following spinal nerves (from top to bottom) and muscular functions:

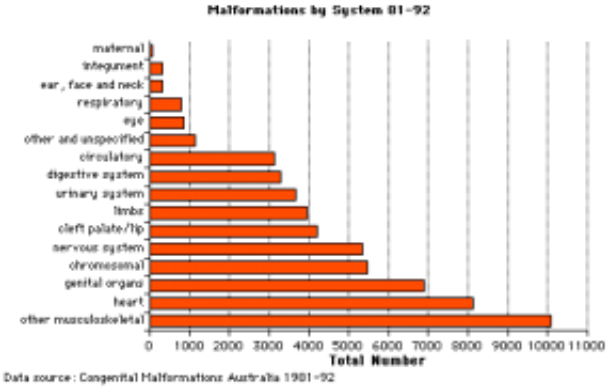
- C3,4 and 5 supply the diaphragm for breathing.
- C5 supply shoulder muscles and muscles to bend our elbow.
- C6 for bending the wrist back.
- C7 for straightening the elbow.
- C8 bends the fingers.
- T1 spreads the fingers.
- T1 –T12 supplies the chest wall and abdominal muscles.
- L2 bends the hip.
- L3 straightens the knee.
- L4 pulls the foot up.
- L5 wiggles the toes.
- S1 pulls the foot down.
- S3,4 and 5 supply the bladder, bowel, sex organs, anal and other pelvic muscles.

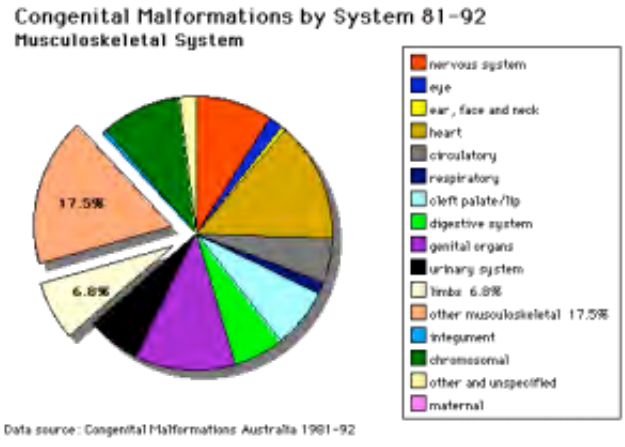
Puberty

- Musculoskeletal mass doubles by the end of puberty
- regulated growth by - sex steroid hormones, growth hormone, insulin-like growth factors
- accumulation of (peak) bone mass during puberty relates to future osteoporosis in old age

Abnormalities

Additional abnormalities will be covered in the limb development lecture. see also Musculoskeletal Abnormalities (http://embryology.med.unsw.edu.au/Notes/skmus2.htm)





Bone

Vertebra

- Spina Bifida - neural tube failure to close, disrupts neural arch formation
- Block vertebra - failure of vertebra separation, lumbar region, chrondrification abnormality
- Klippel-Feil Syndrome - non-segmented cervical vertebra, more female
- see also scoliosis

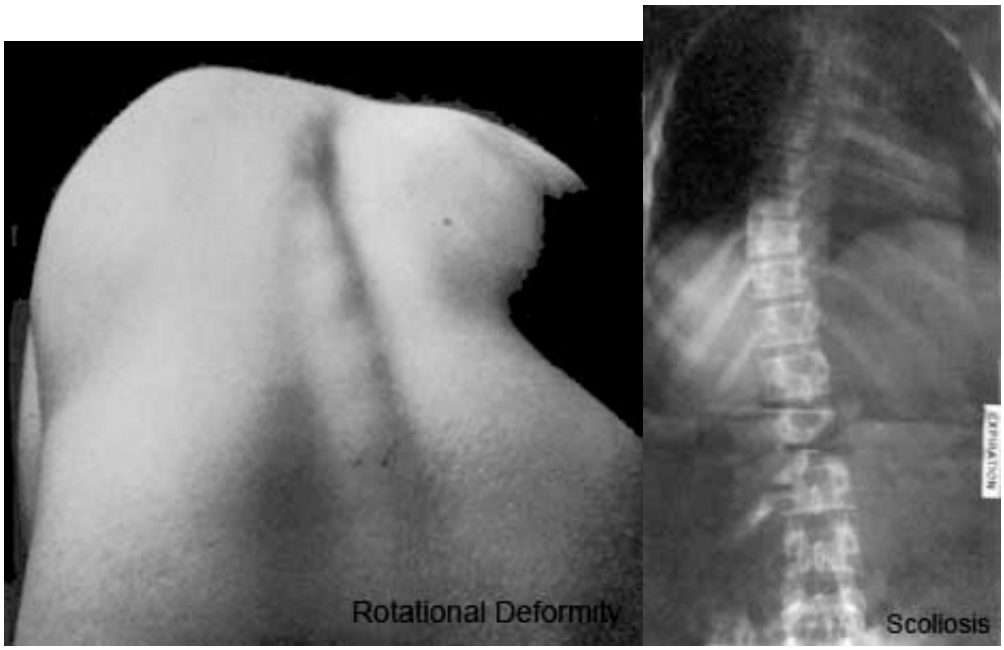
Rib

- Accessory rib (extra rib cervical or lumbar uni- or bilateral), short-rib polydactyly syndrome (lethal, chondroplasia), pigeon chest (rib overgrowth), funnel chest (sternum depression and lower costal cartilages)

Osteogenesis Imperfecta

- brittle-bone syndrome
- abnormal collagen type I, fail to assemble triple helix, degrade imperfect collagen, leads to fragile bones

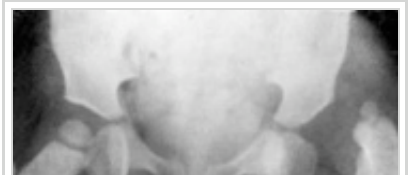
Scoliosis



- assymetric growth impairment of vertebral bodies
- lateral deviation of spine (Lateral flexion, Forward flexion, Rotation of vertebral column on long axis)
- compensated by movement of vertebral column above and below affected region (producing a primary and two secondary curves)
- progresses rapidly in adolescence and becomes fixed once bone growth is completed.

Congenital Hip Dislocation

- Instability: 1:60 at birth; 1:240 at 1 wk: Dislocation untreated; 1:700
- congenital instability of hip, later dislocates by muscle pulls or gravity
- familial predisposition female predominance
- Growth of femoral head, acetabulum and innominate bone are



delayed until the femoral head fits firmly into the acetabulum

Congenital Hip Dislocation

Muscle

MH - Covered in next lecture and lab.

Congenital Myopathies

Muscular Dystrophy

Muscular Dystrophy (http://embryology.med.unsw.edu.au/Notes/skmus2.htm#Muscular%20Dystrophy)

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter Chapter 10 The Pharyngeal Apparatus pp201 - 240.
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 12 Development of the Head, the Neck, the Eyes, and the Ears pp349 - 418.

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Paraxial and intermediate mesoderm (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.chapter.3450) | Myogenesis: The Development of Muscle (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3475) | Osteogenesis: The Development of Bones (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=dbio.section.3479) | Figure 14.10. Conversion of myoblasts into muscles in culture (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.figgrp.3478)

- **Molecular Biology of the Cell** Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 Search Molecular Biology of the Cell (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mboc4.TOC&depth=2) Bone Is Continually Remodeled by the Cells Within It (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.section.4177#4187) Image: Figure 22-52. Deposition of bone matrix by osteoblasts. (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.figgrp.4191) Image: Figure 22-56. The development of a long bone. (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.figgrp.4196)

Search

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UNSW Embryology Links

- **Notes:** Bone Development (http://embryology.med.unsw.edu.au/Notes/skmus9.htm) | Limb Development (http://embryology.med.unsw.edu.au/Notes/skmus7.htm) | Axial Skeleton Development (http://embryology.med.unsw.edu.au/Notes/skmus8.htm) | Bone Development (http://embryology.med.unsw.edu.au/Notes/skmus9.htm) | Skull | Development (http://embryology.med.unsw.edu.au/Notes/skmus8a.htm) Limb (http://embryology.med.unsw.edu.au/Notes/skmus7.htm) | Axial Skeleton (http://embryology.med.unsw.edu.au/Notes/skmus8.htm) | Human Bone (http://embryology.med.unsw.edu.au/Notes/skmus9a.htm) | Endochondral Ossification (http://embryology.med.unsw.edu.au/Notes/skmus9b.htm) | Skeletal Muscle (http://embryology.med.unsw.edu.au/Notes/skmus12.htm) | Cartilage (http://embryology.med.unsw.edu.au/Notes/skmus30.htm) | Joints (http://embryology.med.unsw.edu.au/Notes/skmus31.htm)

- **Lectures:** ANAT2341 - Embryology 2008 - Lecture 16 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture16.htm)
- **Movies:** Mesoderm Movies (http://embryology.med.unsw.edu.au/Movies/mesoderm.htm) | Somite - Myotome body wall (http://embryology.med.unsw.edu.au/Movies/mesoderm/somite2.mov) | Vertebra (http://embryology.med.unsw.edu.au/Movies/mesoderm/vertabra3.mov)

External Links

- **UWA Blue Histology** Skeletal Tissues - Muscle (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Muscle/Muscle.htm) | Skeletal Tissues -Cartilage (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Cartilage/Cartil.htm) | Skeletal Tissues - Bone (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/Bone/Bone.htm)

- **University of Kansas Histoweb** Bone (http://www.kumc.edu/instruction/medicine/anatomy/histoweb/bone/bone.htm)

- **Loyola University Medical Education Network** Part 9: Specialized Connective Tissue: Cartilage and Bone (http://www.lumen.luc.edu/lumen/MedEd/Histo/frames/h_frame9.html) | Part 10: Endochondral Ossification (http://www.lumen.luc.edu/lumen/MedEd/Histo/frames/h_frame10.html)

- **UNSW Embryology** Cartilage and Bone (http://embryology.med.unsw.edu.au/histology/cartilagebone/cartbone1.html)

- **University of Bristol** ossification (http://www.e-radiography.net/articles/ossification/ossification.htm)

Terms

annulus fibrosus - the circularly arranged fibers (derived from sclerotome)that together with the nucleus pulposus (derived from notochord) form the intervertebral disc (IVD) of the vertebral column.

axial mesoderm - (=notochord)

cartilage - connective tissue from mesoderm in the embryo forms the initial skeleton which is replaced by bone. In adult, found on surface of bone joints.

Cbfa1 - Core-Binding Factor 1 (Runx2) transcription factor protein key to the differentiation of bone
OMIM: Cbfa1 (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600211)

centrum - the primordium of the vertebral body formed initially by the sclerotome.

clavicle - (Latin, *clavicle* = little key) bone which locks shoulder to body.

dermatome -

dermomyotome - dorsolateral half of each somite that forms the dermis and muscle.

ectoderm - the layer (of the 3 germ cell layers) which form the nervous system from the neural tube and neural crest and also generates the epithelia covering the embryo.

endochondrial ossification - the process of replacement of the cartilagenous framework by osteoblasts with bone.

epaxial myotome - the dorsal portion of the myotome that generates dorsal skeletal muscles (epaxial muscles), which include other muscles associated with the vertebrae, ribs, and base of the skull.

extracellular matrix - material secreted by and surrounding cells. Consists if fibers and ground substance.

fibroblast growth factors - (FGF) a family of at least 10 secreted proteins that bind membrane tyrosine kinase receptors. A patterning switch with many different roles in different tissues. (FGF8 = androgen-induced growth factor (AIGF)

fibroblast growth factor receptor - receptors comprise a family of at least 4 related but individually distinct tyrosine kinase receptors (FGFR1- 4). They have a similar protein structure, with 3 immunoglobulin-like domains in the extracellular region, a single membrane spanning segment, and a cytoplasmic tyrosine kinase domain.

growth factor - usually a protein or peptide that will bind a cell membrane receptor and then activates an intracellular signaling pathway. The function of the pathway will be to alter the cell directly or indirectly by changing gene expression. (eg shh)

hox - (=**h**omeob**ox**) family of transcription factors that bind DNA and activate gene expression. Expression of different Hox genes along neural tube defines rostral-caudal axis and segmental levels.

hypaxial myotome - the ventral portion of the myotome that generates ventral skeletal muscles (hypaxial muscles) which include some vertebral muscles, the diaphragm, the abdominal muscles, and all limb muscles.

intercostal- the region between adjacent ribs, usually comprising intercostal muscles and connective tissue.

intervertebral disc- (IVD) the annulus fibrosus+nucleus pulposus together form the intervertebral disc (IVD) of the vertebral column. This is the flexible region between each bony vertebra that allows the column to be bent.

lumbar plexus - mixed spinal nerves innervating the lower limb form a complex meshwork (crossing).

mesenchymal progenitor cells - (MPCs) cells able to differentiate in various types of connective tissue, including cartilage, bone and adipose tissue.

mesoderm - the middle layer of the 3 germ cell layers of the embryo. Mesoderm outside the embryo and covering the amnion, yolk and chorion sacs is extraembryonic mesoderm.

myoblast - the undifferentiated mononucleated muscle cells that will fuse together to form a multinucleated myotube, then mature into a muscle fibre.

MyoD - transcription factor involved in the determination of muscle cells in the somite. A basic helix-loop-helix factor which binds DNA.

myotome - the portion of the dermamyotome that generates skeletal muscle. Has 2 components epaxial (dorsal muscles) hypaxial (ventral muscles).

neural crest - cell region at edge of neural plate, then atop the neural folds, that remains outside and initially dorsal to the neural tube when it forms. These paired dorsal lateral streaks of cells migrate throughout the embryo and can differentiate into many different cell types(=pluripotential). Those that remain on the dorsal neural tube form the sensory spinal ganglia (DRG). Neural crest cells migrate into the somites.

osteoblast - The mesenchymal cells that differentiate to form the cellular component of bone and produce bone matrix. Mature osteoblasts are called osteocytes. (More? Musculoskeletal Development - Bone (http://embryology.med.unsw.edu.au/Notes/skmus9.htm))

osteoclast - Cells that remove bone (bone resorption) by enzymatically eroding the bone matrix. These cells are monocyte-macrophage in origin and fuse to form a multinucleated osteoclast. These cells allow continuous bone remodelling and are also involved in calcium and phosphate metabolism. The erosion cavity that the cells lie iwithin and form is called Howship's lacuna. (More? Musculoskeletal Development - Bone (http://embryology.med.unsw.edu.au/Notes/skmus9.htm))

osteocyte - The mature bone-forming cell, which form the cellular component of bone and produce bone matrix. Differentiate from osteoblasts, mesenchymal cells that differentiate to form bone. (More? Musculoskeletal Development - Bone (http://embryology.med.unsw.edu.au/Notes/skmus9.htm))

osteon - The anatomical (histological) unit structure (principal structure) of compact bone. (More? Musculoskeletal Development - Bone (http://embryology.med.unsw.edu.au/Notes/skmus9.htm))

Pax - name derived from Drosophila gene 'paired' (prd) the 'paired box' is a amino end 124 amino-acid conserved domain (signature aa 35-51: **P-C-x(11)-C-V-S**). Transcription factor of the helix-turn-helix structural family, DNA binding, and activating gene expression. In human, nine member proteins from Pax-1 to Pax-9. Regulate differentiation of many different tissues. Some members of the family (PAX3, PAX4, PAX6, PAX7) also contain a functional homeobox domain.

pedicle - (Latin, *pediculus* = small foot) part of the vertebral arch forming the segment between the transverse process and the vertebral body.

primary centre of ossification - the first area where bone growth occurs between the periosteum and cartilage.

sclerotome - ventromedial half of each somite that forms the vertebral body and intervertebral disc.

segmentation - to break a solid structure into a number of usually equal size pieces.

somatic mesoderm - derived from lateral mesoderm closest to the ectoderm and separated from other component of lateral mesoderm (splanchnic, near endoderm) by the intraembryonic coelom.

somite - segmental block (ball) of mesoderm formed from paraxial mesoderm adjacent to notochord (axial mesoderm). Differentiates to form initially sclerotome and dermamyotome (then dermotome and myotome).

somitic mesoderm-

somitocoel - a transient cavity that appears within each of the the early forming somites then is lost.

somitogenesis - the process of segmentation of the paraxial mesoderm to form "mesoderm balls" beginning cranially (humans day20) and extending caudally at 1 somite/90 minutes until approx. 44 pairs have been formed.

sonic hedgehog - (=shh) secreted growth factor that binds patched (ptc) receptor on cell membrane. SHH function is different for different tissues in the embryo. In the nervous system, it is secreted by the notochord, ventralizes the neural tube, inducing the floor plate and motor neurons. In the Limb it is secreted by the zone of polarizing activity (ZPA) organizing limb axis formation.

Tbx - T-box genes (transcription factor) involved in mouse forelimb (Tbx4) and hindlimb (Tbx5) specification.

transcription factor- a factor (protein or protein with steroid) that binds to DNA to alter gene expression, usually to activate. (eg steroid hormone+receptor, Retinoic acid+Receptor, Hox, Pax, Lim, Nkx-2.2).

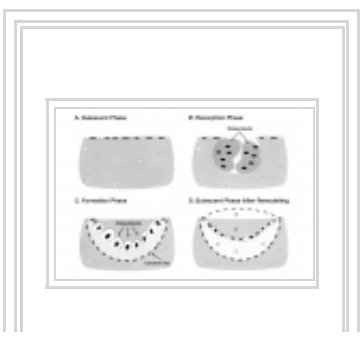
vertebral body- formed by centrum, vertebral arch, facets for ribs. It is the mature vertebral structure formed by the 5 secondary ossification centers after puberty.

vertebral column - name given to the complete structure formed from the alternating segments of vertebra and intervertebral discs which support the spinal cord.

vertebral foramen - the dorsal cavity within each vertebra, generated by the vertebral arch that surrounds the spinal cord.

Wnt7a - The designation 'Wnt' was derived from 'wingless' and 'int'. The Wnt gene was first defined as a protooncogene, int1. Humans have at least 4 Wnt genes: Wnt7a gene is at 3p25 encoding a 349aa secreted glycoprotein. A patterning switch with different roles in different tissues. The mechanism of Wnt distribution (free diffusion, restricted diffusion and active transport) and all its possible cell receptors are still being determined. At least one WNT receptor is Frizzled (FZD). The Frizzled gene family encodes a seven-transmembrane receptor.

Images

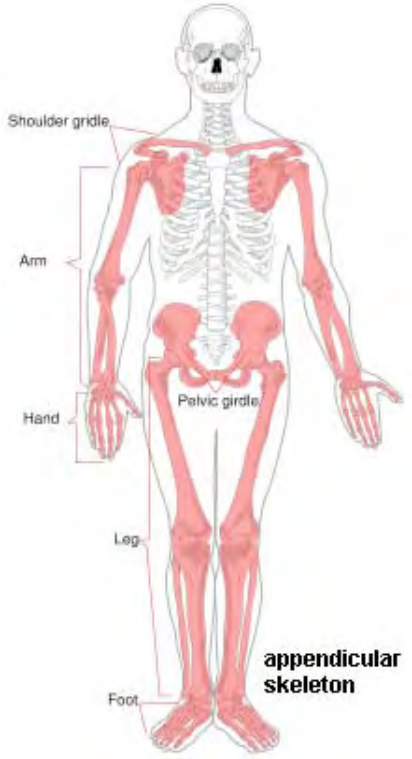


2009 Lecture 14

From Embryology

Contents

Limb Development



Introduction

This lecture is an introduction to the events in limb development. Initially somites develop and then begin to differentiate forming sclerotome, dermomyotome and then dermatome and myotome. The lateral portion of the hypaxial myotome edge migrates at level of limbs (upper limb first then lower) and mixes with somatic mesoderm. Meanwhile the dermotome continues to contribute cells to myotome.

The appendicular skeleton consists of: Shoulder girdle, Upper limb (arm, hand), Pelvic girdle, Lower limb (leg, foot).

UNSW Embryology Limb Development (http://embryology.med.unsw.edu.au/Notes/skmus7.htm) | Limb Abnormalities (http://embryology.med.unsw.edu.au/Notes/skmus72.htm) **2008 Lecture** 2008 Lecture

(http://embryology.med.unsw.edu.au/Science/ANAT2341lecture14.htm) | 1 slide/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L14Limbs1.pdf) | 4 slide/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L14Limbs4.pdf) | 6 slide/page (http://embryology.med.unsw.edu.au/pdf/ANAT2341L14Limbs6.pdf)

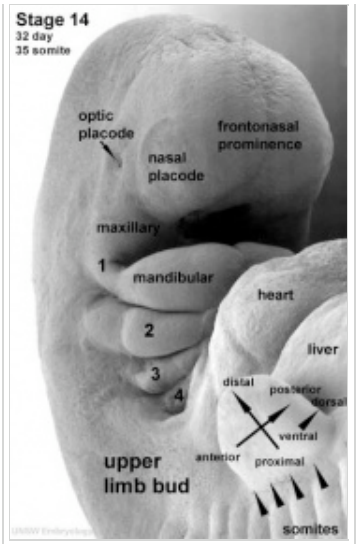
Carnegie stage 1-23

> **Lectopia Audio** Lecture Date: 15-09-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Limb (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48841)

Lecture Objectives

- Understanding of limb positioning

- Understanding of limb positioning
- Understanding of differences in developmental timing of upper and lower limbs
- Understanding of regions and factors determining limb axes
- Understanding of limb rotation
- Understanding of limb muscle, blood vessel, bone and nerve formation
- Brief understanding of limb molecular factors and cell death
- Brief understanding of limb abnormalities



Human Embryo stage 14 SEM

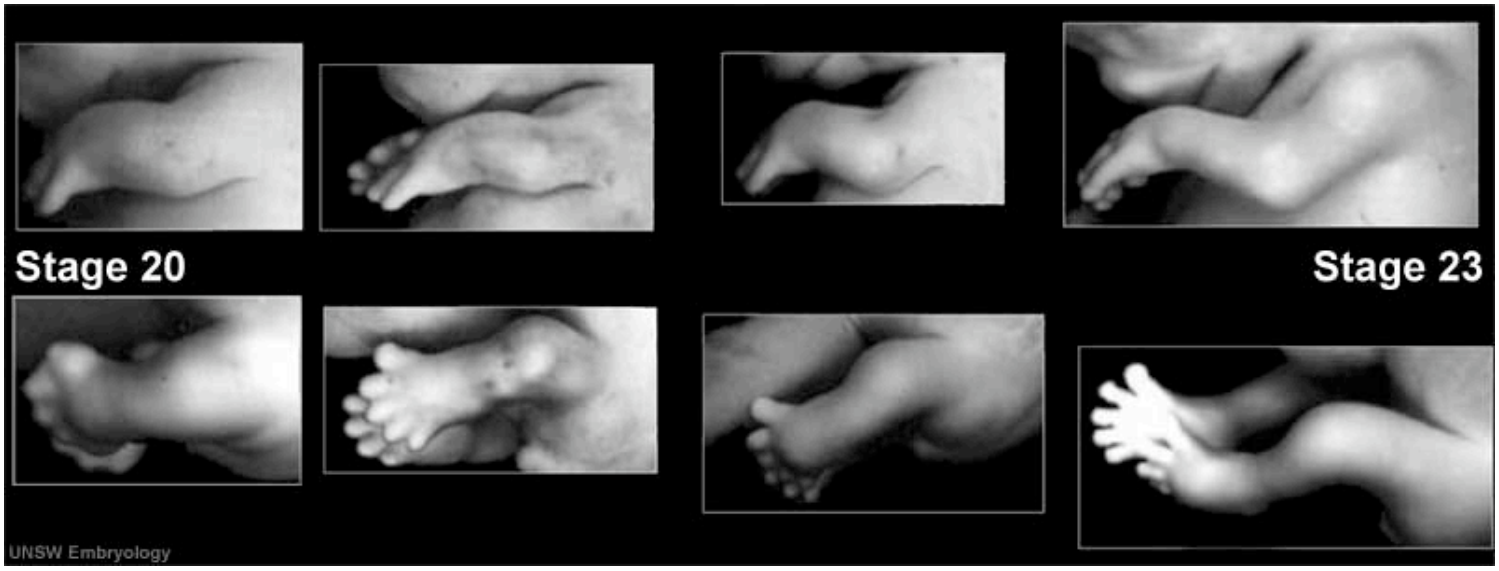
Textbook References

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter 15 the skeletal system
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 11 Limb Development
- Before we Are Born (5th ed.) Moore and Persaud Ch16,17: p379-397, 399-405
- Essentials of Human Embryology Larson Ch11 p207-228

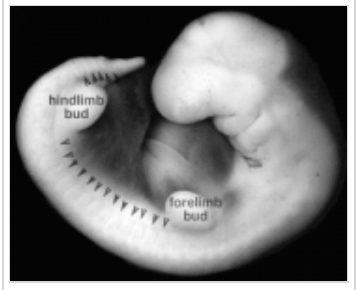
Limb Buds

- Limbs are initially undifferentiated mesenchyme (mesoderm) with an epithelial (ectoderm) covering.
- Blood vessels then begin forming, the largest (marginal vein) is adjacent to tip of the limbbud.

Upper and Lower Limb



Limb development occurs at different times for forelimbs and hindlimbs. In the mid-4th week, human upper limb buds first form and lower limbs about 2 days later. The limbs form at vertebra segmental levels C5-C8 (upper limbs) L3-L5 (lower limbs).



Limb Axis Formation

Four Concepts - much of the work has been carried out using the chicken and more recently the mouse model of development.

1. Limb Initiation
2. Proximodistal Axis
3. Dorsoventral Axis
4. Anteroposterior Axis

Limb Initiation

- Fibroblast growth factor (FGF) coated beads can induce additional limb
- FGF10 , FGF8 (lateral plate intermediate mesoderm) prior to bud formation
- FGF8 (limb ectoderm) FGFR2
- FGF can respecify Hox gene expression (Hox9- limb position)
- Hox could then activate FGF expression

Note that during the embryonic period there is a rostrocaudal (anterior posterior) timing difference between the upper and lower limb development

- this means that developmental changes in the upper limb can precede similar changes in the lower limb (2-5 day difference in timing)

Limb Identity

Forelimb and hindlimb (mouse) identity appears to be regulated by T-box (Tbx) genes, which are a family of transcription factors.

- hindlimb Tbx4 is expressed.
- forelimb Tbx5 is expressed.
- Tbx2 and Tbx3 are expressed in both limbs.

Related Research - PMID: 12490567 (http://www.ncbi.nlm.nih.gov/pubmed/12490567?dopt=Abstract) | Development 2003 Figures (http://dev.biologists.org/cgi/content/figsonly/130/3/623) | Scanning electron micrographs of E9 Limb bud wild-type and Tbx5del/del (http://dev.biologists.org/cgi/content/full/130/3/623/FIG1) A model for early stages of limb bud growth (http://dev.biologists.org/cgi/content/full/130/3/623/FIG7) | PMID: 12736217 (http://www.ncbi.nlm.nih.gov/pubmed/12736217?dopt=Abstract) | Development 2003 Figures (http://dev.biologists.org/cgi/content/figsonly/130/12/2741)

Body Axes

- **Anteroposterior** - (Rostrocaudal, Craniocaudal, Cephalocaudal) from the head end to opposite end of body or tail.
- **Dorsoventral** - from the spinal column (back) to belly (front).
- **Proximodistal** - from the tip of an appendage (distal) to where it joins the body (proximal).

Proximodistal Axis

- Apical Ectodermal Ridge (AER) formed by Wnt7a
- then AER secretes FGF2, 4, 8
- stimulates proliferation and outgrowth

apical ectodermal ridge (http://www.med.unc.edu/embryo_images/unit-mslimb/mslimb_htms/mslimb017.htm) | AER and vascular channel (http://www.med.unc.edu/embryo_images/unit-mslimb/mslimb_htms/mslimb018b.htm)

Dorsoventral Axis

- Somites - provides dorsal signal to mesenchyme which dorsalizes ectoderm
- Ectoderm - then in turn signals back (Wnt7a) to mesenchyme to pattern limb

Wnt7a

- name was derived from 'wingless' and 'int'

- Wnt gene first defined as a protooncogene, int1
- Humans have at least 4 Wnt genes
- Wnt7a gene is at 3p25 encoding a 349aa secreted glycoprotein
- patterning switch with different roles in different tissues
- mechanism of Wnt and receptor distribution still being determined (free diffusion, restricted diffusion and active transport)

One WNT receptor is Frizzled (FZD)

- Frizzled gene family encodes a 7 transmembrane receptor

Fibroblast growth factors (FGF)

- Family of at least 17 secreted proteins
- bind membrane tyrosine kinase receptors
- Patterning switch with many different roles in different tissues
- FGF8 = androgen-induced growth factor, AIGF

FGF receptors

- comprise a family of at least 4 related but individually distinct tyrosine kinase receptors (FGFR1- 4) similar protein structure
    - 3 immunoglobulin-like domains in extracellular region
    - single membrane spanning segment
    - cytoplasmic tyrosine kinase domain

Anteroposterior Axis

- Zone of polarizing activity (ZPA)
- a mesenchymal posterior region of limb
- secretes sonic hedgehog (SHH)
- apical ectodermal ridge (AER), which has a role in patterning the structures that form within the limb
- majority of cell division (mitosis) occurs just deep to AER in a region known as the progress zone
- A second region at the base of the limbbud beside the body, the zone of polarizing activity (ZPA) has a similar patterning role to the AER, but in determining another axis of the limb

Wing as Limb Model

- chicken wing easy to manipulate
    - removal, addition and rotation of limb regions
    - grafting additional AER, ZPA
    - implanting growth factor secreting structures

UNSW Embryology - Axes Formation - Limb (http://embryology.med.unsw.edu.au/MolDev/axes6.htm) | Signal Factors - Wnt (http://embryology.med.unsw.edu.au/MolDev/factor/wnt7a.htm)

Limb Muscle Mass

(a) Skeletal muscle derived from somites, blocks of mesodermal cells (b) Myoblasts form at each edge of a dermomyotome. Axial myoblasts form the myotome Lateral myoblasts migrate to the limb bud (c) Dermotome skin elements (dermis, hypodermis). Myotome to axial muscle.

Origin of limb muscle cells - Migrations traced by grafting cells from a quail embryo into a chick embryo

- two species very similar in development
- quail cells recognizable by distinctive nucleoli
- Quail somite cells substituted for somite cells of 2 day chick embryo
- wing of chick sectioned a week later
- found muscle cells in chick wing derive from transplanted quail somites

Dorsal/Ventral Muscle Mass

Forelimb Muscles

Limb Muscle - Differentiation, Skeletal muscle differentiates the same

1. Muscle precursor cells migrate to the muscle location
2. Form beds of proliferating myoblasts
3. Myoblasts fuse together to form myotubes
4. Myotubes begin to express contractile proteins, form sarcomeres
5. mature into myofibers, Innervation determines final muscle maturation

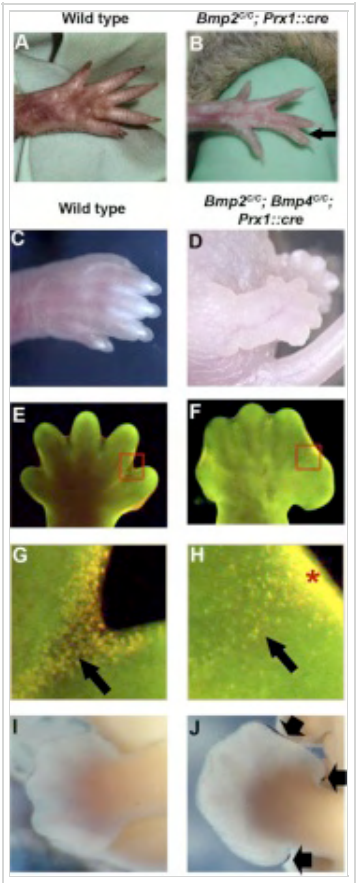
Dermomyotome MyoD

Limb Tissues- Bones (Bone development covered in detail in previous lecture)

- cartilage template, endochondrial ossification
- begins Carnegie stage 18 throughout embryo
- process replaces cartilage with bone (week 5-12), except at future joint sites

Hand and Footplates

- 5th week- hand and footplates appear at the ends of limb buds and ridges form digital rays
- Cells between the digital rays are removed by programmed cell death (apoptosis)
- 3-5 day difference between hand and foot development



Depletion of BMP Signaling Causes Interdigital Syndactyly

hand growth (http://www.med.unc.edu/embryo_images/unit-mslimb/mslimb_htms/mslimb024.htm)

Apoptosis

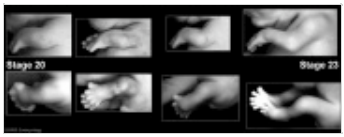
Cell Biology - Cell Death Lecture (http://php.med.unsw.edu.au/cellbiology/index.php?title=2009_Lecture_18) | Cell Biology - Apoptosis Lecture (http://php.med.unsw.edu.au/cellbiology/index.php?title=2009_Lecture_18)

Limb Rotation

- 8th week limbs rotate in different directions (Humans Stage 20-23)
- thumb and toe rostral
- knee and elbow face outward
- **upper limb rotates dorsally**
- **lower limb rotates ventrally**

Limb Innervation

- spinal cord segmental nerves form a plexus adjacent to each limb
- Brachial (upper) lumbar (lower)
- Plexus forms as nerves invade the limb bud mesechyme
- Fetal period - touch pads become visible on hands and feet



brachial plexus origin (http://www.med.unc.edu/embryo_images/unit-mslimb/mslimb_htms/mslimb019.htm)

Limb Abnormalities

Genetic

- Human Gene Mutations - mutation of any of the patterning genes will result in limb abnormalities (Will put Table on Web page mutations and terminology)

Type II syndactyly- HoxD13

brachial plexus

Maternal

- thalidomide Phocomelia
- short ill-formed upper or lower limbs
- hyperthermia

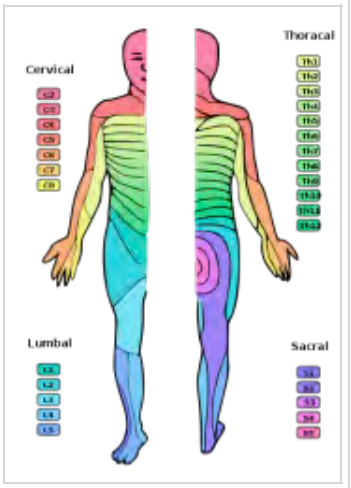
Muscle Development

Duchenne Muscular Dystrophy

- X-linked dystrophy
- large gene encoding cytoskeletal protein- Dystrophin
- progressive wasting of muscle, die late teens

Becker Muscular Dystrophy

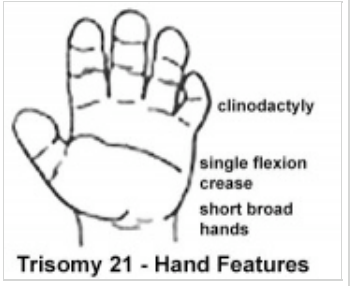
- milder form, adult onset



Adult Dermatomes

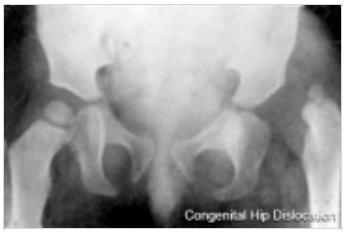
Congenital Hip Dislocation

- Instability: 1:60 at birth; 1:240 at 1 wk: Dislocation untreated; 1:700
- congenital instability of hip, later dislocates by muscle pulls or gravity
- familial predisposition female predominance
- Growth of femoral head, acetabulum and innominate bone are delayed until the femoral head fits firmly into the acetabulum



Online Links

- UNSW Embryology Limb Development (http://embryology.med.unsw.edu.au/Notes/skmus7.htm)
- Embryo Images Limb Unit (http://www.med.unc.edu/embryo_images/unit-mslimb/mslimb_htms/mslimbtoc.htm)
- International J. Dev. Biology Vol 46 Special Issue- Limb Development 2002 (http://www.ijdb.ehu.es/0207contents.htm)
- Research Labs - Rolf Zeller University of Basel Medical School (http://pages.unibas.ch/anatomie/zeller/seiten/seite1.html)



Congenital Hip Dislocation

References

Textbooks

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West -

Online Textbooks

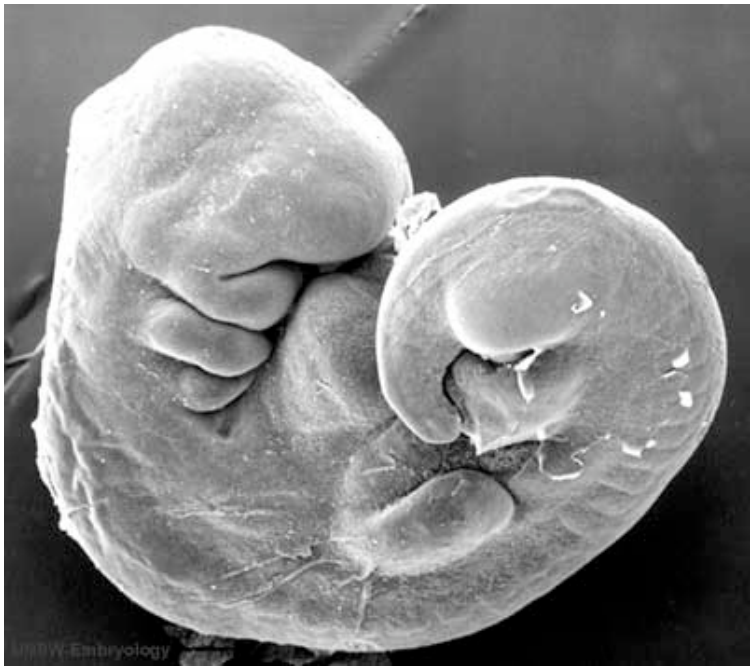
- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000 Formation of the Limb Bud (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3928) | Generating the Proximal-Distal Axis of the Limb (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?&rid=dbio.section.3941)
- **Molecular Biology of the Cell** Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter New York and London: Garland Science; c2002 Figure 21-13. Sonic hedgehog as a morphogen in chick limb development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=limb_development&rid=mboc4.figgrp.3815)
- **Madame Curie Bioscience Database** Chapters taken from the Madame Curie Bioscience Database (formerly, Eurekah Bioscience Database)

Search

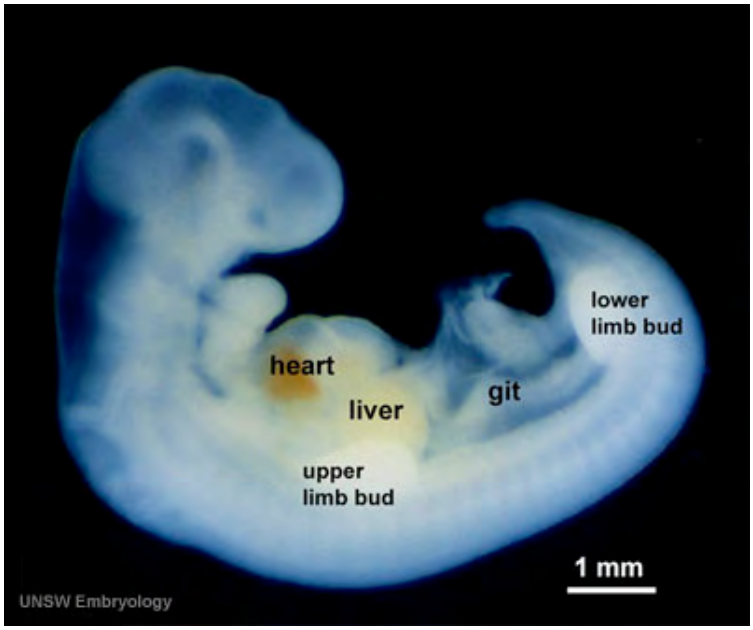
- **Bookshelf** limb development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=limb_development)
- **Pubmed** limb development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=limb_development)

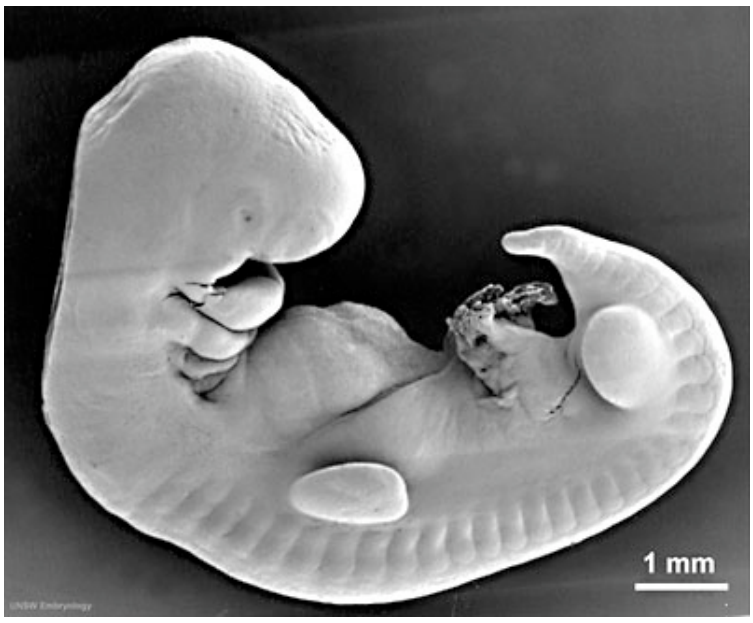
Images

Stage13



Stage14


lower
limb bud
heart
liver
git
upper
limb bud
1 mm
UNSW Embryology


1 mm

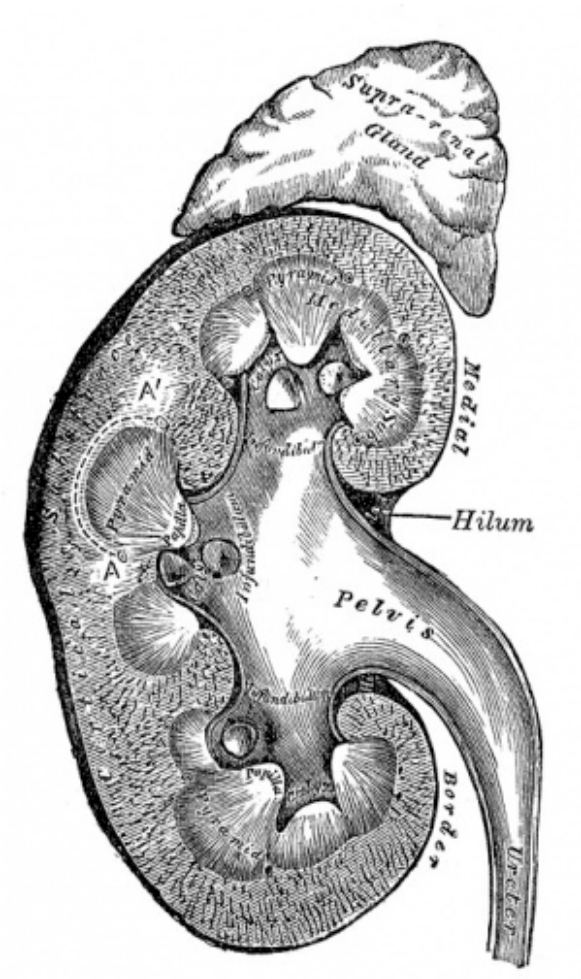
2009 Lecture 15

From Embryology

Contents

Kidney Development

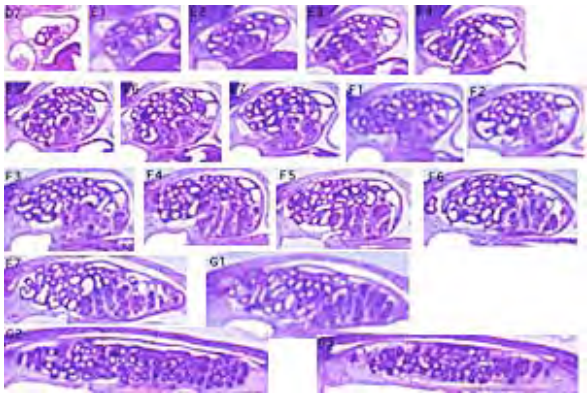
Introduction



The paired adult kidneys filter blood, excrete waste, reabsorb water and have endocrine functions. In the embryo, there are several stages in their development closely linked to genital development. The nephron, the functional unit of the kidney, is also a classical epithelial/mesenchyme type of interaction.

The urinary system is developmentally and anatomically associated with genital development, often described as the urogenital system. Tomorrow's lecture will describe the associated genital development.

Lecture Objectives



Understand the 3 main stages of kidney development. Understand development of the nephron and renal papilla.

- Brief understanding of the mechanisms of nephron development.
- Understand the development of the cloaca, ureter and bladder.
- Brief understanding of abnormalities of the urinary system.

Textbook References

- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter 13 p303-346
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 10 p261-306

Lectopia Audio Lecture Date: 21-09-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Renal (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48830)

2008 Lecture: Lecture 11 (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture11.htm) | 1 slide/page viewing 48 pages (http://embryology.med.unsw.edu.au/pdf/ANAT2341L11Kidneys1.pdf) | 4 slide/page printing 12 pages (http://embryology.med.unsw.edu.au/pdf/ANAT2341L11Kidneys4.pdf) | 6 slide/page printing 8 pages (http://embryology.med.unsw.edu.au/pdf/ANAT2341L11Kidneys6.pdf)

Background

- Mesoderm then intermediate mesoderm
- Vascular Development
- Gastrointestional
- Cloacal development
- Endocrine - covered in future lecture/lab

Kidney Anatomy

- Nephron - Functional unit of kidney
- Humans up to 1 million
- Filtration of waste from blood
- Endocrine
- Blood pressure regulation

Ureter

- Bladder - Urine storage
- Endoderm allantois

Mesoderm

- Intermediate mesoderm - Lies between somites and lateral plate Intermediate mesoderm (http://www.med.unc.edu/embryo_images/unit-genital/genital_htms/genital001.htm)

Cervical Nephrotomes, Mesonephros and Metanephros Movie (http://embryology.med.unsw.edu.au/Movies/larsen/10-2.mov)

Intermediate Mesoderm

- development occurs laterally symmetrical (left right)
- intermediate mesoderm lying beside the **dorsal aorta**
- initially form **mesonephric tubules** (epithelial)
- these tubules connect to a common duct, **mesonephric duct**
- the mesonephric duct then extends within the mesoderm, rostro-caudally
- eventually making contact with the **cloaca**

Mesonephric Duct

Later in development, both the mesonephric duct and the cloaca both continue to differentiate and undergo extensive remodelling (and renaming)

Uteric Bud

- arise near the cloacal connection of the mesonephric duct

- branch from the mesonephric duct laterally into the intermediate mesoderm
- induce the surrounding mesoderm to differentiate - metanephric blastema
    - this mesoderm will in turn signal back to differentiate the uteric bud

Epithelial - mesenchymal interaction

Uteric Bud forms - ureter, pelvis, calyces, collecting ducts

Metanephric Blastema

- forms glomeruli, capsule, nephron tubules
- this development continues through fetal period

Nephros Development

- 3 pairs during development

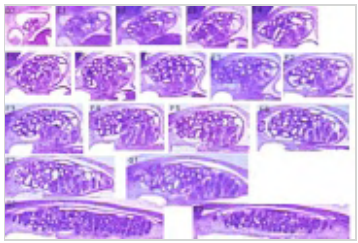
1. pronephros
2. mesonephros
3. metanephros

Pronephros

- week 4 few cells in cervical region fish
- Human E18, Mouse E7.5pronephric duct forms first with associated nephrogenic mesenchyme
- grows rostro caudally cervical -> cloaca
- E22 nephrogenic mesenchyme differentiates to form pronephroi not functional in mammals degenerates rapidly

Mesonephros

- Human E24, Mouse E9.5 caudal to pronephros
- forms by induction from pronephros
- pronephric duct now becomes mesonephric duct (also called Wolffian Duct)



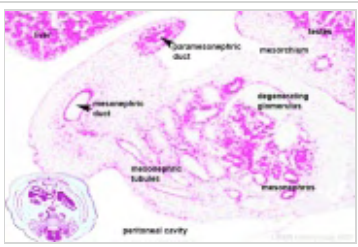
Stage 13 mesonephros

Metanephros

- Human E35-37, Mouse E11 epithelia bud at end of mesonephric duct uteric bud and associated metanephric mesenchyme

metanephric kidney (http://www.med.unc.edu/embryo_images/unit-genital/genital_htms/genital017.htm)

Stage 13 3D movie (http://embryology.med.unsw.edu.au/Movies/GIT3dmodel.htm) | Stage 22 3D movie (http://embryology.med.unsw.edu.au/Movies/UG3dmodelst22.htm)



Stage 22 mesonephros

Uteric Bud

- induced by metanephric mesenchyme to differentiate
- forms collecting tubules, renal pelvis, ureter
- metanephric mesenchyme induced by uteric to differentiate forms nephron

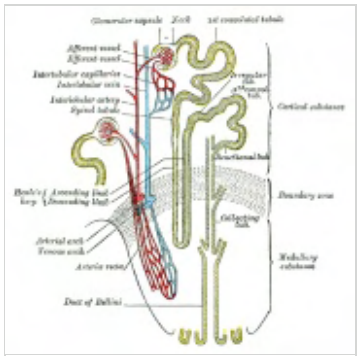
Nephron

Development has four developmental stages:

1. vesicle (V) stage (13-19 weeks)
2. S-shaped body (S) stage (20-24 weeks)
3. capillary loop (C) stage (25-29 weeks)
4. maturation (M) stage (infants aged 1-6 months)

Media:Nephron development.mov

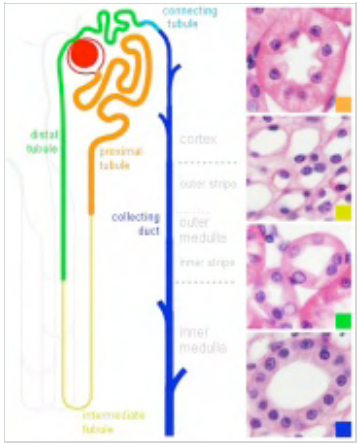
- mean glomerular number shown to level at 36 weeks, increasing from about 15,000 at 15 weeks to 740,000 at 40 weeks.



Adult nephron structure

Nephron Development

- disorganised mesenchymal cells become a highly organised epithelial tubule
- Condensation - groups of about 100 cells condense tightly together to form a distinct mass
- Epithelialisation - condensed cells lose their mesenchymal character and gain epithelial
- At end of this period formed a small epithelial cyst complete with a basement membrane, cell-cell junctions and a defined cellular apico-basal polarity.



Nephron histology

Early morphogenesis

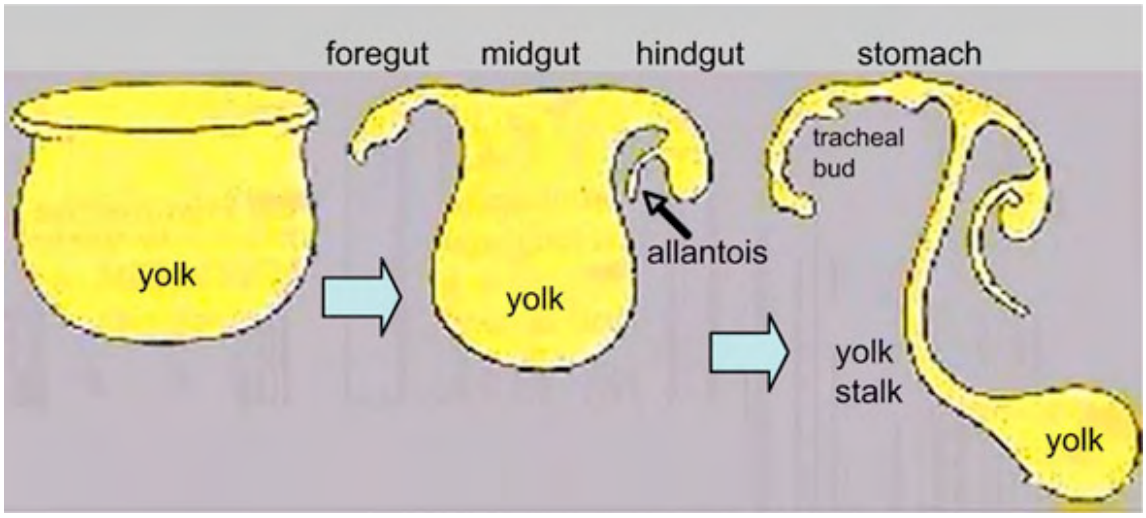
- cyst invaginates twice to form a comma
- then a S-shaped body one invagination site later becomes the glomerular cleft
- At about this time blood vessel progenitors invade cleft to begin construction of vascular component of glomerulus
- Tubule maturation specialised transporting segments of nephron differentiate complex of convoluted tubules is created

Endocrine Kidney

Covered also in Endocrine Development lecture

- Renin - Increase Angiotensin-aldosterone system
- Prostaglandins - decrease Na+ reabsorption
- Erythropoietin - Increase Erythrocyte (rbc) production
- 1,25 (OH)2 vitamin D - Calcium homeostasis
- Prekallikreins - (plasma protein inactive precursor of kallikrein) Increase kinin production (altered vascular permeability)

Cloaca



- hindgut region ending at the cloacal membrane
- divided (ventro-dorsally) by the urogenital septum
  - ventral - common urogenital sinus
  - dorsal - rectum

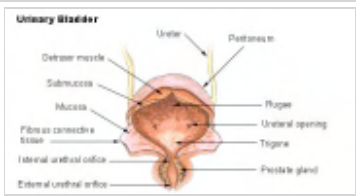
Cloacal septation animation (http://embryology.med.unsw.edu.au/movies/git/cloacal_septum.mov)

Common urogenital sinus

- superior end continuous with **allantois**
- common urogenital sinus and mesonephric duct fuse (connect)
- differentiates to form the bladder
- inferior end forms **urethra**
  - this will be different in male and female development

Urinary Bladder

- early origins of the bladder at the superior end of the common urogenital sinus
- 8 open inferiorly to the cloaca and superiorly to the allantois
- Septation of the claoca - divides the anterior region to the primordial bladder component from the posterior rectal component.
- associated ureters and urethra



Adult bladder

Dorsal view of developing bladder

Trigone formation animation | small animation (http://embryology.med.unsw.edu.au/Movies/larsen/trigone.mov)

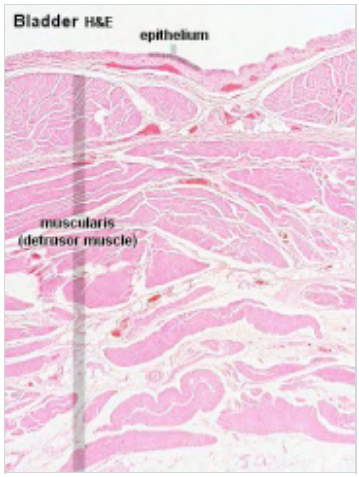
- Ultrasound measurement of the bladder size can be used as a diagnostic tool for developmental abnormalities.

Bladder Structure

Can be described anatomically by its 4 layers from outside inward:

Can be described anatomically by its 4 layers from outside inward:

- Serous - the superior or abdominal surfaces and the lateral" surfaces of the bladder are covered by visceral peritoneum, the serous membrane (serosa) of the abdominal cavity, consisting of mesthelium and elastic fibrous connective tissue.
- Muscular - the detrusor muscle is the muscle of the urinary bladder wall.
- Submucosa - connects the muscular layer with the mucous layer.
- Mucosa - (mucus layer) a transitional epithelium layer formed into folds (rugae).



Bladder histology

Detrusor Muscle

- The adult detrusor muscle consists of three layers of smooth (involuntary) muscle fibres.
  - external layer - fibres arranged longitudinally
  - middle layer - fibres arranged circularly
  - internal layer - fibres arranged longitudinally

Ureter Development

- The adult ureter is a thick-walled muscular tube, 25 - 30 cm in length, running from the kidney to the urinary bladder.
- Anatomically can be described in two parts the abdominal part (pars abdominalis) and pelvic part (pars pelvina).
- The ureter is composed of three layers: outer fibrous layer (tunica adventitia), muscular layer (tunica muscularis) and mucous layer (tunica mucosa).
- The muscular layer can also be subdivided into 3 fibre layers: an external longitudinal, a middle circular, and an internal longitudinal.

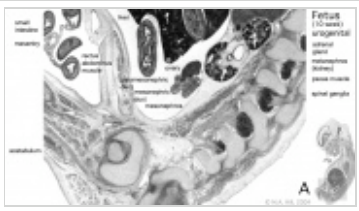
Trigone Development

Media:Trigone_3.mov

Kidney Ascent

- Pro-, Meso-, Meta- Early development descending
- Metanephros - initially pelvic, beside aorta
- Growth and straightening of body - Kidneys in abdomen and displace laterally

Media:Kidney_ascent_3.mov



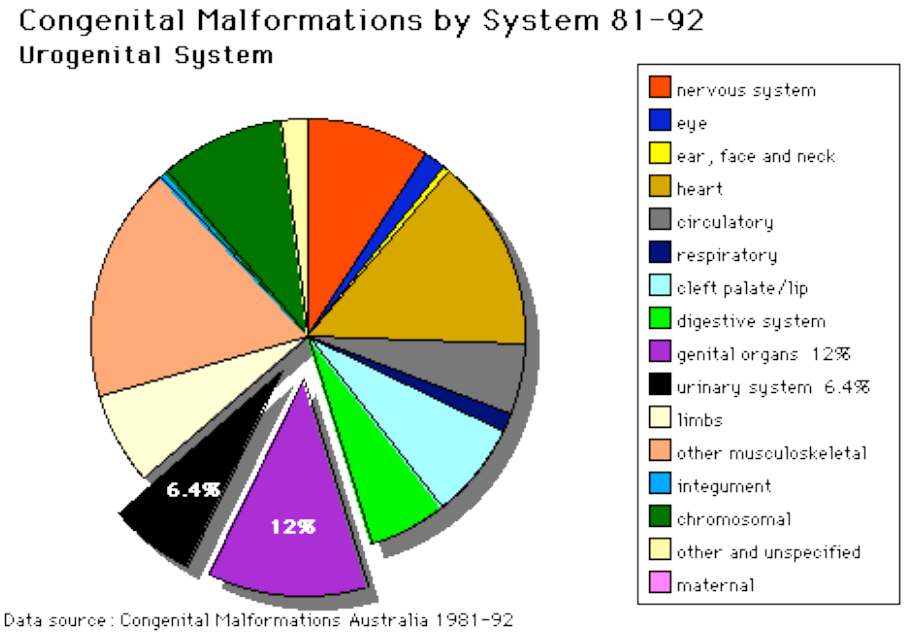
early fetal kidney

Renal Arteries

- Arise with ascent and inferior branches lost
- Sequential, 25% population have 2 or more renal arteries
- branch of abdominal aorta, divides into 4-5 branches
  - each gives off small branches to suprarenal glands, ureter, surrounding cellular tissue and muscles

Note: Frequently a second renal artery (inferior renal) from abdominal aorta at a lower level, supplies lower portion of kidney

Abnormalities



duplications.

Urorectal Septum Malformation

- thought to be a deficiency in caudal mesoderm which in turn leads to the malformation of the urorectal septum and other structures in the pelvic region.
- Recent research has also identified the potential presence of a persistent urachus prior to septation of the cloaca (common urogenital sinus).

Bladder

- absent or small bladder -

associated with renal agenesis.

Bladder Exstrophy

- developmental abnormality associated with bladder development.
- origins appear to occur not just by abnormal bladder development, but by a congenital malformation of the ventral wall of abdomen (between umbilicus and pubic symphysis).
- There may also be other anomolies associated with failure of closure of abdominal wall and bladder (epispadias, pubic bone anomolies).

Ureter and Urethra

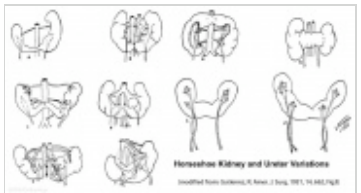
- Ureter - Duplex Ureter
- Urethra- Urethral Obstruction and Hypospadias

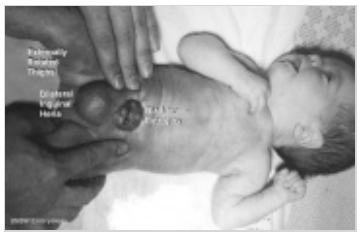
Polycystic Kidney Disease

- diffuse cystic malformation of both kidneys

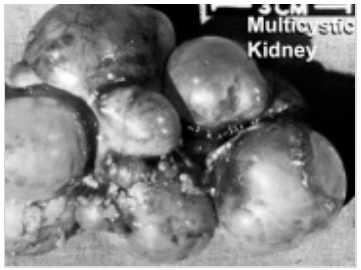
Horseshoe Kidney

fusion of the lower poles of the kidney.
During migration from the sacral region the two metanephric blastemas can come into contact, mainly at the lower pole.
The ureters pass in front of the zone of fusion of the kidneys.
The kidneys and ureters usually function adequately but there is an increased incidence of upper urinary tract obstruction or infection.
Some horseshoe variations have been described as having associated ureter abnormalities including


Horseshoe kidney


Bladder_Exstrophy

- cystic malformations of liver and lung often associated, Often familial disposition
- Two types
  - Infantile (inconsistent with prolonged survival)
  - Adult (less severe and allows survival)
- Autosomal dominant PKD disease - recently identified at mutations in 2 different human genes encoding membrane proteins (possibly channels)

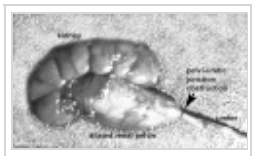
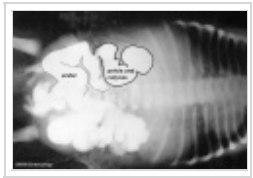


Multicystic kidney

Wilms' Tumor

- (nephroblastoma) Named after Max Wilms, a German doctor who wrote first medical articles 1899
- most common type of kidney cancer children
- WT1 gene - encodes a zinc finger protein
- Both constitutional and somatic mutations disrupting the DNA-binding domain of WT1 result in a potentially dominant-negative phenotype
- some blastema cells (mass of undifferentiated cells) persist to form a ‘nephrogenic rest’
- Most rests become dormant or regress but others proliferate to form hyperplastic rests
- any type of rest can then undergo a genetic or epigenetic change to become a neoplastic rest
- can proliferate further to produce a benign lesion (adenomatous rest) or a malignant Wilms’ tumour

Prune Belly Syndrome


Prune_belly

- lower urinary tract obstruction
- mainly male
- fetal urinary system ruptures leading to collapse and "prune belly" appearance.

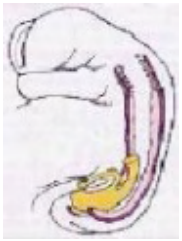
Online Links

- **UNSW Embryology** Introduction (http://embryology.med.unsw.edu.au/Notes/urogen.htm) | Nephron Development (http://embryology.med.unsw.edu.au/Notes/urogen7.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/urogen2.htm) | References (http://embryology.med.unsw.edu.au/References/urogen_ref.htm) | Stage13/14 (http://embryology.med.unsw.edu.au/Notes/urogen3.htm#Pig) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/urogen4.htm#Human) | Selected Human highpower (http://embryology.med.unsw.edu.au/Notes/urogen4.htm#high%20power) | Genital (http://embryology.med.unsw.edu.au/Notes/genital.htm) | Genital Abnormalities (http://embryology.med.unsw.edu.au/Notes/genital2.htm) | Urogenital Movies} | [http://embryology.med.unsw.edu.au/Notes/urogenlink.htm WWW Links (http://embryology.med.unsw.edu.au/Movies/urogen.htm)

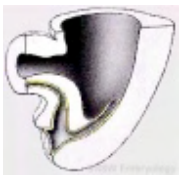
- **UNSW Embryology Movies:** Cervical Nephrotomes, Mesonephros and Metanephros (http://embryology.med.unsw.edu.au//Movies/larsen/10-2.mov) (553Kb) | Development of the Renal

Collecting System (http://embryology.med.unsw.edu.au//Movies/larsen/henle.mov) (298Kb) | Development of the Primitive Urogenital Sinus (http://embryology.med.unsw.edu.au//Movies/larsen/10-9.mov) (476Kb) | Trigone (http://embryology.med.unsw.edu.au//Movies/larsen/trigone.mov) (187Kb) | Male Gonadal Development (http://embryology.med.unsw.edu.au//Movies/larsen/ma.mov) (434 Kb) | Femal Gonadal Development (http://embryology.med.unsw.edu.au//Movies/larsen/fe.mov) (315Kb) | Formation of Uterus and Vagina (http://embryology.med.unsw.edu.au//Movies/larsen/10-17.mov) (706Kb) | Male Genitalia Development (http://embryology.med.unsw.edu.au//Movies/larsen/Male.mov) (434 Kb) | Female Genitalia Development (http://embryology.med.unsw.edu.au//Movies/larsen/Female.mov) (357Kb) | Descent of the Testes (http://embryology.med.unsw.edu.au//Movies/larsen/testes.mov) (221Kb) | Movies (http://embryology.med.unsw.edu.au//Movies/Movies.htm)

Movies

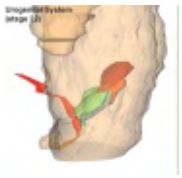


Urogenital Sinus



Urogenital Septum

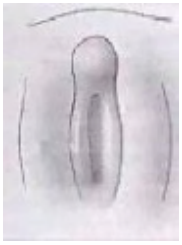
Trigone



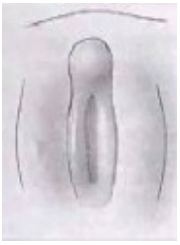
Urogenital

Renal Nephron

Uterus



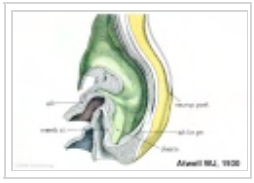
Female External



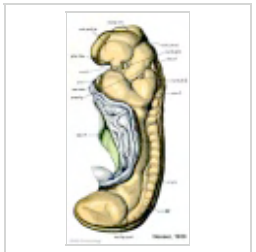
Male External

Testis Descent

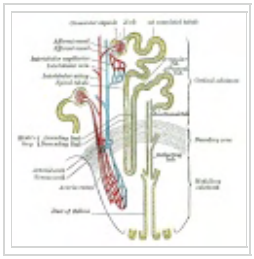
Images



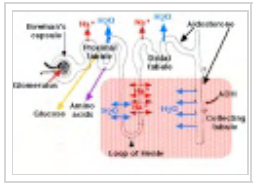
Stage 11 historic Atwell (1930)



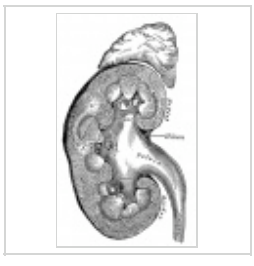
Stage 11 historic Heuser (1930)

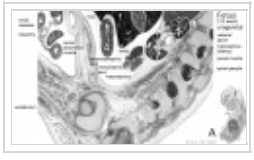


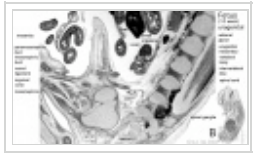
Nephron structure

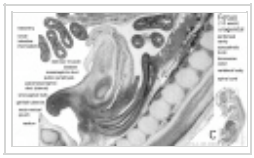
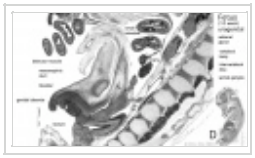
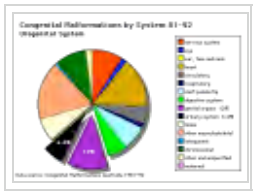
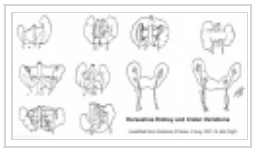
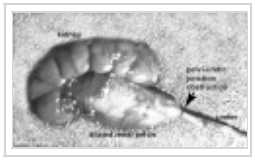
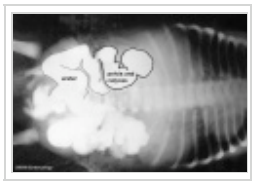
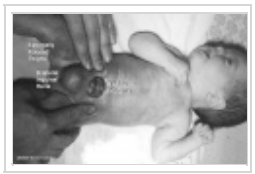


Nephron physiology







Kidney and adrenal gland (adult)	Endoderm cartoon	Fetal urogenital region most lateral right	Fetal urogenital region lateral right
 Fetal urogenital region medial	 Fetal urogenital region midline	 Bladder histology	
 Horseshoe kidney	 Hydronephrosis	 Multicystic kidney	 Prune belly
 Renal outflow obstruction	 Bladder Exstrophy		

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- **The Developing Human: Clinically Oriented Embryology** (8th Edition) by Keith L. Moore and T.V.N Persaud - Moore & Persaud Chapter 13 p303-346
- **Larsen's Human Embryology** by GC. Schoenwolf, SB. Bleyl, PR. Brauer and PH. Francis-West - Chapter 10 p261-306
- **Before We Are Born** (5th ed.) Moore and Persaud Chapter14 p289-326
- **Essentials of Human Embryology**, Larson Chapter 10 p173-205
- **Human Embryology**, Fitzgerald and Fitzgerald Chapter 21-22 p134-152

Online Textbooks

- **Developmental Biology** by Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000

Chapter 14 Intermediate Mesoderm (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.section.3498) | Figure 14.18. General scheme of development in the vertebrate kidney (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=dbio&part=A3498&rendertype=figure&id=A3500) | Figure 23-23. Mechanism of mesenchymal inductive effect on the ureteric bud (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mcb.figgrp.6814) | Figure 14.21. Ureteric bud growth is dependent on GDNF and its receptor (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=dbio&part=A3498&rendertype=figure&id=A3507)

- **Molecular Cell Biology** by Lodish, Harvey; Berk, Arnold; Zipursky, S. Lawrence; Matsudaira, Paul; Baltimore, David; Darnell, James E. New York: W. H. Freeman & Co.; c1999 Reciprocal Epithelial-Mesenchymal Interactions Regulate Kidney Development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mcb.figgrp.6811) | Figure 23-21. Embryonic development of the kidney (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mcb.figgrp.6811)

Reviews

- Quaggin SE, Kreidberg JA. Development of the renal glomerulus: good neighbors and good fences. Development. 2008 Feb;135(4):609-20. PMID: 18184729 (http://www.ncbi.nlm.nih.gov/pubmed/18184729)
- Brenner-Anantharam A, Cebrian C, Guillaume R, Hurtado R, Sun TT, Herzlinger D. Tailbud-derived mesenchyme promotes urinary tract segmentation via BMP4 signaling. Development. 2007 May;134(10):1967-75. PMID: 17442697 (http://www.ncbi.nlm.nih.gov/pubmed/17442697)
- Forefronts Symposium on Nephrogenetics: from development to physiology March 8-11, 2007 Danvers, MA (http://www.nature.com/ng/meetings/nephrogenetics/index.html) A meeting to synthesize an integrated view of the normal development and function of the kidney from the genetic standpoint.
- Costantini F. Renal branching morphogenesis: concepts, questions, and recent advances. Differentiation. 2006 Sep;74(7):402-21. PMID: 16916378 (http://www.ncbi.nlm.nih.gov/pubmed/16916378)

Search

- **Bookshelf** intermediate mesoderm (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=intermediate_mesoderm) | kidney development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=kidney_development) | renal development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=renal_development) | ureteric bud (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=ureteric+bud) | nephron development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=nephron_development) | bladder development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=bladder+development)

- **Pubmed** intermediate mesoderm (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=intermediate_mesoderm) | kidney development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=kidney_development) | renal development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=renal_development) | ureteric bud (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=ureteric_bud) | nephron development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=nephron_development) | bladder development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=bladder+development)

Terms

bladder exstrophy - A congenital malformation with bladder open to ventral wall of abdomen (between umbilicus and pubic symphysis) and may have other anomolies associated with failure of closure of abdominal wall and bladder (epispadias, pubic bone anomolies).

blastema - Term used to describe a mass of undifferentiated cells. (More? [#Wilms_tumour Wilm's tumour])

diabetes insipidus - The disorder is related to the hormone antidiuretic hormone (ADH, also called vasopressin) its synthesis, secretion, receptors and signaling pathway. In diabetes insipidus there is an excretion of large amounts (up to 30 litres/day) of a watery urine and an unremitting thirst (More? [urogen2.htm#Diabetes_Insipidus Kidney Abnormalities - Diabetes Insipidus])

hydronephrosis - (congenital hydronephrosis, Greek, *hydro* = water) A kidney abnormality due to partial or complete obstruction at the pelvi-ureteric junction. This leads to a grossly dilated renal pelvis causing extensive renal damage before birth.

hyperplastic rests - In kidney development, embryonic blastema cells can persist and proliferate to form a pool of cells, which under either genetic or epigenetic influence can then change to become a neoplastic rest. Normally the majority of nephrogenic rests either regress or become dormant.

mesonephros - The second temporary stage of kidney development (pro-, meso-, meta-). The intermediate mesonephros develops and disappears with the exception of its duct, the **mesonephric duct**, which will form the male reproductive duct system. In males, the mesonephric tubules go on to form the ducts of the testis. In females, these degenerate. A few mesonephric tubules remain as efferent ductules in the male and vestigial remnants in the female.

mesonephric duct - (= Wollfian duct) An early developing urogenital duct running the length of the embryo that will differentiate and form the male reproductive duct system. In females this duct degenerates (some remnants may remain associated in broad ligament).

metanephros - The adult kidney, third stage of mammalian kidney (pro-, meso-, **meta-**) development within the intermediate mesoderm.

metanephric cap - In kidney development, the intermediate mesoderm which surrounds the ureteric bud and will develop into nephrons.

Multicystic Kidney - There is no functional kidney tissue present in the kidney and it is replaced by a multilocular cyst. This is non-familial and is produced by atresia of a ureter and is always unilateral.

neoplastic rest - In kidney development, a neoplastic rest can develop under either genetic or epigenetic influence from a hyperplastic rest, originating from an embryonic blastema cell. Normally the majority of nephrogenic rests either regress or become dormant.

nephrogenic rest - A kidney term used to describe the embryonic blastema cells which persist and under either genetic or epigenetic can change to become a neoplastic rest. These neoplastic rests can develop postnatally as a benign form (adenomatous rest) or a malignant [W.htm#Wilms_tumour Wilm's tumour] form. The rests are further characterised by the time of generation leading to different anatomical kidney locations: early intralobar nephrogenic rests (within the renal lobe) and late pelilobar nephrogenic rests (periphery of the renal lobe) (More? [#Wilms_tumour Wilm's tumour] | [urogen2.htm Urogenital Abnormalities])

nephron - (Greek, *nephros* = kidney) The functional unit of the kidney.

nephros - (Greek, *nephros* = kidney) Term used to describe features associated with the kidney. (pronephros, mesonephros, metanephros, nephric, nephron, nephroblastoma).

podocyte - (visceral epithelial cell) kidney glomerulus cell forming the main component of the glomerular filtration barrier.

podocyte specific proteins - podocalyxin, glomerular epithelial protein-1, podocin, nephrin, synaptopodin, and alpha-actinin-4), podocyte synthesized proteins (vascular endothelial growth factor and novH), transcription factors (WT1 and PAX2).

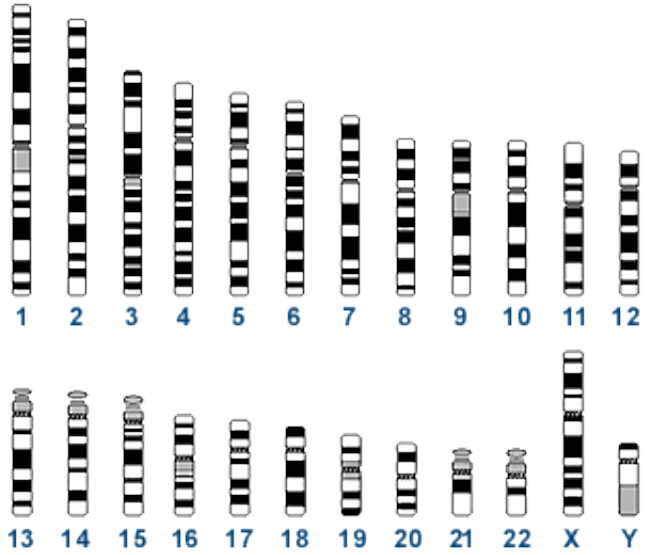
2009 Lecture 16

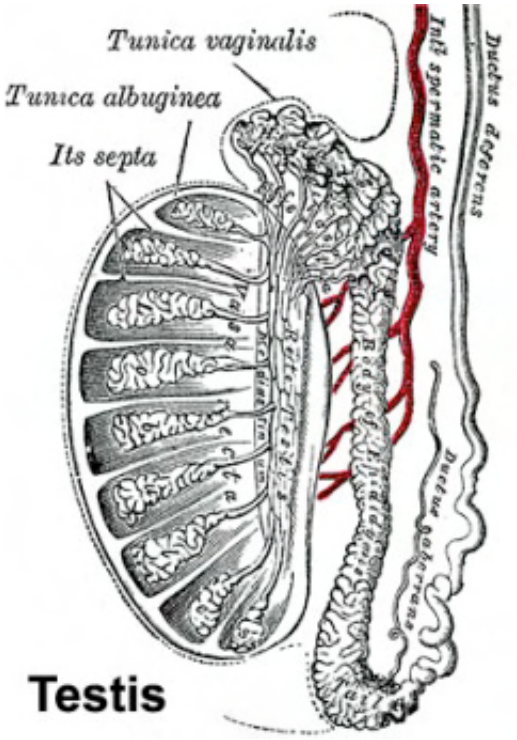
From Embryology

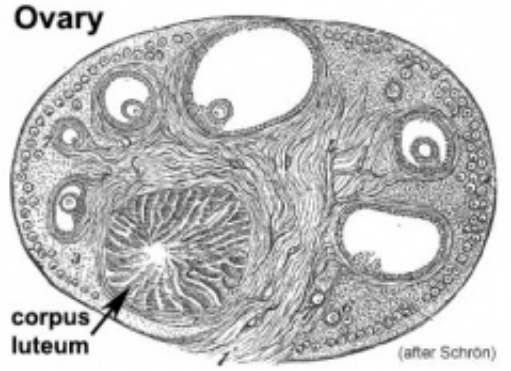
Contents

Genital Development

Introduction

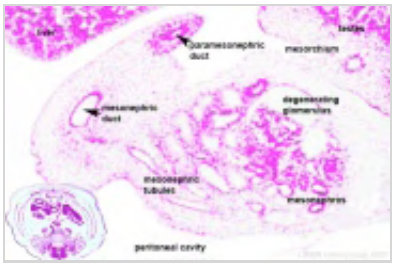






This section of notes covers genital development. Differences in development are dependent on a protein product of the Y chromosome SRY gene. Mesonephric duct (Wolffian Duct) and paramesonephric (Mullerian Duct) contribute the majority of male and female internal genital tract respectively.

Objectives



Stage 22 mesonephros

- Understand the role of the Y chromosome in sex determination.
- Understand the differences in male/female duct develpoment (mesonephric/paramesonephric).
- Compare the development of the cloaca in the male and female.
- Understand the developmental abnormalities in male and female development.

Textbooks

- **Human Embryology** (2nd ed.) Larson Ch10 p261-306
- **The Developing Human: Clinically Oriented Embryology** (6th ed.) Moore and Persaud Chapter 13 p303-346

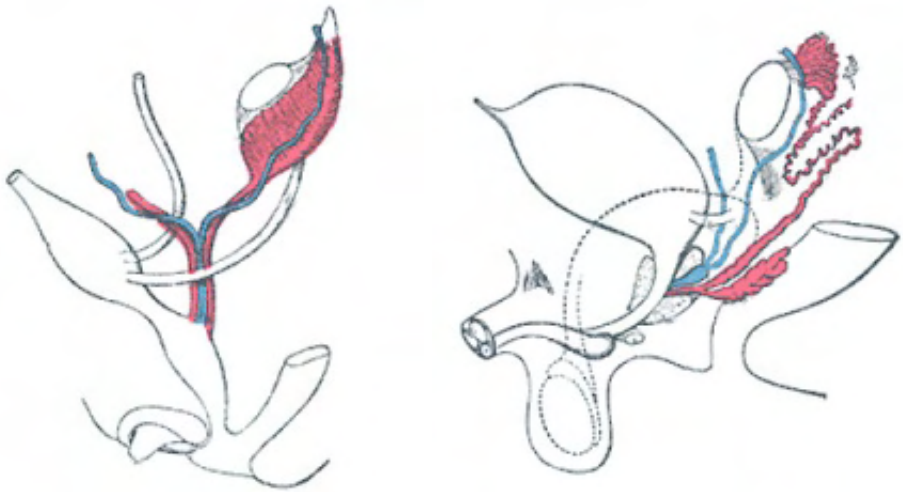
Lecture Audio Lecture Date: 22-09-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Genital (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48842)

Three Stages

The mesonephric/paramesonephric duct changes are one of the first male/female differences that occur in development, while external genitaila remain indeterminate in appearance for quite a while.

1. Differentiation of gonad (Sex determination)
2. Differentiation of internal genital organs
3. Differentiation of external genital organs

The 2nd and 3rd stages dependent on endocrine gonad. Reproductive development has a long maturation timecourse, begining in the embryo and finishing in puberty. (More? Puberty (http://embryology.med.unsw.edu.au/Child/puberty.htm))



Development Overview

Sex Determination

- Humans (week 5-6)
- Germ cells migrate into gonadal ridge
- Gonads (male/female) identical at this stage, indifferent

Gonad development

- dependent on sex chromosome
- Y testes
- No Y ovary

SRY

- SRY protein (Testes determining factor, TDF) binds DNA
- Transcription factor, Bends DNA 70-80 degrees

Internal Genital Organs

- All embryos form paired
- Mesonephric duct, see kidney development
- Paramesonephric duct, Humans 7th week Invagination of coelomic epithelium Cord grows and terminates on urogenital sinus
- Male Gonad (testes) secretes Mullerian duct inhibitory factor (MDIF) which causes regression of paramesonephric duct
- Male Gonad (testes) secretes Testosterone which retains mesonephric duct

External Genital Organs

- All embryos initially same (indifferent)
- Testosterone differentiates male

Human Timeline

- 24 days - intermediate mesoderm, pronephros primordium
- 28 days - mesonephros and mesonephric duct
- 35 days - uteric bud, metanephros, urogenital ridge

- 42 days - cloacal divison, gonadal primordium (indifferent)
- 49 days - paramesonephric duct, gonadal differentiation
- 56 days - paramesonephric duct fusion (female)
- 100 days - primary follicles (ovary)

Kidney

- kidneys and genital ridge develop from intermediate mesoderm, which lies between the lateral plate mesoderm and the somites.
- kidney develops in multiple stages, which occur in a rostrocaudal sequence.
- earliest structure to form is the pronephros, in week 4, featuring a pronephric duct with associated nephrogenic mesenchyme.
- pronephros degenerates early on, leaving only the duct system running down to the cloaca – this becomes known as the mesonephric duct, in the embryo.
- next stage is the formation of the mesonephros, also in week 4. Its differentiation is induced by the pronephros.
- mesonephros is also a transient structure. It provides a template for the adult metanephros, beginning on day 35-37.

Sex Determination

MBoC - Figure 20-18. Influence of Sry on gonad development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mboc4.figgrp.3716)

Male (XY)

- Y chromosome - 200+ genes, 50 million base pairs
- Sry was discovered (1990) by studying a human XY female, resulting from a deletion in the Y chromosome that did not allow testis development. Subsequent mapping of this deletion allowed isolation and characterization of the SRY gene.

- SRY encodes: encodes a 204 amino acid protein (Mr 23884 Da) that is a zinc-finger transcription factor. Transcription factors bind to specific sites of DNA and regulates the transcription (expression) of other genes, we still do not know all the genes SRY regulates.

- SRY is expressed: when testes begin to form, in gonadal tissue and does not require the presence of germ cells.
- induces cells to differentiate into Sertoli cells

Sertoli cells

- produce signals that promote development of male characteristics
- suppress development of female characteristics
- induce primordial germ cells to commit to sperm development

Female (XX)

- 1400+ genes, 150 million base pairs
- In contrast to the Y chromosome, the X chromosome contains about 5% of the haploid genome and encodes house-keeping and specialized functions. The genetic content of the X chromosome has been strongly conserved between species.

- Genes such as Wnt-4 and DAX-1 necessary for initiation of female pathway ovary development
  - female not considered a default process
- An early discovery (1961) was that in order to have correct levels of X chromosome gene/protein expression (gene dosage), females must "inactivate" a single copy of the X chromosome in each and every cell. The initiator of the X inactivation process was discovered (1991) to be regulated by a region on the inactivating X chromosome encoding an X inactive specific transcript (XIST), that acts as RNA and does not encode a protein.

- X inactivation occurs randomly throughout the embryo, generating a mosaic of maternal and paternally derived X chromosome activity in all tissues and organs.

Primordial Germ Cells

Primordial Germ Cell Migration (http://embryology.med.unsw.edu.au/Movies/genital/germcell.htm)

- thought to be the first population of cells to migrate through the primitive streak in early gastrulation.
- This population of cells then lie at the hindgut yolk sac junctional region and later migrate into the genital ridge (germinal ridge) in early embryonic development.
- It is not the primordial germ cells which respond to SRY presence or absence, but the supporting cells within the developing gonad.

Gametogenesis

- forming PGCs and getting them into genital ridge as gonad forms
- formation of germ plasm and determination of PGCs
- migration of PGCs into developing gonads
- process of meiosis and modifications of meiosis for forming sperm and eggs
- differentiation of sperm and egg
- hormonal control of gamete maturation and ovulation

Male Gonadal Development

Media:Male_gonad_2.mov This looped animation shows the development of the male gonad showing medullary sex cords.

- The paramesonephric duct (red, left) degenerates under the influence of Mullerian duct inhibitory factor (MDIF) secreted by sertoli cells (differentiated by SRY expression).
- The mesonephric duct (purple) differentiates under the influence of Testosterone secreted by Leydig cells. Within the testes these mesonephric tubules grow towards the medullary sex cords and will form the rete teste. The mesonephric duct extending out of the gonad forms the ductus deferens.
- The medullary sex cords (orange) form testis cords that later differentiate into solid seminiferous tubules which become hollow and actively produce spermatazoa during puberty.

The tunica albuginea (white) covers the testis and bands extend inward to form connective tissue septa.

Anti-Mullerian Hormone

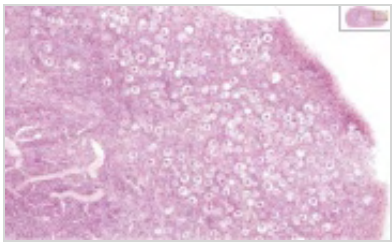
Anti-Mullerian hormone (AMH) or Mullerian Inhibiting Substance (MIS) hormone with at least two gonadal related functions:

- In males, it is produced by supporting gonadal Sertoli cells and inhibits the development of the paramesonephric (Mullerian) duct system that forms the internal female genital tract. The hormone is

also involved in Leydig cell steroidogenesis.
- In females, it is produced by supporting gonadal granulosa cells and is involved in ovarian follice development.

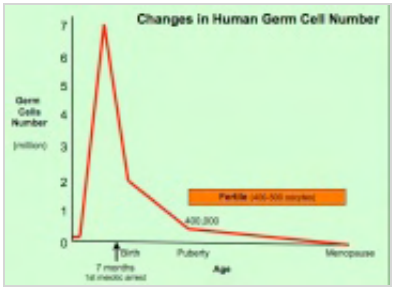
Female Gonadal Development

File:Female gonad 2.mov This looped animation shows the development of the female gonad showing cortical sex cords.



Infant ovary

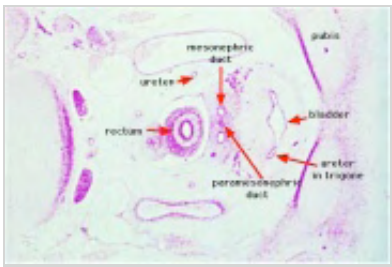
- The mesonephric duct (purple) degenerates, small remnants may remain as epoophoron and paroophoron (in the mesentry of the ovary) and Gartner's cycts (near vagina).
- The paramesonephric duct (red, left) grows forming the oviduct (uterine horn) and the end opens into the peritoneal cavity and terminates in fimbria (finger-like extensions). Away from the ovary, the two paramesonephric ducts fuse in the midline to form the uterus.
- The cortical sex cords (orange) form after the primary sex cords degenerate and mesothelium forms secondary cords. The surrounding connective tissue (pink) differentiates to form follicle cells.



human oocyte number

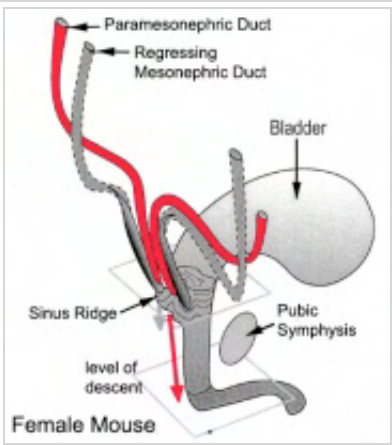
Internal Genital Tract

- Week 7 – duct regression or preservation begins
- All embryos initially form 2 paired indifferent duct systems
  - Mesonephric duct (also called the Wolffian duct)
  - Paramesonephric duct (also called the Mullerian duct)
- Testes secretions - Mullerian duct inhibitory factor (MDIF) causes regression of paramesonephric ducts and testosterone retains mesonephric ducts.
- No Testes - Paramesonephric ducts retained and mesonephric duct regresses.



Vagina Development

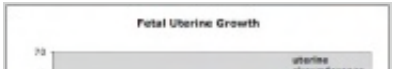
- The embryonic origin of the vagina has been a historically hotly debated issue with several different contributions and origins described.
- One description shows the vagina arising by downward growth of Wolffian and Mullerian ducts. The sinovaginal bulbs are the caudal ends of the Wolffian ducts. Vaginal development is also under negative control of androgens.



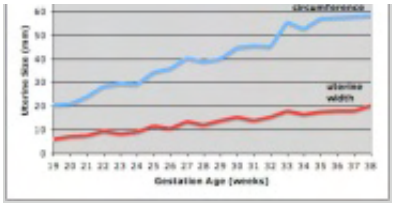
Paramesonephric duct

Fetal

- late embryonic male genital development and now in fetal development we will firstly observe early fetal female development.



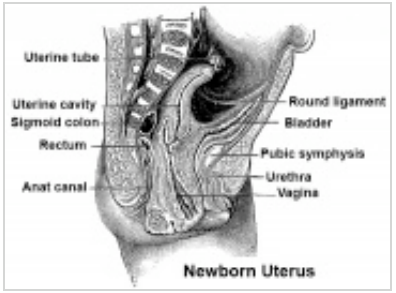
External Genitalia


Fetal uterus growth

External Genital (http://embryology.med.unsw.edu.au/Medicine/BGDlabXYXX_4.htm) | Endocrinology - Diagram of the development of the external genitalia (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972&rendertype=box&id=A1026)

- The external genitalia are initially identical and undergo male and female differentiation under the influence or absence of modified steroidal sex hormone.
- Indifferent stage - cloaca divided by proliferating mesenchyme forming urorecal septum, ventral urethral, dorsal anal pit.
- Difference stage - locally in this region the presence or absence of dihydroxytestosterone (DHT), generated from testosterone, determines male/female development.
    - Presence- DHT locally in this region leads to genital tubercle growth, maintenance and fusion of external male genitalia.
    - Absence- of DHT, genital tubercle remains small, bends caudally to form the clitoris. Urethral folds persist, do not fuse, and form labia minora. The open urogenital sinus forms a cleft into which urethra and vagina open. The labioscrotal swellings become the labia majora.

Female Genitalia Development



Newborn uterus

This looped animation shows the development of external female genitalia from the indifferent external structure, covering the approximate period of week 9 to 12.

Note the original cloacal membrane becomes separated into the urogenital membrane and anal membrane. The urogenital folds beneath the genital tubercle remain separate (unfused), forming the inner labia minora and second outer skin folds form the larger labia majora either side of the developing vestibule of the vagina. Note at the top of the animation, the changing relative size of the genital tubercle as it forms the glans of the clitoris.

Male Genitalia Development

Endocrinology - Box 6.6 The roles of testosterone (T) and 5α-dihydrotestosterone (DHT) (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972&rendertype=box&id=A1027)

This looped animation shows the development of external male genitalia from the indifferent external structure, covering the approximate period of week 9 to 12.

Note the original cloacal membrane becomes separated into the urogenital membrane and anal membrane (identical to female). The urogenital folds beneath the genital tubercle begin to fuse in the midline. The skin folds either side for the scrotum, which too has a midline fusion, the raphe. The scrotal sac is initially empty and is an attachment site for the gubernaculum, descent of the testes begins generally during week 26 and may take several days.

Gonad Descent

- Both kidney and gonads develop retroperitoneally, with the gonads moving into the abdomen or

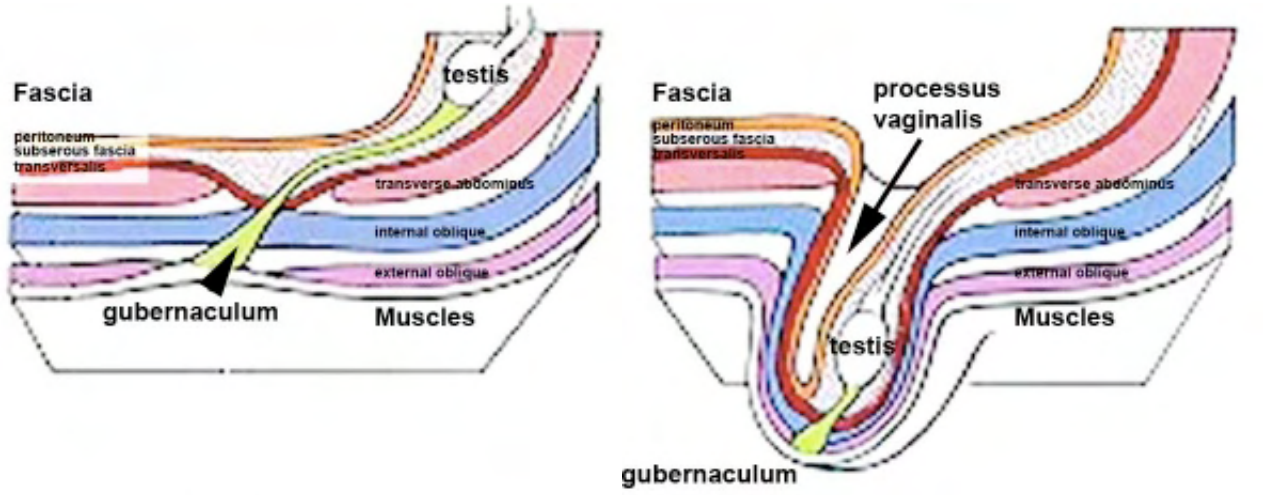
eventually into the scrotal sacs.
- During fetal development the gubernaculum and fetal growth in both male and female, changes the gonads' relative positions finally reaching their adult locations.

MH - These positional changes will be covered in this weeks lab.

Both female and male gonads undergo anatomical descent.

- **Ovaries** - undergo caudal and lateral shifts to be suspended in the broad ligament of the uterus, gubernaculum does not shorten, it attaches to paramesonephric ducts, causing medial movement into the pelvis.

- **Testes** - two anatomical phases in descent, transabdominal and transinguinal, under the influence of the shortening gubernaculum.



The testis (white) lies in the subserous fascia (spotted) a cavity processus vaginalis evaginates into the scrotum, and the gubernaculum (green) attached to the testis shortens drawing it into the scotal sac. As it descends it passes through the inguinal canal which extends from the deep ring (transversalis fascia) to the superficial ring (external oblique muscle). Descent of the testes into the scrotal sac begins generally during week 26 and may take several days. The animation shows the path of a single testis. Incomplete or failed descent can occur unilaterally or bilaterally, is more common in premature births, and can be completed postnatally.

Data from a recent study of male human fetal (between 10 and 35 weeks) gonad position.

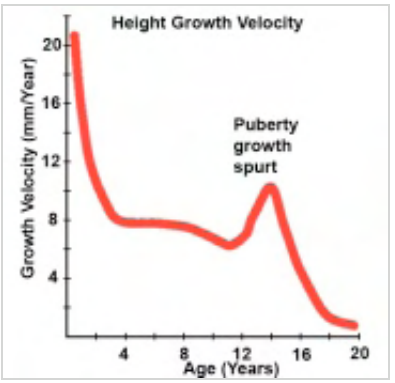
- 10 to 23 weeks - (9.45%) had migrated from the abdomen and were situated in the inguinal canal
- 24 to 26 weeks - (57.9%) had migrated from the abdomen
- 27 to 29 weeks - (16.7%) had not descended to the scrotum

Postnatal - Puberty

Puberty can occur over a broad range of time and differently for each sex:

Puberty can occur over a broad range of time and differently for each sex.

- girls (age 7 to 13)
- boys (age 9 to 15)



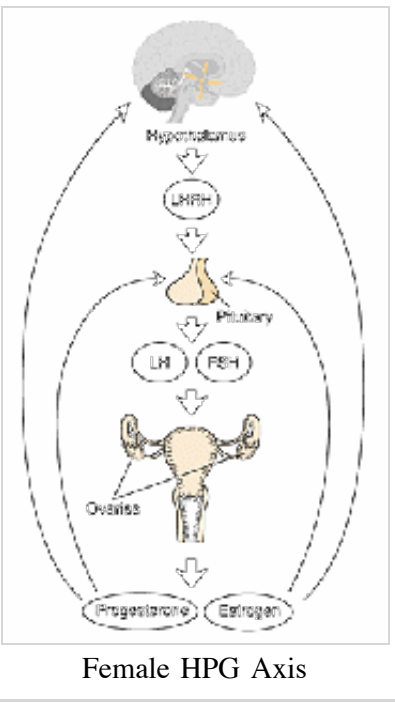
Puberty growth

The physical characteristics that can be generally measured are: genital stage, pubic hair, axillary hair, menarche, breast, voice change and facial hair.

Female

In females, menarche (the first menstruation or a period) usually occurs after the other secondary sex characteristics, and will continue until menopause (permanent cessation of reproductive fertility).

The diagram shows the hormonal regulation pathway from the brain to the ovary and subsequent impact on uterine changes during the menstral cycle.



Female HPG Axis

LHRH = Luteinizing Hormone-Releasing Hormone, also called gonadotropin-releasing hormone (GnRH). This peptide hormone is a decapeptide (10 amino acids) with a short half life (<15 minutes).

LH = Luteinizing Hormone

FSH = Follicle Stimulating Hormone

A similar endocrine axis is also found for regulation of the male gonad.

Puberty Abnormalities

- **Precocious Puberty** - Premature development of the signs of puberty which can occur in both girls (before age 7 or 8) and in boys (before age 9).
- **Delayed Puberty** - Determined in boys by a lack of increase in testicular volume by the age of 14 years. In girls, no breast development by the age of 13.5 years and a lack of menstruation by the age of 16 years. There can also be a "pubertal arrest" where there is no progress in puberty over 2 year period.

Sex Differences in Adult and Developing Brains

- not known significance of brain sex differences
- transient sex differences in gene expression in developing brains may cause permanent differences in brain structure
- may prevent as well, by compensating for potentially differentiating effects of sex differences in gonadal hormone levels and sex chromosomal gene expression

- Brains of males and females differ
  - in regions specialized for reproduction
  - in other regions (controlling cognition, etc) where sex differences are not necessarily expected
  - Differentially susceptible to neurological and psychiatric disease

2 sources of sexually dimorphic information

- complement of sex chromosome genes

- mix of gonadal hormones

Abnormalities

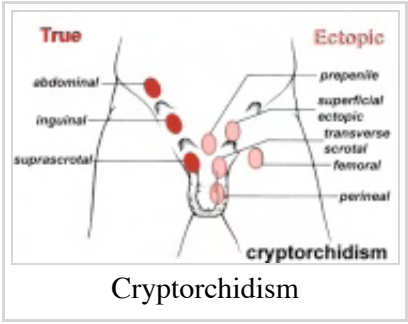
Human genital abnormalities are currently described as "Disorders of Sex Development" (DSD) and include: chromosomal, gonadal dysfunction, tract abnormalities, external genitalia and gonadal descent. Genital Abnormalities (http://embryology.med.unsw.edu.au/Notes/genital2.htm)

Congenital adrenal hyperplasia

- impairment of cortisol production by the adrenal cortex, is one of the most common causes of intersex genitalia at birth
- genetically male (XY) infants born with undervirilized genitalia (androgen insensitivity syndrome, cloacal exstrophy) are generally assigned and reared as girls.

Cryptorchidism

- abnormality of either unilateral or bilateral testicular descent, occurring in up to 30% premature and 3-4% term males.
- Descent may complete postnatally in the first year, failure to descend can result in sterility.



Cryptorchidism

Testis descent is thought to have 2 phases:

1. transabdominal descent - dependent on insulin-like hormone 3 (INSL3).
2. inguinoscrotal descent - dependent on androgens.

Undescended Ovaries

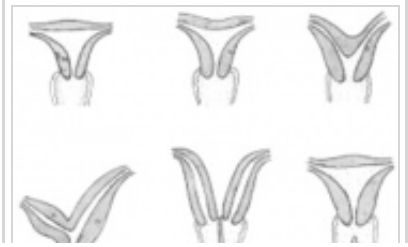
- reasonably rare gonad abnormality, often detected following clinical assessment of fertility problems and may also be associated with other uterine malformations (unicornuate uterus).
- Due to the relative positions of the male (external) and female (internal) gonads and the pathways for their movement, failure of gonad descent is more apparent and common in male cryptorchidism than female undescended ovaries.

Hydrocele

- Male Hydrocele is a fluid-filled cavity of either testis or spermatic cord, where peritoneal fluid passes into a patent processus vaginalis.
- Female Hydrocele is a similar, but rarer, fluid-filled cavity occuring in the female as a pouch of peritoneum extending into the labium majorum (canal of Nuck).

Tract Abnormalities

Many different forms



- Uterine: associated with other anomolies, unicornuate uterus
- Vagina: agenesis, atresia
- Ductus Deferens: Unilateral or bilateral absence, failure of mesonephric duct to differentiate

Uterine abnormalities

Uterine Duplication (uterus didelphys, double uterus, uterus didelphis) A rare uterine developmental abnormality where the paramesonephric ducts (Mullerian ducts) completely fail to fuse generating two separate uterus parts each connected to the cervix and having an ovary each.

Septate Uterus

Cervical: cervical agenesis, cervical duplication

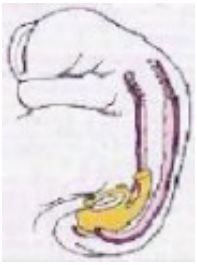
Vaginal: Mayer-Rokitansky syndrome (MRK anomaly, Rokitansky-Küster-Hauser syndrome, RKH syndrome, RKH) congenital absence of the vagina, dyspareunia, vaginal agenesis.

Unicornate uterus

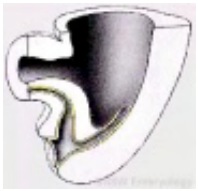
External Genitalia - Hypospadia

- most common penis abnormality (1 in 300) from a failure of male urogenital folds to fuse in various regions and resulting in a proximally displaced urethral meatus.
- The cause is unknown, but suggested to involve many factors either indivdually or in combination including: familial inheritance, low birth weight, assisted reproductive technology, advanced maternal age, paternal subfertility and endocrine-disrupting chemicals. Infants with hypospadias should not undergo circumcision.

Movies



Urogenital Sinus

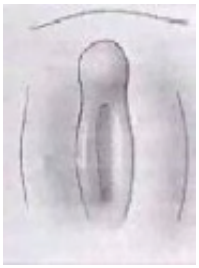


Urogenital Septum

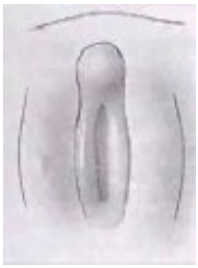
Trigone

Renal Nephron

Uterus



Female External



Male External

Testis Descent

References

Textbooks

- **Before We Are Born** (5th ed.) Moore and Persaud Chapter 14 p289-326
- **Essentials of Human Embryology**, Larson Chapter 10 p173-205
- **Human Embryology**, Fitzgerald and Fitzgerald Chapter 21-22 p134-152

Online Textbooks

- **Developmental Biology** (6th ed.) Gilbert Chapter14 Intermediate Mesoderm (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.section.3498)

Search

- **Bookshelf** genital development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=genital+development) | gonad development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=gonad+development) | sex determination (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=sex+determination)

- **Pubmed** genital development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=genital+development) | gonad development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=gonad+development) | sex determination (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=sex+determination)

Online Links

- **UNSW Embryology** Abnormalities (http://embryology.med.unsw.edu.au/Notes/genital2.htm) | Y chromosome (http://embryology.med.unsw.edu.au/Notes/genitalY.htm) | Male (http://embryology.med.unsw.edu.au/Notes/genitalXY.htm) | X chromosome (http://embryology.med.unsw.edu.au/Notes/genitalX.htm) | Female (http://embryology.med.unsw.edu.au/Notes/genitalXX.htm) | Stage 13/14 Embryo (http://embryology.med.unsw.edu.au/Notes/genital3.htm) | Stage 22 Embryo (http://embryology.med.unsw.edu.au/Notes/genital4.htm) | Stage 22 Highpower (http://embryology.med.unsw.edu.au/Notes/genital5.htm)

- **UNSW Embryology Movies:** Urogenital Movies (http://embryology.med.unsw.edu.au/Movies/urogen.htm)

- **Embryo Images Unit:** Embryo Images Online (http://www.med.unc.edu/embryo_images/) | Urongenital Development (http://www.med.unc.edu/embryo_images/unit-genital/genital_htms/genitaltoc.htm) | Internal Genitalia (http://www.med.unc.edu/embryo_images/unit-genital/genital_htms/genital008.htm) | Definitive Kidney (http://www.med.unc.edu/embryo_images/unit-genital/genital_htms/genital017.htm) | External Genitalia (http://www.med.unc.edu/embryo_images/unit-genital/genital_htms/genital020.htm)

- **Histology:** Male Reproductive System (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/MaleRepro/malerepro.htm) | Female Reproductive System (http://www.lab.anhb.uwa.edu.au/mb140/CorePages/FemaleRepro/femalerepro.htm)

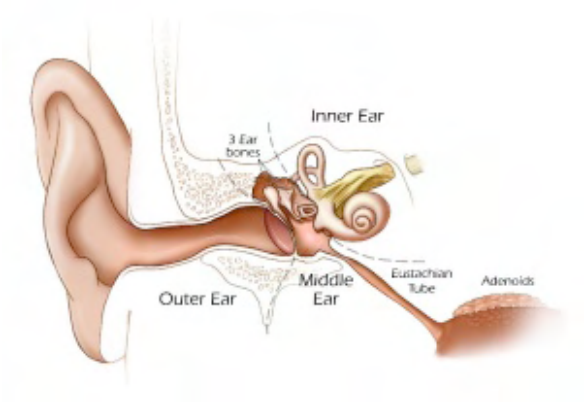
2009 Lecture 17

From Embryology

Contents

Sensory Development - Hearing

Introduction



We use the sense of balance and hearing to position ourselves in space, sense our surrounding environment, and to communicate. Portions of the ear appear very early in development as specialized region (otic placode) on the embryo surface that sinks into the mesenchyme to form a vesicle (otic vesicle = otocyst) that form the inner ear.

This region connects centrally to the nervous system and peripherally through specialized bones to the external ear (auricle). This organisation develops different sources forming the 3 ear parts: inner ear (otic placode, otocyst), middle ear (1st pharyngeal pouch and 1st and 2nd arch mesenchyme), and outer ear (1st pharyngeal cleft and 6 surface hillocks).

This complex origin, organisation, and timecourse means that abnormal development of any one system can impact upon the development of hearing.

Textbooks

- Human Embryology (2nd ed.) Larson Chapter 12: p375-409
- The Developing Human: Clinically Oriented Embryology (6th ed.) Moore and Persaud Chapter 19: p491-511
- UNSW Embryology - Systems Notes - Hearing (http://embryology.med.unsw.edu.au/Notes/ear.htm)

2008: 2008 Lecture Hearing (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture17.htm) | 1 slide/page viewing 48 pages (http://embryology.med.unsw.edu.au/pdf/ANAT2341L17Ears1.pdf) | 4 slide/page viewing 12 pages (http://embryology.med.unsw.edu.au/pdf/ANAT2341L17Ears4.pdf)

2009: Medicine Lecture - Face and Ear Development

Lecture Audio Lecture Date: 28-09-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill Hearing (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48831)

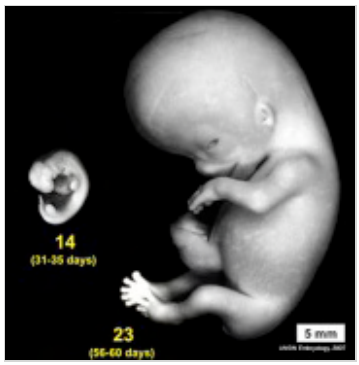
Objectives

- Understanding of structures and functions of the auditory pathway

- Understanding of inner, middle and external ear origins
- Understanding of timecourse of auditory development
- Understanding of abnormalities of auditory development
- Brief understanding of central auditory pathway and molecular development

Development Timing

- Week 3 - otic placode, otic vesicle
- Week 5 - cochlear part of otic vesicle elongates (humans 2.5 turns)
- Week 9 - Mesenchyme surrounding membranous labryinth (otic capsule) chondrifies
- Week 12-16 - Capsule adjacent to membranous labryinth undegoes vacuolization to form a cavity (perilymphatic space) around membranous labrynth and fills with perilymph
- Week 16-24 - Centres of ossification appear in remaining cartilage of otic capsule form petrous portion of temporal bone. Continues to ossify to form mastoid process of temporal bone.



Comparison of size at stage 14 to 23

- 3rd Trimester - Vibration acoustically of maternal abdominal wall induces startle response in fetus.

Embryonic Origin Overview

External Ear

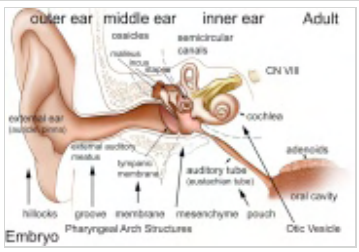
- Auricle - Pharyngeal Arches 1 and 2 (ectoderm, mesoderm)
- External Auditory Meatus - Pharyngeal Arch 1 groove (ectoderm)
- Tympanic Membrane - Pharyngeal Arch 1 membrane (ectoderm, mesoderm, endoderm)

Middle Ear

- Middle Ear Ossicles
  - Malleus and incus - Pharyngeal Arch 1 cartilage Neural crest (ectoderm)
  - Stapes - Pharyngeal Arch 2 cartilage Neural crest (ectoderm)
- Middle Ear Muscles
  - Tensor tympani - Pharyngeal Arch 1 (mesoderm)
  - Stapedius - Pharyngeal Arch 2 (mesoderm)
- Middle ear cavity - Pharyngeal Arch 1 cleft (endoderm)

Inner Ear

- Inner Ear Labyrinth
  - Cochlea - Otic vesicle - Otic placode (ectoderm)
  - Semicircular canals - Otic vesicle - Otic placode (ectoderm)
  - Saccule and utricle - Otic vesicle - Otic placode (ectoderm)
- Cranial Nerve VIII
  - Auditory component - Otic vesicle and neural crest (ectoderm)
  - Vestibular component - Otic vesicle and neural crest (ectoderm)

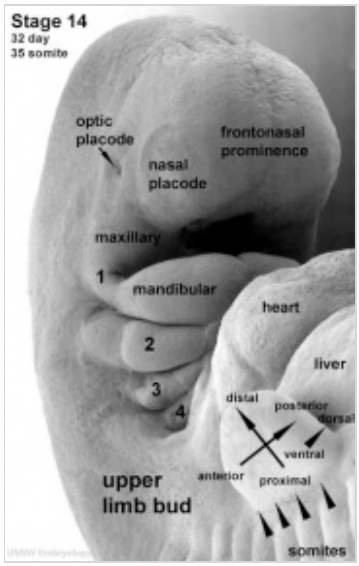


Adult hearing embryonic origins

Sensory Placodes

- week 4 a series of thickened surface ectodermal patches form in pairs rostro-caudally in the head region.
    - Recent research suggests that all sensory placodes may arise from common panplacodal primordium origin around the neural plate, and then differentiate to eventually have different developmental fates. (More? Schlosser G.)

- sensory placodes will later contribute key components of each of our special senses (vision, hearing and smell).
- Other species have a number of additional placodes which form other sensory structures (fish, lateral line receptor).
- Note that their initial postion on the developing head is significantly different to their final position in the future sensory system.



Stage 14 sensory placodes

Otic Placode

- stage 13/14 embryo (shown below) the otic placode has sunk from the surface ectoderm to form a hollow epithelial ball, the otocyst, which now lies beneath the surface surrounded by mesenchyme (mesoderm).
- The epithelia of this ball varies in thickness and has begun to distort, it will eventually form the inner ear membranous labyrinth.

Lens Placode

- lies on the surface, adjacent to the outpocketing of the nervous system (which will for the retina) and will form the lens.

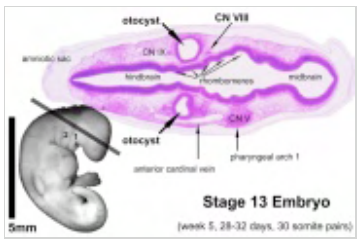
Nasal Placode

- 2 components (medial and lateral) and will form the nose olefactory epithelium.

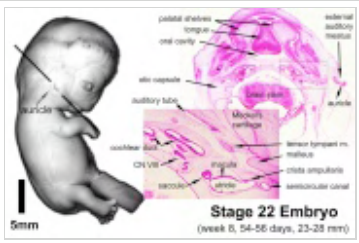
Inner Ear

Neuroscience - The Inner Ear
(http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.section.894)

- The inner ear is derived from a pair of surface sensory placodes (otic placodes) in the head region.
- These placodes fold inwards forming a depression, then pinch off entirely from the surface forming a fluid-filled sac or vesicle (otic vesicle, otocyst).
- The vesicle sinks into the head mesenchyme some of which closely surrounds the otocyst forming the otic capsule.
- The otocyst finally lies close to the early developing hindbrain (rhombencephalon) and the developing vestibulo-cochlear-facial ganglion complex.



Stage 13 otocyst



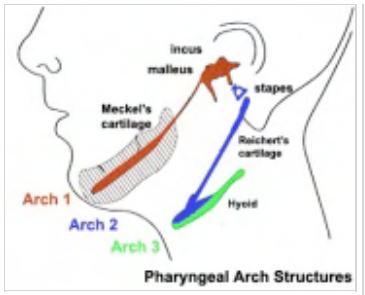
Stage 22 ear

Middle Ear

Neuroscience - The Middle Ear
(http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.section.893)

- The middle ear ossicles (bones) are derived from 1st and 2nd arch

mesenchyme.
- The space in which these bones sit is derived from the 1st pharyngeal pouch.



Pharyngeal arch cartilages

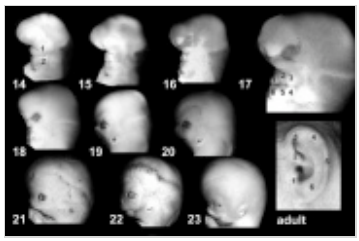
Outer Ear

- The external ear is derived from 6 surface hillocks, 3 on each of pharyngeal arch 1 and 2.
- The external auditory meatus is derived from the 1st pharyngeal cleft.
- The newborn external ear structure and position is an easily accessible diagnostic tool for potential abnormalities or further clinical screening.

Outer

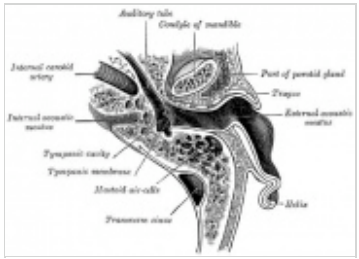
Neuroscience - The External Ear (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.section.891)
Pinna- Auricle

- develops from six aural hillocks
- 3 on first arch
- 3 on second arch
- originally on neck, moves cranially during mandible development



External ear stages 14-23 and adult (not to scale)

Pharyngeal Arch	Hillock	Auricle Component
Arch 1	1	tragus
	2	helix
	3	cymba concha
Arch 2	4	concha
	5	antihelix
	6	antitragus


outer ear and external auditory meatus

- Outer- external auditory meatus

- derived from first pharyngeal cleft
- ectodermal diverticulum
- week 5 - extends inwards to pharynx
- until week 18 has ectodermal plug - plug forms stratified squamous epithelia of canal and outer eardrum

Embryonic period	Ectodermal cells proliferate and fill the entire lumen forming a meatal plug
10 weeks	Meatal plug extends in a disc-like fashion. In the horizontal plane the meatus is boot-shaped with a narrow neck and the sole of the meatal plug spreading widely to form the future tympanic membrane medially. Proximal portion of the neck starts to be resorbed.
13 weeks	Disc-like plug innermost surface in contact with the primordial malleus, contributes to the formation of the tympanic membrane.
16.5 week	Meatus is fully patent throughout its length, lumen is still narrow and curved.
18 week	Meatus is already fully expanded to its complete form.

(Nishimura, 1992}

Outer Ear Genes

- controlled by genes that regulate arch 1 and 2 development
- related to hindbrain segmentation (rhombomere 4)
- Mouse - Hox a1/Hoxb1, goosecoid, Endothelin1, dHAND

Middle

tympanic cavity

- derived from first pharyngeal pouch
- extends as tubotympanic recess - during week 5 recess contacts outer ear canal
- mesoderm between 2 canals forms tympanic membrane
- expands to form tympanic recess
- stalk of recess forms auditory tube(eustachian tube, pharyngotympanic tube)

Ossicles

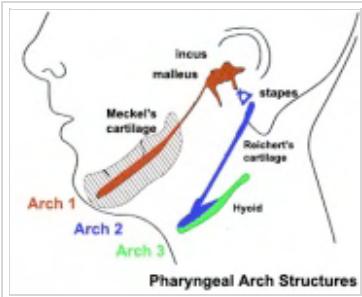
- develop from first and second pharyngeal arches
- tympanic cavity enlarges to incorporate
- coats with epithelia

- first arch mesoderm

- tensor tympani muscle
- malleus and incus

- second arch mesoderm

- stapedius muscle and stapes

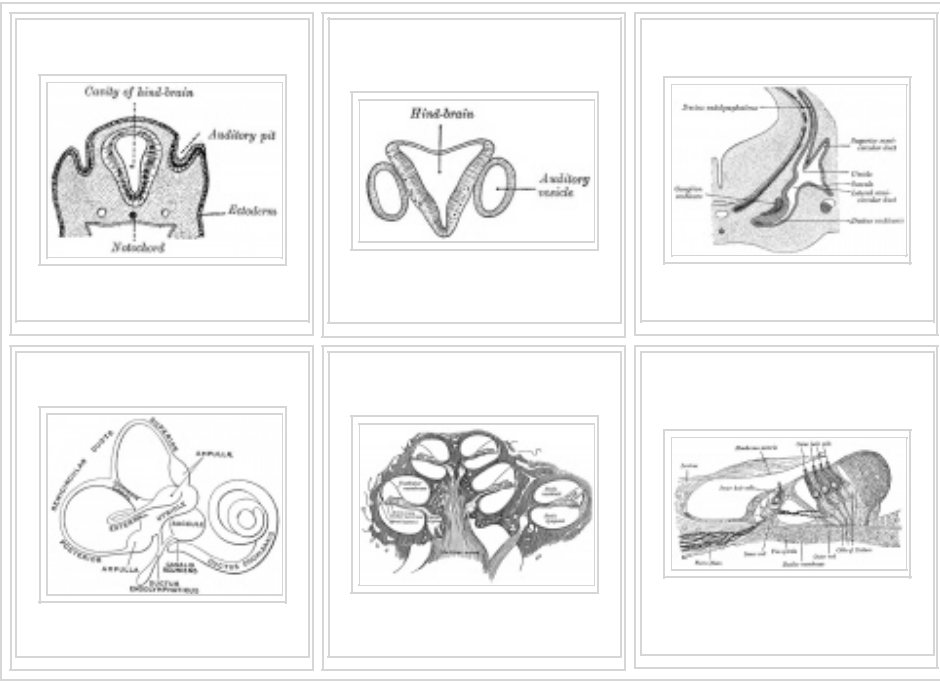


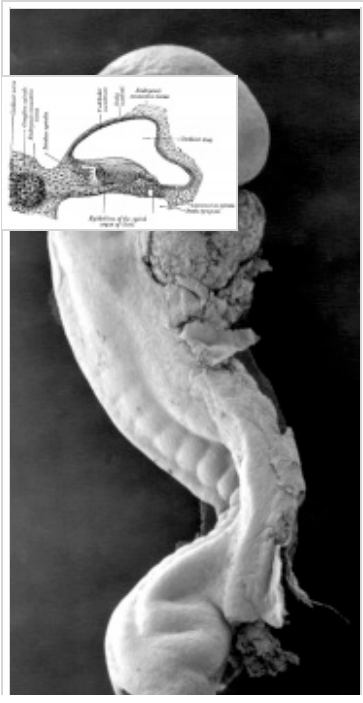
Pharyngeal arch cartilages

Middle Ear Genes - gooscoid, RARs, Prx1, Otx2, Hoxa1, Hoxb1, endothelian related molecules

Inner

Otocyst



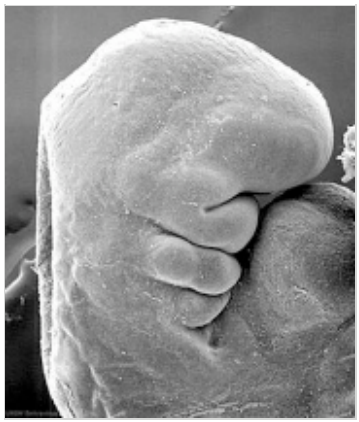


- week 3 otic placode forms on surface ectoderm
- otic placode sinks into mesoderm
- forms otocyst (otic vesicle)
- branches form and generate endolymphatic duct and sac
- forms vestibular (dorsal) and cochlear (ventral) regions
- differentiation of otic vesicle to membranous labyrinth

Carnegie Stage 12 otic placode

Vestibular Sac

- generates 3 expansions - form semicircular ducts
- remainder forms utricle
- epithelia lining generates - hair cells, ampullary cristae, utricular macula
- Vestibular - Otoconia, otoconin- inner ear biominerals



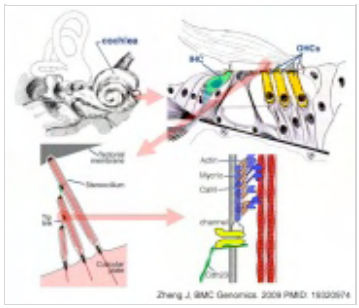
Carnegie Stage 13 otic vesicle

Cochlear sac

- generates coiled cochlear duct (humans 2 1/2 turns)
- remainder forms saccule
- epithelia lining generates
- hair cells
- structures of organ of corti
- saccular macula

Bony Labyrinth

- formed from chrondified mesoderm
- Periotic Capsule
- mesenchyme within capsule degenerates to form space filled with perilymph



Inner ear hair cells

Vestibulocochlear Nerve

- forms beside otocyst
- from wall of otocyst and neural crest cells
- bipolar neurons
- vestibular neurons
  - outer end of internal acoustic meatus
  - innervate hair cells in membranous labyrinth
  - axons project to brain stem and synapse in vestibular nucleus
- cochlear neurons
  - cell bodies lie in modiolus
  - central pillar of cochlear
  - innervate hair cells of spiral organ
  - axons project to cochlear nucleus

Inner Ear Genes

- hindbrain segmentation occurs at same time placode arises
- otocyst adjacent to rhombomere 5
- may influence development
- Hoxa1, kreisler, Fgf3
- genes regulating neural crest cells (neural genes)
- Pax2 Ko affects cochlear and spiral ganglion, but not vestibular apparatus
- nerogenin 1 affects both ganglia

Semicircular canal

- Otx1- cochlear and vestibular normal

- Hmx3, Prx1, Prx2

Sensory Organs

- thyroid hormone receptor beta
- Zebrafish-mindbomb mutant has excess hair cells but not supporting cells, Notch-Delta signaling

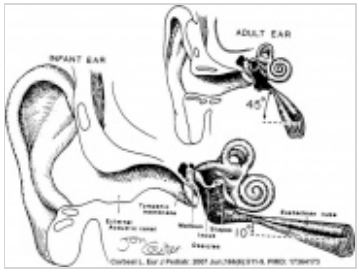
- Gene Expression-inner ear

- Brn-3c and Hair cell development
- Supporting Cells- p27kip
- Thyroid Hormone
- Ganglion neurons require growth factors
- vestibular neurons- BDNF, NT3
    - survival not development

Postnatal Changes

Newborn to adult Eustachian (auditory, otopharyngeal or pharyngotympanic) tube.

- Connects middle ear cavity to nasopharynx portion of pharynx



Eustacian tube angle changes

Functions

- Ventilation - pressure equalization in the middle ear
- Clearance - allow fluid drainage from the middle ear Tube is normally closed and opened by muscles

At birth

- shorter (17-18 mm), narrower and runs almost horizontal Tube is opened by a single muscle, tensor palati muscle

Adult

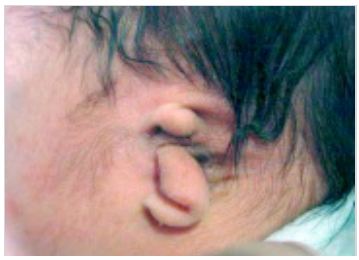
- longer (twice as long), wider and runs at approximately 45 degrees to the horizontal. Tube is opened by two separate muscles, tensor palati and levator palati

Abnormalities

- Inner - common cavity, severe cochlear hypoplasia
- Middle - rare and can be part of first arch syndrome, Malleus, Incus and Stapes Fixation
    - Cholesteatoma- Epithelium trapped within skull base in development, erosion of bones: temporal bone, middle ear, mastoid
- Outer - Several genetic effects and syndromes, Environmental Effects

Outer Ear Abnormalities

- Microtia - abnormally small external ear
- Preauricular sinus - occurs in 0.25% births, bilateral (hereditary) 25-50%, unilateral (mainly the left), duct runs inward can extend into the parotid gland, Postnatally sites for infection



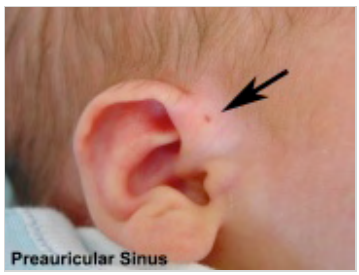
Fetal Alcohol Syndrome

- Postion- Lower or uneven height, "railroad track" appearance, curve

at top part of outer ear is under-developed, folded over parallel to curve beneath

Microtia

Congenital Deafness

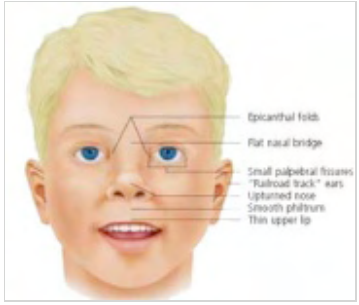


Preauricular sinus

Sensorineural - cochlear or central auditory pathway

- Hereditary
- recessive- severe
- dominant- mild
  - can be associated with abnormal pigmentation (hair and irises)

- Acquired
  - rubella (German measles), maternal infection during 2nd month of pregnancy, vaccination of young girls
  - streptomycin
  - antibiotic
  - thalidomide



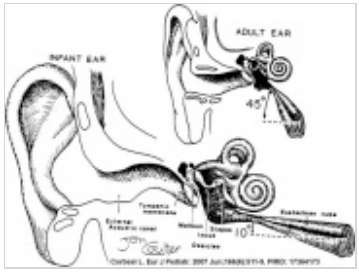
Fetal Alcohol Syndrome Face

Conductive - disease of outer and middle ear

- produced by otitis media with effusion, is widespread in young children.
- temporary blockage of outer or middle ear

Bionic Ear

Cochlear Implant - Professor Graeme Clark (1960s, Australia) Array of electrodes implanted within cochlea, direct electrical stimulation to auditory nerve fibres



Eustacian tube angle

Conductive Hearing Loss

- Conductive Hearing Loss Produces a Reversible Binaural Hearing Impairment David R. Moore, Jemma E. Hine, Ze Dong Jiang, Hiroaki Matsuda, Carl H. Parsons, and Andrew J. King J. Neurosci. 1999;19 8704-8711 http://www.jneurosci.org/cgi/content/abstract/19/19/8704
  - tested ferrets by lon-term plugging of ear canal
  - Repeated testing during the 22 months after unplugging revealed a gradual return to normal levels of unmasking.
  - Results show that a unilateral conductive hearing loss, in either infancy or adulthood, impairs binaural hearing both during and after the hearing loss.
  - Show scant evidence for adaptation to the plug and demonstrate a recovery from the impairment that occurs over a period of several months after restoration of normal peripheral function.

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- **Before We Are Born** (5th ed.) Moore and Persaud Chapter 20: p460-479
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- **Neuroscience** Purves, Dale; Augustine, George J.; Fitzpatrick, David; Katz, Lawrence C.; LaMantia, Anthony-Samuel; McNamara, James O.; Williams, S. Mark. Sunderland (MA): Sinauer Associates, Inc. ; c2001 The Auditory System (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.chapter.879) | The Inner Ear (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.section.894) | The Middle Ear (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.section.893) | The External Ear (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.section.891) | Early Brain Development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.chapter.1447) | Construction of Neural Circuits (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.chapter.1546) | Modification of Brain Circuits as a Result of Experience (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=neurosci.chapter.1640)

- **Molecular Biology of the Cell** (4th Edn) Alberts, Bruce; Johnson, Alexander; Lewis, Julian; Raff, Martin; Roberts, Keith; Walter, Peter. New York: Garland Publishing; 2002. Neural Development (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.section.3963) | The three phases of neural development (http://www.ncbi.nlm.nih.gov:80/books/bv.fcgi?db=Books&rid=mboc4.figgrp.3966)

- **Clinical Methods** 63. Cranial Nerves IX and X: The Glossopharyngeal and Vagus Nerves (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cm.chapter.1949) | The Tongue (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cm.chapter.3847) | 126. The Ear and Auditory System (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cm.chapter.3777) | An Overview of the Head and Neck - Ears and Hearing (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cm.chapter.3627#3654) | Audiometry (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cm.chapter.3897)

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- **Eurekah Bioscience Collection**Cranial Neural Crest and Development of the Head Skeleton (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=eurekah.chapter.53006)

Search

- **Bookshelf** hearing development (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=hearing+development)

- **Pubmed** hearing development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=hearing+development)

Links

- UNSW Embryology - Systems Notes - Hearing (http://embryology.med.unsw.edu.au/Notes/ear.htm) | Systems Notes - Senses (http://embryology.med.unsw.edu.au/Notes/senses.htm)

- Embryo Images - Hearing (http://www.med.unc.edu/embryo_images/unit-ear/ear_htms/eartoc.htm)
- NIDCD - Balance Disorders (http://www.nidcd.nih.gov/health/balance/balance_disorders.asp)

Terms

altricial animal - Term used to describe an animal born in a helpless state, with incomplete development of sensory systems at birth. For example rats and mice are born with incomplete development of visual and auditory systems.

ampulla - Term used to describe an anatomical dilation of a tube or canal lumen. Anatomical description of the opening end of the uterine tube lying above the ovary and the enlarged initial segmeny of the semicircular canals of the inner ear vestibular system. (More? [ear6.htm Inner Ear] | [genitalXXuterus.htm Genital System - Female Uterus])

aneurism - (Greek, *aneurysma* = a widening, aneurysm) A term used to describe an abnormal widening of a vessel or anatomical tubal structure.

aquaeductus vestibuli - see vestibular aqueduct

auditory neuropathy - (AN) abnormality of transmission of sound information to the brain.

auditory tube - (eustachian tube) between the middle ear and oral cavity, has a bony (tympanic 1/3) and cartilaginous (pharyngeal 2/3) portion. The main role is equalization of pressure and fluid drainage in the middle ear.

auricular hillock - see hillock

atresia - narrowing, usually of an anatomical tube or cavity.

autophagocytosis - (Greek, auto = self, phagy = eating, also called autophagy) a cell death mechanism that uses the cell's own lysosomes to self digest.

border cells - columnar cells within the organ of Corti on the medial portion of the basilar membrane.

canalis reuniens - (ductus reuniens, canaliculus reuniens, canalis reuniens, Hensen's canal, Hensen's duct, uniting canal, canalis reuniens of Hensen) short narrow canal connecting the cochlea duct to the saccule. (Victor Hensen, 1835-1924)

cerumen - (ear wax) produced by glands in the skin of the outer portion of the ear canal.

chondrified - the developmental differentiation of cartilage from mesenchye, an embryonic connective tissue.

cristae ampullaris - located in the ampulla of the membranous semicircular canals a region with both supporting and hair cells. The hair cell cilia are embedded in the gelatinous cupula.

claudius cells - (cells of Claudius) columnar cells with microvilli overlying the basilar membrane and extend from Hensen's cells to the spiral prominence. Barrier cells that lie external to the organ of corti in endolymph.

cochlear sac - embryonic structure, which will form the coiled cochlear duct and contribute to the saccule.

cochlear aqueduct - a bony channel containing the fibrous periotic duct. It connects the basal turn of the cochlea perilymphatic space with the subarachnoid space of the posterior cranial cavity.

cochlin - major constituent of the inner ear extracellular matrix.

collagen type II - major constituent of the inner ear extracellular matrix.

conductive loss - term used to describe one of the two major classes of hearing loss involving external and middle ear abnormalities (other form is Sensorineural loss).

connexins - channel proteins of the gap junctions that allow rapid communication between adjacent cells. The two connexins Cx26 and Cx30 are the major proteins of cochlear gap junctions.

connexin 26 - A strikingly high proportion (50%) of congenital bilateral nonsyndromic sensorineural deafness cases have been linked to mutations in the GJB2 coding for the connexin26

cupular deposits - basophilic material on the cupulae of the semicircular ducts, an postnatal ageing phenomenon seen in some vestibular labyrinth.

clinical weeks - taken from last menstrual period (LMP) and therefore approximately two weeks before fertilization occurs.

Deiters' cells

discoidin domain receptor 1 - (DDR1) a tyrosine kinase receptor activated by native collagen, expressed in the basement membrane and with fibrillar collagens. Found in basal cells of the stria vascularis, type III fibrocytes, and cells lining the basilar membrane of the organ of Corti. {Meyer zum Gottesberge, 2008 #1877}

ductus utriculosaccularis -

endochondral ossification - the process of bone formation from a pre-existing cartilage template.

endoderm -

endolymphatic fluid -

endolymphatic sac - inner ear structure that has anatomically both an intraosseous and extraosseous component. Th e sac has functions regulating endolymph that are both secretory and absorptive. Also the site of endolymphatic sac tumors either sporadical occurring or associated with the autosomal-dominant von Hippel-Lindau (VHL) disease, due to a germ line mutation.

embryological weeks - taken from the time of fertilization which typically occurs around the middle (day 14), or just after, of the typical 28 day menstrual cycle.

Emx2 - homeobox gene affecting middle ear and inner ear development.

eustachian tube - (auditory tube) A cavity linking the pharynx to the middle ear, which develops from the first pharyngeal pouch. Named after Bartolomeo Eustachi (1500 - 1574) an Italian anatomist.

external auditory meatus - (ear canal) develops from the first pharyngeal cleft.

ear wax - see cerumen.

epithelia -

espins - calcium-resistant actin-bundling proteins enriched in hair cell stereocilia and sensory cell microvilli and spiral ganglion neurons (SGNs)

eustachian tube - (auditory tube) between the middle ear and oral cavity, equalization of pressure in the middle ear.

external auditory canal -

fenestra ovalis - (oval window) separates the tympanic cavity from the vestibule of the osseous labyrinth.

fenestra rotunda - (round window) separates the tympanic cavity from the scala tympani of the cochlea.

fetus - (foetus) term used to describe human development after the 8th week (10th clinical week, LPM) and covers the developmental periods of second and third trimester.

fibroblast growth factor 1 - (Fgf-1) a growth factor released from cochlea sensory epithelium which stimulates spiral ganglion neurite branching.

fibroblast growth factor 8 - (Fgf-8) a growth factor released by inner hair cells which regulates pillar cell number, position and rate of development.

fibroblast growth factor receptor 3 - (Fgfr-3) a tyrosine kinase receptor with a role in the commitment, differentiation and position of pillar cells in the organ of corti

fundamental frequency - (natural frequency) the lowest frequency in a harmonic series, for the female voice this is about 225 Hz.

helicotrema - term used to describe the cochlear apex.

Hes - (hairy and enhancer of split) family of factors, which has been shown to be a general negative regulator of neurogenesis {Zheng, 2000 #1936}.

hillock - a small hill, used to describe the six surface elevations on pharyngeal arch one and two.

Hindbrain - Invaginate -

Incus - (anvil) auditory ossicle

inner phalangeal cells

inner pillar cells - organ of Corti cells arranged in rows and form a boundary between the single row of inner hair cells and three rows of outer hair cells. These cells have surface-associated microtubule bundles.

inner sulcus - area of the cochlear duct

interdental region -

internal auditory meatus - (internal acoustic meatus, IAM) Anatomical canal in which CN VII and CN VIII ganglia reside and pass through to the brainstem. This bony canal lies between the posterior surface of the petrous pyramid and the bony labyrinth within the dense petrous bone. Also associated clinically with the site where acoustic neuromas may occur.

Kolliker's organ - (Kollicker's organ, greater epithelial ridge) Developing cochlear structure consisting of columnar-shaped supporting cells filling the inner sulcus and lying directly under the tectorial membrane. This transient organ regresses and generates the space of the inner sulcus. Rudolph Albert von Kolliker (1817-1905)??

lateral semicircular duct - Limbus -

LMP - acronym for last menstrual period, used to clinically measure gestation.

malleus - (hammer) auditory ossicle

mastoid process - of temporal bone

Math1 - homolog of the Drosophila proneural gene atonal, necessary and sufficient for the production of hair cells in the mouse inner ear. {Chen, 2002 #1932}Negatively regulated by Hes1 and Hes5

meatal plug - temporary blockage of the external auditory meatus which forms at the end of the embryonic period and remains present until the seventh month.

meatus - anatomical opening, cavity or space (external acoustic meatus,internal auditory meatus)

Meckel's cartilage - first pharyngeal ach cartilage, located within the mandibular prominence. This cartilage first appears at stage 16, stage 20 the beginning of membranous ossification. Named after Johann Friedrich Meckel, (1781 - 1833) a German anatomist. (http://www.whonamedit.com/doctor.cfm/1840.html)

membranous labyrinth - Mesenchyme - Mesoderm - Microtia - Modiolus -

mucopolysaccharidosis - (MPS IIIB, Sanfilippo Syndrome type B) abnormality caused by a deficiency in the lysosomal enzyme N-acetyl-glucosaminidase (Naglu). Children with MPS IIIB develop abnormal hearing, and mental functioning culminating in early death.

netrin-1 - secreted growth factor, expressed in the organ of Corti and spiral ganglion cells, role in process outgrowth.

neural tube -

olivocochlear - brainstem cholinergic and GABAergic efferent system that innervates sensory cells and sensory neurons of the inner ear.

organ of Corti - organ of Corti protein II - (OCP-II) cytosolic protein or transcription factor?

otolithic membrane - extracellular matrix that cover the sensory epithelia of the inner ear.

ossicle - (small bone) the individual bone of the three middle ear bones (auditory ossicles), which reduce vibrational amplitude but increase force to drive fluid-filled inner ear.

ossify -

otic capsule -

otic cup

otic placode -

otic vesicle -

otoconin - inner ear biominerals required for vestibular apparatus function.

otogelin - (Otog) an inner ear specific glycoprotein expressed in cochlea cells at different developmental times.

otolithic membrane - a membrane within the utricle and saccule containing embedded hair cell cilia and small crystalline bodies of calcium carbonate (otoliths). Functions to detect head motion.

otoliths - small crystalline bodies of calcium carbonate found within the otolitic membrane of the utricle and saccule.

ototoxic - compound or drug causing temporary or permanent hearing loss.

outer hair cells - (OHCs) three rows of hair cells that function to increase basilar membrane motion through a local mechanical feedback process within the cochlea, the "cochlear amplifier".

outer pillar cells - arranged in rows and form a boundary between the single row of inner hair cells and three rows of outer hair cells.

paratubal musculature - muscles lying beside the auditory (Eustachian) tube. The tensor veli, palatini (TVP) and tensor tympani muscles.

perilymph - perilymphatic space - Periotic Capsule - petrous portion - of temporal bone

pejvakin gene - in humans, two missense mutations in this gene cause nonsyndromic recessive deafness (DFNB59) by affecting the function of auditory neurons.

pharyngeal archpharyngeal pouchpharyngeal membranePharynx

pillar cells - (PC) form an inner and outer row of support cells that form a boundary between inner and outer hair cells.

Placode

preyer reflex - ear flick in mouse in response to sound.

presbyacusis

prestin - a motor protein structurally similar to the anion transporter family expressed in cochlear outer hair cells.

preauricular tag - skin tags located in front of the external ear opening, are common in neonates and in most cases are normal, though in some cases are indicative of other associated abnormalities.

primordium-

protocadherin 15 - (Pcdh15) required for initial formation of stereocilia bundles and changes in the actin meshwork within hair cells. The Ames waltzer (av) mouse mutant has both auditory and vestibular abnormalities from a mutation in this gene.

Reichert's cartilage - pharyngeal ach 2 cartilage, named after Karl Bogislaus Reichert (1811 - 1883) a German anatomist.

Reissner's membrane - (vestibular membrane, vestibular wall) is a membrane located inside the cochlea separating the scala media from scala vestibuli. Named after Ernst Reissner (1824-1878) a German anatomist. ‚ÄúIt primarily functions as a diffusion barrier, allowing nutrients to travel from the perilymph to the endolymph of the membranous labyrinth.

rhombomere -

Saccular macula -

Saccule - (Latin, sacculus = a small pouch)

sacculocollic reflex -

scala tympani - one of the three Cochlea cavities, it is filled with perilymph.

Scarpa's ganglion - (vestibular ganglion) primary afferent vestibular neuron ganglion of the vestibular nerve. Located within the internal auditory meatus.

semicircular canals - series of fluid-filled loops of the inner ear required for balance and sensing acceleration.

sensorineural - term used to describe one of the two major classes of hearing loss involving the central pathway from the cochlear (other form is conductive loss).

space of Nuel - within the cochlea, an organ of Corti space between the outer pillar cells and the phalangeal and hair cells. Named after Jean-Pierre Nuel (1847-1920) a Belgian ophthalmologist.

spiral ganglion neurons - (SGN) innervate the inner (Type I) and outer (Type II) hair cells of the cochlea.

stapedius muscle - (innervated by CN VII tympanic branch) one of the two muscles in the middle ear,

contraction of this muscle pulls the stapes and dampens auditory ossicle movement.

stapes - (stirrup) a middle ear auditory ossicle (bone).stapes footplate - startle response -

stereocilia -finger-like projections from the apical surface of sensory hair cells forming the hair bundle in the cochlea. Formed by tightly cross-linked parallel actin filaments in a paracrystalline array with cell surface specializations (tip links, horizontal top connectors, and tectorial membrane attachment crowns).

stratified squamous epithelia - classification of epithelium which transiently forms a plug in external ear canal to the outer eardrum.

stria vascularis - forms the outer wall of the cochlear duct of the mammalian cochlea is composed primarily of three types of cells. Marginal cells line the lumen of the cochlear duct and are of epithelial origin. Basal cells also form a continuous layer and they may be mesodermal or derived from the neural crest. Intermediate cells are melanocyte-like cells, presumably derived from the neural crest, and are scattered between the marginal and basal cell layers. The stria forms endolymph and also contains a rich supply of blood vessels.

sulcus -

synostotically - anatomically normally separate skeletal bones fused together.

tectorial membrane - extracellular matrix that cover the sensory epithelial hair cells of the organ of corti within the cochlea.

alpha-tectorin and beta- (TECTA, TECTB) major non-collagenous protein component of the tectorial membrane forming a striated-sheet matrix. Synthesized as glycosylphosphatidylinositol-linked, membrane bound precursors.

temporal bone -

tensor tympani - (innervated by CN V mandibular nerve) one of the two muscles in the middle ear, contraction of this muscle pulls the malleus and tenses the tympanic membrane, dampening auditory ossicle movement. The muscle arises from auditory tube (cartilaginous portion) and is inserted into the malleus (manubrium near the root).

teratogens - trilaminar embryo -

tonotopy - term describing the mapping along the tectorial membrane within the cochlea of the different sound frequencies.

tympanic cavity - tympanic membrane -Utricle -Vacuolization - Vesicle - vestibular apparatus - vestibular evoked myogenic potential (VEMP) test

vestibular ganglion - (Scarpa's ganglion) primary afferent vestibular neuron ganglion of the vestibular nerve. Located within the internal auditory meatus.

vestibular membrane - (Reissner's) extends from the spiral lamina to the outer wall and divides the cochlea into an upper scala vestibuli, a lower scala tympani.

Vestibulocochlear Nerve - Cranial Nerve VIII

Whirlin - A PDZ scaffold protein expressed in hair cells at the stereocilia tips, essential for the stereocilia elongation process. The DFNB31 gene mutations cause hearing loss in human and mouse. This protein can interact with membrane-associated guanylate kinase (MAGUK) protein, erythrocyte protein p55 (p55).

Wnt7a - signaling through the Wnt pathway regulates the development of hair cell unidirectional stereociliary bundle orientation.

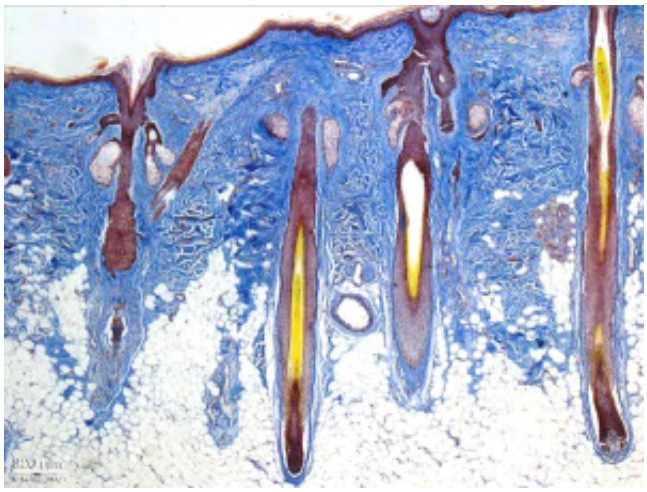
2009 Lecture 18

From Embryology

Contents

Integumentary System

Introduction



The skin provides a barrier between ourselves and our environment, it also contains specializations in different regions including hair, nails, glands and sensory receptors.

The two major tissue organizations of epithelial (ectoderm, epidermis) and mesenchyme (mesoderm connective tissue, dermis and hypodermis) are shown within skin. In addition, we have aslo extensive populating by melanocytes (neural crest) and sensory nerve endings.

It remains today as possibly the first epithelial specialization from which arose other epithelial specializations now located inside the body. The external skin specializations have many different roles and functions. This system is also an excellent model for distribution or "pattern" that is of interest.

Textbooks

- **Human Embryology** Larson Chapter 14 p443-455
- **The Developing Human: Clinically Oriented Embryology** (6th ed.) Moore and Persaud Chapter 20: P513-529

Lecture Audio Lecture Date: 29-09-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Integumentary (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48843)

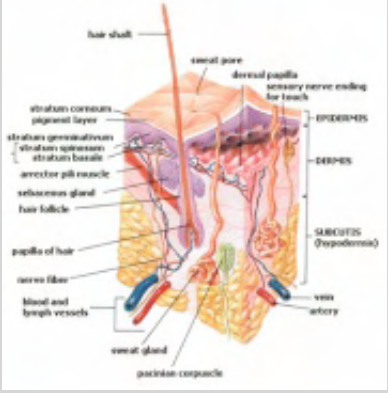
Objectives

- Understand the embryonic origin and differentiation of the epidermis and dermis.
- Understand the formation of hair and nails.
- Understand the formation of sweat glands, mammary glands.

- Understand the formation of teeth.
- Brief understanding of associated abnormalities.

Skin Origins

Skin is our largest organ, providing a protective layer between us and our environment



Skin structure

- **Ectoderm** forms the surface epidermis and the associated glands.
- **Mesoderm** forms the underlying connective tissue of dermis and hypodermis.
- **Neural crest** cells also migrate into the forming epidermis and the skin is also populated by specialized sensory endings.
- epithelia/mesenchyme (ectoderm/mesoderm) interaction an inductive manner (last weeks lecture on kidney)
- 2 main types of histological skin - thin (most of body) thick (soles of feet and hands) based on ectoderm, not the thickest skin including dermis (top of back)

Regional Specializations

- skin has different structures associated with different regions of the body
- nails, hail, glands, teeth, eyelashes, eyebrow

Development Overview

4 weeks

- simple ectoderm epithelium over mesenchyme.

1-3 months

- ectoderm - germinative (basal) cell repeated division of generates stratified epithelium.
- mesoderm - somite dermatome spreads out under the epithelium, differentiates into connective tissue and blood vessels.

4 months

- basal cell- proliferation generates folds in basement membrane.
- neural crest cells- (melanocytes) migrate into epithelium. These are the pigment cell of the skin.
- embryonic connective tissue- differentiates into dermis, a loose ct layer over a dense ct layer. Beneath the dense ct layer is another loose ct layer that will form the subcutaneous layer.
- Ectoderm contributes to nails, hair follictles and glands.
- Nails form as thickening of ectoderm epidermis at the tips of fingers and toes. These form germinative cells of nail field.
- Cords of these cells extend into mesoderm forming epithelial columns. These form hair follocles, sebaceous and sweat glands.

5 months

- Hair growth initiated at base of cord, lateral outgrowths form associated sebaceous glands.
- Other cords elongate and coil to form sweat glands.
- Cords in mammary region branch as they elongate to form mammary glands. These glands will

complete development in females at puberty. Functional maturity only occurs in late pregnancy.

Epidermis

- week 4-5 early skin is a single ectodermal layer, stratum germinativum basal layer
- week 11 forms intermediate layer
- periderm then lost replaced by stratum corneum, keratinization and desquamification
- week 10 epidermial ridges are formed by proliferation

Neural crest cells

- Neural crest cells migrate into skin (late embryonic) form melanoblasts
- day 40-50 differentiate into then melanocytes - form pigment granules
- different content of melanin (Greek, *melas* = "black") accounts for differet skin colour

Dermis

- lateral plate mesodermal in origin
- forms connective tissue
- afferent nerves influence dermal ridge formation

Dermal pattern fingerprint

Blood Vessels

- lateral plate mesodermal in origin
- week 5 blood vessels form in mesenchyme
- form capillary beds, extensive remodelling with development

Skin Dermatomes

- pattern of skin innervation
- area supplied by single spinal nerve
- motor and sensory DRG
- cutaneous nerve area

Keratin

- large family of intermediate filament protein, 17+ isoforms
- skin disease associated with mutations in keratin genes

Keratins are the major structural proteins of the vertebrate epidermis and its appendages, constituting up to 85% of a fully differentiated keratinocyte. Together with actin microfilaments and microtubules, keratin filaments make up the cytoskeletons of vertebrate epithelial cells. Traced as far back in the evolutionary kingdom as mollusks, keratins belong to the superfamily of intermediate filament (IF) proteins that form alpha-helical coiled-coil dimers which associate laterally and end-to-end to form 10-nm diameter filaments. The evolutionary transition between organisms bearing an exoskeleton and those with an endoskeleton seemed to cause considerable change in keratin. Keratins expanded from a single gene to a multigene family. Of the approximately 60 IF genes in the human genome, half encode keratins, and at least 18 of these are expressed in skin. Vertebrate keratins are subdivided into two sequence types (I and II)

that are typically coexpressed as specific pairs with complex expression patterns. The filament-forming capacity of a pair is dependent upon its intrinsic ability to self-assemble into coiled-coil heterodimers, a feature not required of the invertebrate keratins (Weber et al 1988). Approximately 20,000 heterodimers of type I and type II keratins assemble into an IF. Mutations that perturb keratin filament assembly in vitro can cause blistering human skin disorders in vivo. (from Review Article)

Development of Glands

- 2 main types - sebaceous and sweat
- both ectodermal in origin
- form as ingrowth of ectoderm into the mesoderm

Sebaceous

- associated with hair development
- except plans penis and labia minora
- these glands secrete vernix

Sweat Glands

- mostly eccrine some apocrine
- apocrine in axilla, pubic and nipple regions
    - see also mammary gland development

Vernix Caseosa

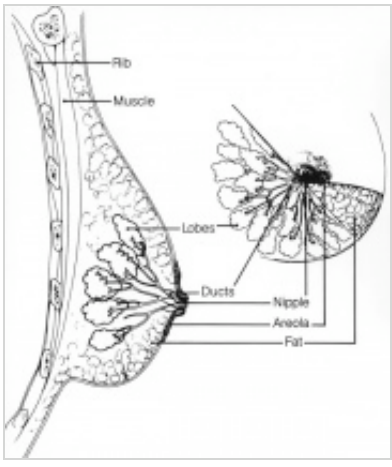
- (Latin, *vernix caseosa* = varnish)
- covers fetal skin- secretion from sebaceous glands
- protects skin from extraembryonic fluids amnion, urine
- slippery and helps with parturition

Mammary Glands

UNSW Embryology - Mammary Glands (http://embryology.med.unsw.edu.au/Notes/skin7a.htm)

- week 6 epidermis downgrowth into dermis, modified sweat glands
    - epithelia/mesenchyme inductive interaction, mesenchyme forms connective tissue and fat
- mammary ridges - mammary bud formation, pair of ventral regions axilla to inguinal
    - pectoral regions generate breasts
- buds branch to form lactiferous ducts, only main duct formed at birth

- mammary pit - forms fetal period
- areola - depressed region at gland, proliferation of connective tissue postnatally
- prior to puberty male and female glands the same



Mammary anatomy

Puberty

- sex hormone estrogen stimulate growth, full development approx 20 years

- growth also influenced by other hormones - progereterone, prolactin, corticoids, growth hormone
- mainly fat and connective tissue deposition

Pregnancy

- raised estrogens and progesterone stimulate gland development
- hemispherical shape due to fat deposition
- lactation supports development

Breast cancer

- In 1994, two breast cancer susceptibility genes were identified: BRCA1 on chromosome 17 BRCA2 on chromosome 13
- When an individual carries a mutation in either BRCA1 or BRCA2, they are at an increased risk of being diagnosed with breast or ovarian cancer at some point in their lives. Normal function of these genes was to participate in repairing radiation-induced breaks in double-stranded DNA. It is though that mutations in BRCA1 or BRCA2 might disable this mechanism, leading to more errors in DNA replication and ultimately to cancerous growth.

Breast Cancer Detection - reduce mortality is through early detection (general screening of the population for BRCA1 and BRCA2 is not yet recommended). New strategies to find anti-cancer drugs are constantly being developed. The latest, called 'synthetic lethal screening' looks for new drug targets in organisms such as yeast and fruit flies. In the same way that studies in yeast recently helped to identify the functions of BRCA1 and BRCA2, it is thought that drugs that work in more primative organisms will also be applicable to humans.

Hair Development

UNSW Embryology - Hair (http://embryology.med.unsw.edu.au/Notes/skin8.htm)

Hair formation, or follicle development, is an example of two distinct developmental processes: epithelio-mesenchymal interactions and pattern formation. The differentiated hair follicle will eventually contain 20 or more different cell types. Melanocytes, which provide the hair colour, have a neural crest origin, and with ageing their numbers decline leading to whitening (grey) of the hair process.

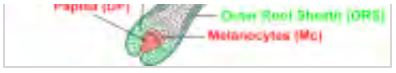
Hair follicle development in humans begins as an epithelial-mesenchymal interaction at week 9 - 12. This initial lanugo hair is replaced in the late fetal or early neonate by vellus and terminal hairs. A second round of development occurs during puberty under the influence of steroidal hormones (More? Puberty).

- Before birth we have embryonic hair that has an imporant role in binding the skins waxy protective coating against our watery environment.
- After birth we have early postnatal hair that is gradually replaced by the mature form.
- At puberty we have a second round of hair formation under endocrine regulation by sex hormones.
- The hair follicle is also a site for stem cells, allowing replacement of the follicle.

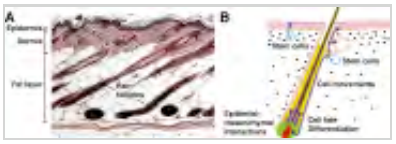
Hair Follicle

- follicle forms in stratum germinativum of epidermis
- **hair bud** then hair bulb forms hair
- mesenchyme forms hair papilla
- germinal matrix cells become keratinized to form hair shaft
- week 12 - lanugo hair (Latin, *lana* = wool) - first hair formed

replaced postnatally, role in binding vernix to skin
- arrector pili muscle - develop in mesenchyme and form the muscles that move hair.
- hair colour - melanocytes (neural crest) produce melanin which influences hair colour.
- Puberty - coarse hair in pubis and axilla in both male and female (in males also on face and other body regions chest, etc)



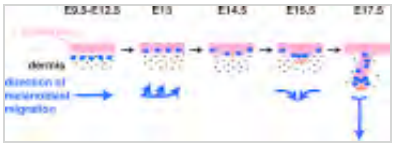
Hair development stages



Hair follicle cell development

Fetal Hair

- Month 5 - hair appears on the head and beginning of vernix caseosa deposition.
- Month 6 - body is covered by fine hairs (lanugo) and the deposit of vernix caseosa is considerable. Skin papilla are developed and the free border of the nail projects from the corium of the dermis.
- Month 8 - skin now completely coated with vernix caseosa, and the lanugo begins to disappear. Skin is also pink in colour and subcutaneous fat being deposited (hypodermis layer).
- Month 9 - lanugo has largely disappeared from the trunk.



Melanoblast migration

Lanugo Hair

- From about the third month lanugo hair (Latin, *lana* = wool) hiar is initially formed and it has a role in binding vernix to skin.
- Hair grows over the entire body at the same rate, so the hairs are the same length, and is shed abut 4 weeks before birth. Premature infants can still be covered with these hairs.

Neonatal Hair

Newborn infants have two types of hair:

- **Vellus Hairs** - short hairs, only a centimetre or two long, and contain little or no pigment, follicles that produce them do not have sebaceous glands and never produce any other kind of hairs
- **Terminal Hairs** - long hairs that grow on the head and in many people on the body, arms and legs, produced by follicles with sebaceous glands, the hairs in these follicles gradually become thinner and shorter until they look like vellus hairs

Hair Follicle Phases

There are several phases of hair follicle growth.

- **Anagen Phase** - active phase
- **Catagen Phase** - apoptosis-driven involution, end of active growing phase of the life cycle of the hair, between growing phase (anagen) and resting stage (telogen).
- **Telogen Phase** - hair follicle resting phase of hair growth cycle.

Puberty Hair Development

The appearance of pubic hair occurs along with ther secondary sexual characteristics (also Tanner staged) and is under endocrine control.

- Estrogens- (1 beta-estradiol, E2) involved in skin physiology and are potent hair growth modulators.
- Testosterone- Face, trunk and extremities increases hair follicle anagen phase (active) and increases

also hair growth rate, thickness, medullation and pigmentation. Effects due to high hormone levels and target organ conversion to 5 alpha-dihydrotestosterone. Pubic hair develops even in absence of 5 alpha-reductase effect.

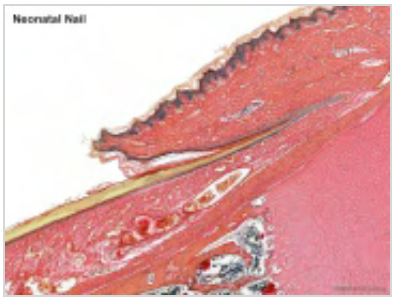
Tanner Stage	Pubic Hair Development
1	None
2	Few darker hairs along labia or at base of penis
3	Curly pigmented hairs across pubes
4	Small adult configuration
5	Adult configuration with spread onto inner thighs
6	Adult configuration with spread to linea alba

Table based upon the Tanner stages of secondary sexual development. (Tanner JM. Growth at Adolescence. 2nd ed. Oxford: Blackwell Scientific, 1962.)

Nail Development

UNSW Embryology - Nails (http://embryology.med.unsw.edu.au/Notes/skin12.htm)

- Forelimb before hindlimb - week 10 fingernails, week 14 toe nails
- nail field - appears at tip and migrates to dorsal surface
- thickened epidermis - surrounding cells form nail fold
- keratinization of proximal nail fold forms nail plate



Neonatal nail

Nails reach Digit Tip

- week 32 fingernails
- week 36 toenails
    - nail growth indicator of prematurity

Nail Terms

- nail plate - visible part of the nail
- nail bed - skin beneath the nail plate
- cuticle - tissue that overlaps the plate and rims the base of the nail
- nail folds - skin folds that frame and support the nail on three sides
- lunula - half-moon at the base of the nail
- matrix - hidden part of the nail unit under the cuticle

Embryo Images - Human (day 64) primary nail fields (http://www.med.unc.edu/embryo_images/unit-mslimb/mslimb_htms/mslimb026.htm)

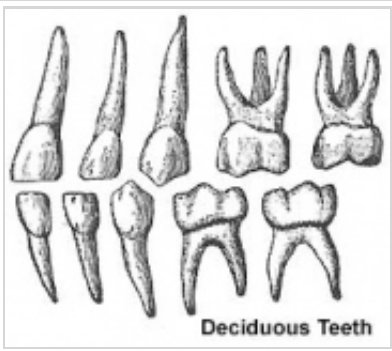
Teeth

UNSW Embryology - Teeth (http://embryology.med.unsw.edu.au/Notes/skin10.htm)

- integumentary system specialization by epitheilal/mesenchymal interactions in development and develops with a major contribution from the neural crest.
    - ectoderm of the first pharyngeal arch and neural crest,

ectomesenchymal cells.
- week 6 - odontogenesis begins, tooth bud
- 4 morphological stages describing the early tooth development: bud, cap, bell, and terminal differentiation
- 2 sets of teeth: 20 deciduous teeth, 32 permanent teeth
- differential rates of growth, shed at different times over 20 year period
- ectoderm, mesoderm and neural crest mesenchyme contribute
- inductive influence of neural crest with overlying ectoderm
- tooth growth occurs in ossifying jaws


Fetal Head (12 weeks) lateral



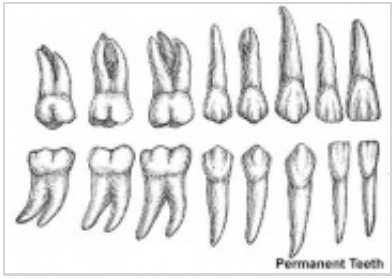
Deciduous teeth

odontoblasts

- neural crest-derived mesenchymal cells which differentiate under the influence of the enamel epithelium. Cells secrete predentin, calcifies to form dentin.

ameloblasts

- inner enamel epithelium forms pre-ameloblasts differentiate and produce enamel



Permanent teeth

periodontal ligament

- tooth is not anchored directly onto its bony socket (alveolar bone) but held in place by the periodontal ligament (PDL), a specialized connective tissue structure that surrounds the tooth root coating of cementum.
- ligament also act as; a shock absorber, transmitter of chewing forces (from tooth to bone), sensory information (heat, cold, pressure and pain).
    - collagen fiber bundles within the ligament are called "Sharpey's fibres".

Teeth Postnatal

Deciduous teeth

- 6-24 months erupt from gums by pushing toward surface
- 2 years - all deciduous teeth present

Permanent teeth

- 6 years until early adult
- tooth bud lie in gums beneath deciduous teeth
- osteoclasts resorb deciduous teeth roots
- growth affects face shape

Molecular

- Role of homeobox genes in the patterning, specification, and differentiation of ectodermal appendages in mammals. Duverger O, Morasso MI. J Cell Physiol. 2008 Aug;216(2):337-46. Review. PMCID: 18459147 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18459147) | Figure 1 Key steps in the development of three major ectodermal appendages (http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2561923&rendertype=figure&id=F1)

Abnormalities

The list below represents only a selection of associated abnormalities.

Skin

- **Ehlers-Danlos Syndrome** - (EDS I and EDS II) loose-jointedness and fragile, bruisable skin that heals with peculiar scars. The syndrome is caused by mutation in the collagen gene. Infants are born prematurely due to premature rupture of fetal membranes.
- **Epidermolysis Bullosa Simplex** - autosomal dominant disease of keratin, generating skin fagility and non-scarring blisters of the skin caused by little or no trauma. Four clinical subtypes: 1. EBS - Weber-Cockayne - mild blistering of the hands and feet 2. EBS - Koebner, 3. EBS - mottled pigmentation, 4. EBS - Dowling-Meara - generalized blistering which can be fatal.
- **Autosomal Recessive Congenital Ichthyosis** - an excessive keratinization disorder.
- **Cutis Aplasia** - congenital absence of the skin, particularly on the scalp, larger defects may extend to the dura or meninges. Generally isolated lesions, but can also be associated with a variety of other genetic disorders. Heals as a flat scar or keloid lump.
- **Incontinentia Pigmenti** - X-linked dominant disorder with most but not all cases affecting females. The skin changes follow characteristic four stages. In the neonatal period the first stage is noted with blisters often preceded or accompanied by erythema. These involve any part of the body but usually not the face. They do not cross the midline. These lesions are best seen in the second photograph in the groin and suprapubic region. The lesions follow a linear distribution in the limbs and circumferentially around the trunk. Crops of lesions may occur over a period of weeks to few months. During that stage, peripheral eosinophilia may be noted. The second stage follows and is characterised by hyperkeratosis or verrucous changes. At times the 2 stages occur simultaneously as noted in the first and third photograph. The third stage is that of hyperpigmentation typically appearing as streaks or whorls. It may be present throughout childhood. The fourth stage seen in teenage or adults is that of pale or atrophic streaks.
- **Haemangiomas** - relatively common (10% of infants), more common more common in preterm infants and girls. Initially present neonatally as a small "spot" or blanched vascular area which grows over the next 6 months before gradually involuting, usually over the next few years.

Breast

- occurs in 1% of female population
- **polymastia** - extra breast
- **polytheli** - extra nipple, supernumerary nipple (relatively common in males)

Hair

- **androgenetic alopecia** - male- and female-pattern hair loss.
- **telogen effluvium** - alteration of the normal hair cycle, due to many different stress stimuli (severe stress, chemotherapy, childbirth, major surgery, severe chronic illness, rarely occurance in vaccination)
- **alopecia areata** - autoimmune disease, form antibodies against some hair follicles, distinct circular pattern of hair loss.

Nail

- **Congenital hyponychia** or **anonychia** - (hyponychium is the thickened epidermis beneath the free distal end of the digit) fingernails and toenails are absent without significant bone anomalies.
    - **Total anonychia congenita** - all absent, is a rare condition and may have an autosomal

dominant inheritance patternis a rare condition, potentially autosomal dominant inheritance.
- **Nail-patella syndrome** - small, poorly developed nails and kneecaps, autosomal dominant inheritance.
- **Ectodermal dysplasias** - group of syndromes all deriving from abnormalities of the ectodermal structures.
- Brachydactylies

Teeth

- **adontia** - total lack of tooth development.
- **amelogenesis imperfecta** - abnormal tooth enamel formation (AMELX, ENAM, KLK4, MMP20).
- **dentinogenesis imperfecta** - discoloured teeth with an opalescent sheen, dentin does not support enamel (dentin sialophosphoprotein mutation)
- **dens evaginatus** - dental anomaly mainly affecting premolars in people of Mongolian origin.
- **hypodontia** - lack of development of one or more teeth.
- **hypohidrotic ectodermal dysplasia** - maldevelopment of one or more ectodermal-derived tissues.
- **microdontia** - small teeth.

Links

- UNSW Embryology - Introduction (http://embryology.med.unsw.edu.au/Notes/skin.htm) | Detailed Overview of Skin components (http://embryology.med.unsw.edu.au/Notes/skin3a.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Notes/skin2.htm) | Stage 13/14 (http://embryology.med.unsw.edu.au/Notes/skin3.htm) | Stage 22 (http://embryology.med.unsw.edu.au/Notes/skin4.htm) | Histology (http://embryology.med.unsw.edu.au/Notes/skin5.htm) | Dermatomes (http://embryology.med.unsw.edu.au/Notes/skin6.htm) | Glands (http://embryology.med.unsw.edu.au/Notes/skin7.htm) | Mammary Glands (http://embryology.med.unsw.edu.au/Notes/skin7a.htm) | Teeth (http://embryology.med.unsw.edu.au/Notes/skin10.htm) | Hair (http://embryology.med.unsw.edu.au/Notes/skin8.htm) | Nails (http://embryology.med.unsw.edu.au/Notes/skin12.htm)

- Teeth - University of Helsinki - Gene Expression in Tooth (http://bite-it.helsinki.fi/) | American Dental Association Overview - Tooth (http://www.ada.org/public/topics/tooth.asp) | Columbia University Medical Centre - Illustrations: How a Tooth Decays (http://www.simplestepsdental.com/SS/ihtSS/r.WSIHW000/st.31843/t.31886/pr.3.html) | Merck - Tooth disorders (http://www.merck.com/mmhe/sec08/ch114/ch114a.html) | Nemours Foundation - Teething Tots (http://kidshealth.org/parent/pregnancy_newborn/common/teething.html)

- Neonatal Dermatology - NZ National Women's Health (http://www.adhb.govt.nz/newborn/TeachingResources/Dermatology/Dermatology.htm)
- Dermatology Image Atlas - DermAtlas (http://dermatlas.med.jhmi.edu/derm/)

References

- Before We Are Born (5th ed.) Moore and Persaud Chapter 21: P481-496
- Essentials of Human Embryology Larson Chapter 14: P303-315
- Color Atlas of Clinical Embryology Moore Persaud and Shiota Chapter 15: p231-236

- Nature - Milestones in Cutaneous Biology (http://www.nature.com/milestones/skinbio/index.html) "highlights groundbreaking advances in cutaneous biology over the past 100 years."
- International Journal Developmental Biology 2004 - Skin Development special issue

(http://www.ijdb.ehu.es/04023contents.htm)

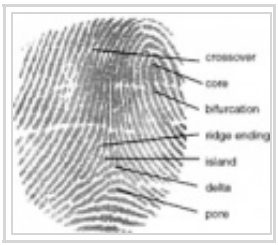
Online Textbooks

Developmental Biology 6th ed. Gilbert, Scott F. Sunderland (MA): Sinauer Associates, Inc.; c2000. Development of the hair follicles in fetal human skin (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.figgrp.2934) | Image - Coordinated differentiation and morphogenesis in the mammalian tooth (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.figgrp.3140) | Tooth Development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=dbio.box.3139)

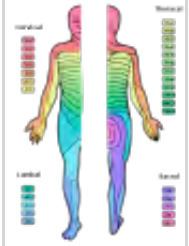
Eurekah Bioscience Collection Role of GLI proteins in embryonic hair follicle development (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=eurekah.figgrp.42334)

Molecular Biology of the Cell FGF5 is a negative regulator of hair formation (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=mboc4.figgrp.1651)

Images



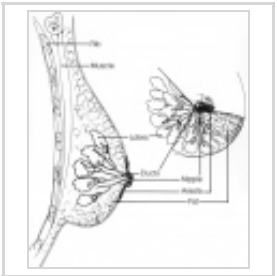
Fingerprint



Dermatomes

Hair histology

Neonate hair



Mammary anatomy

Terms

dermal papilla - the extensions of the dermis into the epidermis.

dermatoglyphic patterns - (Greek, *derma* = "skin", *glyph* = "carving") fingers, palms, toes, and soles skin patterns.

epidermal growth factor receptor - expressed on cells in the epidermis basal layer, signaling stimulates

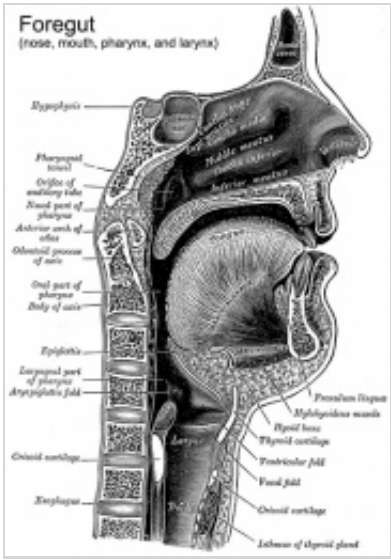
2009 Lecture 20

From Embryology

Contents

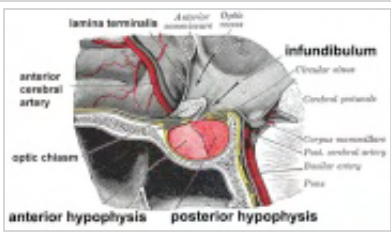
Introduction

The endocrine system resides within specific endocrine organs and both organs and tissues with other specific functions. Epithelia (ectoderm and endoderm) form the majority of the “ductless” endocrine glands like gastrointestinal and skin associated “ducted” glands. Differentiation of several also organs involves a epithelial/mesenchye interaction, seen in repeated in many differentiation of many different tissues. The endocrine glands produce hormones, which are distributed by the vascular system to the many body tissues, subsequently these organs are richly vascularized.



Head and Neck

Hormones “orchestrate” responses in other tissues, including other endocrine organs, and these overall effects can be similar or different in different tissues. These signaling pathways are often described as "axes" the two major types are the: **HPA** (**H**yothalamus-**P**ituitary-**A**drenal) and **HPG** (**H**ypothalamus-**P**ituitary-**G**onad). These hormone effects (like music) can be rapid, slow, brief, diurnal, or long-term. Hormone effects can be mimicked, stimulated, and blocked by therapeutic drugs, nutritional and environmental chemicals. Importantly, fetal endocrine development is required for normal fetal growth and differentiation.



Pituitary

> **Lecture Audio** Lecture Date: 06-10-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Endocrine (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48844)

2008: Lecture - Endocrine Development (http://embryology.med.unsw.edu.au/Science/ANAT2341lecture21.htm) | lecture 1 slide/page PDF (http://embryology.med.unsw.edu.au/pdf/ANAT2341L21Endocrines1.pdf) | lecture 4 slides/page PDF (http://embryology.med.unsw.edu.au/pdf/ANAT2341L21Endocrines4.pdf) |

2009: Medicine Lecture - Endocrine Development (http://embryology.med.unsw.edu.au/Medicine/BGDlectureEndocrine.htm) | lecture 1 slide/page PDF (http://embryology.med.unsw.edu.au/Medicine/BGD09Endocrines1.pdf)

Lecture Objectives

- Understanding of hormone types

- Understanding of endocrine gland development
- Understanding of endocrine developmental functions
- Brief understanding of endocrine abnormalities

Textbooks

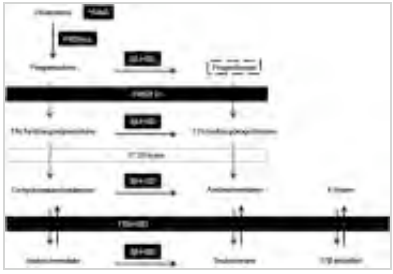
In general, not dealt with as a system in many textbooks, so various chapters: nervous system, head, gastrointestinal tract, reproductive organs, etc.

- **Human Embryology** (3rd ed.) Larson Chapter 9 Gastrointestinal, Chapter 10 Gonad, Kidney Chapter 12 Head
- **The Developing Human: Clinically Oriented Embryology** (6th ed.) Moore and Persaud Chapters 10: p230-233; Ch12: p280-282; Ch13: p319-347

Hormones

Hormone Types

- **Amino acid derivatives** - noradrenaline (norepinepherine), adrenalin (epinepherine) , thyroid hormone
- **Proteins, peptides** - thyroid stimulating hormone, leutenising hormone, follicle stimulating hormone
- **Steroids** - androgens, glucocorticoids, mineralocorticoids



Steroid biosynthesis pathway

Hormone Actions

- Autocrine - acts on self (extracellular fluid)
- Paracrine - acts locally (extracellular fluid)
- Endocrine - acts by secretion into blood stream (endocrine organs are richly vascularized)

Hormone Receptors

Hormones are recognised by either cell surface receptors (modified amino acids, peptides, proteins) or cytoplasmic/nuclear receptors (steroids).

MH - Interested in hormone history? Listen ABC Radio Ockham's Razor 2005-07-31 6.2 Mb mp3 Centenary of the word 'hormone' (http://embryology.med.unsw.edu.au/Podcast/OckhamRazor/CentenaryofHormone.mp3) , Sydney medical scientist and writer Dr John Carmody commemorates the centenary of the entry of the word 'hormone' into the English language.

Endocrine Origins

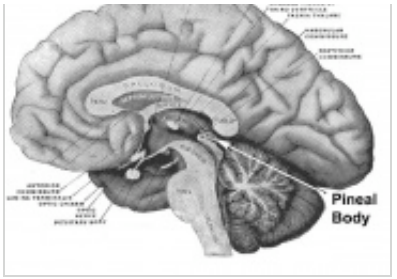
- Derived from epithelia - covering embryo, lining gastrointestinal tract, lining coelomic cavity
- Also mesenchymal contribution

Pineal Gland

UNSW Embryology - Pineal Development

(http://embryology.med.unsw.edu.au/Notes/endocrine12.htm)

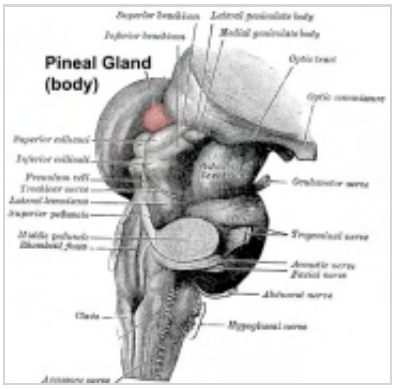
- part of epithalmus - neurons, glia and pinealocytes
- pinealocytes secrete melatonin - cyclic nature of activity, melatonin lowest during daylight
  - inhibit hypothalamic secretion of GnRH until puberty, pineal gland then rapidly regresses.
- other activities - possibly gamete maturation, antioxidant effect, protect neurons?



Adult pineal body

Pineal Development

- Neuroectoderm - prosenecephalon then diencephalon
- caudal roof, median diverticulum, epiphysis
- Initially a hollow diverticulum, cell proliferation to solid, pinealocytes (neuroglia), cone-shaped gland innervated by epithalmus



Pineal gland position

Hypothalmus

Lecture - Head Development | Lecture - Early Neural Development | Lecture - Late Neural Development | UNSW Embryology - Hypothalmus Development (http://embryology.med.unsw.edu.au/Notes/endocrine16.htm)

Hormones - Thyrotrophin releasing hormone (TRH), Corticotrophin releasing hormone (CRH), Arginine vasopressin (AVP), Gonadotrophin releasing hormone (GnRH), Growth hormone releasing hormone (GHRH), Somatostatin, Prolactin relasing factor (PRF), Dopamine

Hypothalmus Development

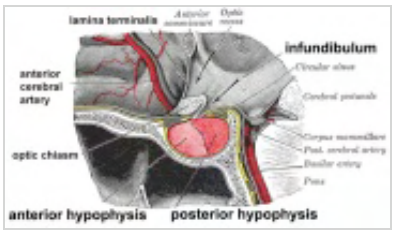
- Neuroectoderm - prosenecephalon then diencephalon
- ventro-lateral wall intermediate zone proliferation
- Mamillary bodies - form pea-sized swellings ventral wall of hypothalamus

Pituitary

Lecture - Head Development | UNSW Embryology - Pituitary Development (http://embryology.med.unsw.edu.au/Notes/endocrine7.htm)

Anterior pituitary hormones - Thyroid-stimulating hormone (TSH), Adrenocorticotrophic hormone (ACTH), Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), Somatotrophin/growth hormone (GH), Prolactin (PRL), Melanocyte-stimulating hormone (MSH)

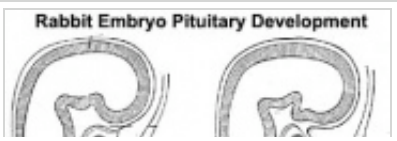
Posterior pituitary hormones - Oxytocin, Arginine vasopressin



Adult pituitary

Pituitary Development

- Dual ectoderm origins
  - Ectoderm - ectoderm roof of stomodeum, Rathke's pouch, adenohypophysis
  - Neuroectoderm - prosenecephalon then diencephalon,



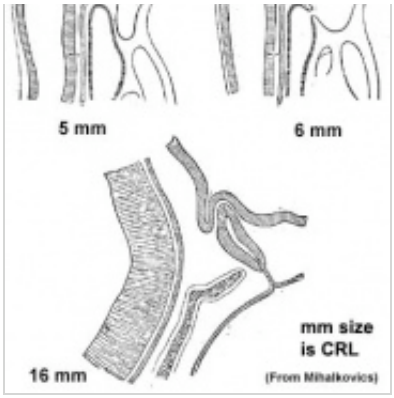
neurohypophysis

Adenohypophysis

- Anterior wall proliferates - pars distalis
- Posterior wall little growth – pars intermedia
- Rostral growth around infundibular stem – pars tuberalis

Neurohypophysis

- Infundibulum – median eminence, infundibulum, pars nervosa



Pituitary rabbit development

Pituitary Timeline

- Week 4 - hypophysial pouch, Rathke's pouch, diverticulum from roof
- Week 5 - elongation, contacts infundibulum, diverticulum of diencephalon
- Week 6 - connecting stalk between pouch and oral cavity degenerates
- Week 10 - growth hormone and ACTH detectable
- Week 16 - adenohypophysis fully differentiated
- Week 20 to 24 - growth hormone levels peak, then decline

Thyroid

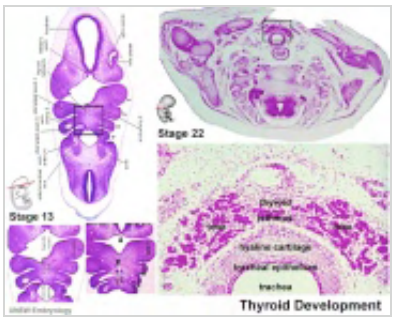
Lecture - Head Development | UNSW Embryology - Thyroid Development (http://embryology.med.unsw.edu.au/Notes/endocrine8.htm)

- Functions from wk10, required for neural development, stimulates metabolism (protein, carbohydrate, lipid), reduced/absence = cretinism (see abnormalities)

Hormones - (amino acid derivatives) Thyroxine (T4), Triiodothyronine (T3)

Thyroid Development

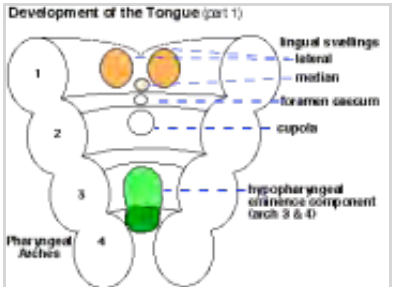
- thyroid median endodermal thickening in the floor of pharynx, outpouch – thyroid diverticulum
- tongue grows, cells descend in neck
- thyroglossal duct - proximal end at the foramen cecum of tongue thyroglossal duct (http://www.upstate.edu/cdb/grossanat/imgs/tgdfig2.jpg)
- thyroid diverticulum - hollow then solid, right and left lobes, central isthmus



Stage 13 and Stage 22 thyroid development

Thyroid Timeline

- 24 days - thyroid median endodermal thickening in the floor of pharynx, outpouch – thyroid diverticulum
- Week 11 - colloid appearance in thyroid follicles, iodine and thyroid hormone (TH) synthesis



growth factors (insulin-like, epidermal) stimulates follicular growth

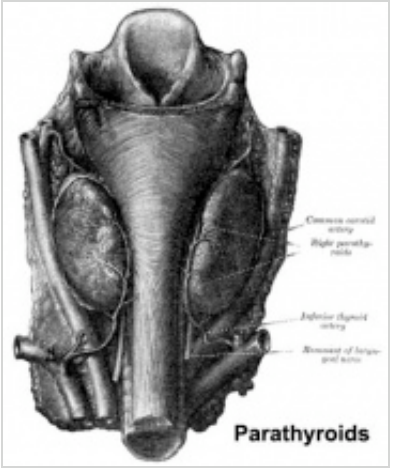
Fetal Thyroid Hormone

- Initial secreted biologically inactivated by modification, late fetal secretion develops brown fat
- Iodine deficiency- during this period, leads to neurological defects (cretinism)
- Birth - TSH levels increase, thyroxine (T3) and T4 levels increase to 24 h, then 5-7 days postnatal decline to normal levels


foramen caecum

Parathyroid

Lecture - Head Development | UNSW Embryology - Parathyroid (http://embryology.med.unsw.edu.au/Notes/endocrine17.htm)



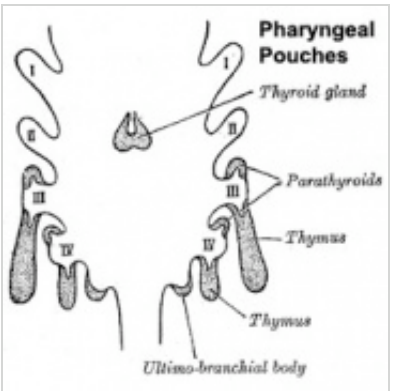
Parathyroid adult

- Parathyroid Hormone - Increase calcium ions [Ca2+], stimulates osteoclasts, increase Ca GIT absorption (opposite effect to calcitonin)
- Adult Calcium and Phosphate - Daily turnover in human with dietary intake of 1000 mg/day
- secreted by chief cells

Principal cells cords of cells

Parathyroid Development

- Endoderm - third and fourth pharyngeal pouches, could also have ectoderm and neural crest
  - 3rd Pharyngeal Pouch - inferior parathyroid, initially descends with thymus
  - 4th Pharyngeal Pouch - superior parathyroid
- Week 6 - diverticulum elongate, hollow then solid, dorsal cell proliferation
- Fetal parathyroids - respond to calcium levels, fetal calcium levels higher than maternal



Pharyngeal pouches

Thymus

Lecture - Head Development | UNSW Embryology - Thymus Development (http://embryology.med.unsw.edu.au/Notes/endocrine13.htm)

- Thymus - bone-marrow lymphocyte precursors become thymocytes, and subsequently mature into T lymphocytes (T cells)
- Thymus hormones - thymosins stimulate the development and differentiation of T lymphocytes

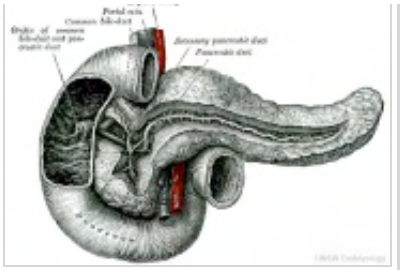
Thymus Development

- Endoderm - third pharyngeal pouch
- Week 6 - diverticulum elongates, hollow then solid, ventral cell proliferation
- Thymic primordia - surrounded by neural crest mesenchyme, epithelia/mesenchyme interaction

Pancreas

Lecture- Gastrointestinal Tract Development | UNSW Embryology -

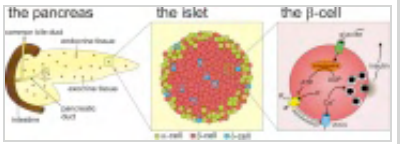
Pancreas Development (http://embryology.med.unsw.edu.au/Notes/endocrine10.htm) see also GIT Notes- Pancreas (http://embryology.med.unsw.edu.au/Notes/git9.htm)



Pancreas adult

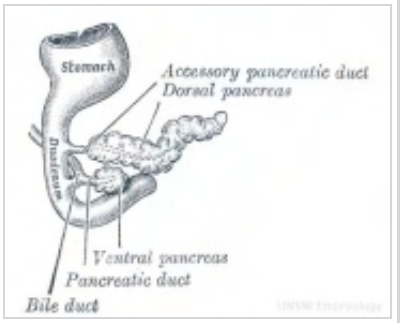
- Functions - exocrine (amylase, alpha-fetoprotein), 99% by volume; endocrine (pancreatic islets) 1% by volume
- Exocrine function - begins after birth
- Endocrine function - from 10 to 15 weeks onward hormone release
  - exact roles of hormones in regulating fetal growth?

Pancreas Development



pancreas structure

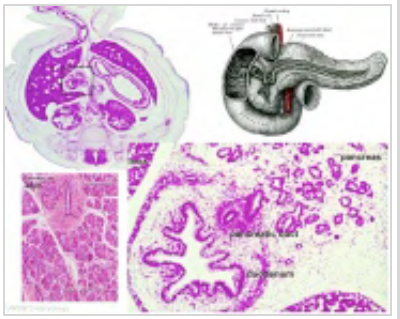
- Pancreatic buds - duodenal level endoderm, splanchnic mesoderm forms dorsal and ventral mesentery, dorsal bud (larger, first), ventral bud (smaller, later)
- Pancreas Endoderm - pancreas may be opposite of liver
  - Heart cells promote/notochord prevents liver formation
  - Notochord may promote pancreas formation
  - Heart may block pancreas formation



Pancreatic buds and duct developing

- Duodenum growth/rotation - brings ventral and dorsal buds together, fusion of buds
- Pancreatic duct - ventral bud duct and distal part of dorsal bud, exocrine function
- Islet cells - cords of endodermal cells form ducts, from which cells bud off to form islets

Pancreatic Islets



Stage22 pancreas

- Islets of Langerhans - 4 endocrine cell types
- **Alpha** - glucagon, mobilizes lipid
- **Beta** - insulin, increase glucose uptake
  - Beta cells, stimulate fetal growth, continue to proliferate to postnatal, in infancy most abundant
- **Delta** - somatostatin, inhibits glucagon, insulin secretion
- **F-cells** - pancreatic polypeptide

Pancreas Timeline

- Week 7 to 20 - pancreatic hormones secretion increases, small amount maternal insulin
- Week 10 - glucagon (alpha) differentiate first, somatostatin (delta), insulin (beta) cells differentiate, insulin secretion begins
- Week 15 - glucagon detectable in fetal plasma

Adrenal

Lecture - Neural Crest Development | UNSW Embryology - Adrenal Development (http://embryology.med.unsw.edu.au/Notes/endocrine9.htm)

- Richly vascularized - arterioles passing through cortex, capillaries from cortex to medulla, portal-like circulation
- Fetal Cortex - produces a steroid precursor (DEA), converted by placenta into estrogen

- Adult Medulla - produces adrenalin (epinephrine), noradrenaline (norepinephrine)
- Fetal adrenal hormones - influence lung maturation

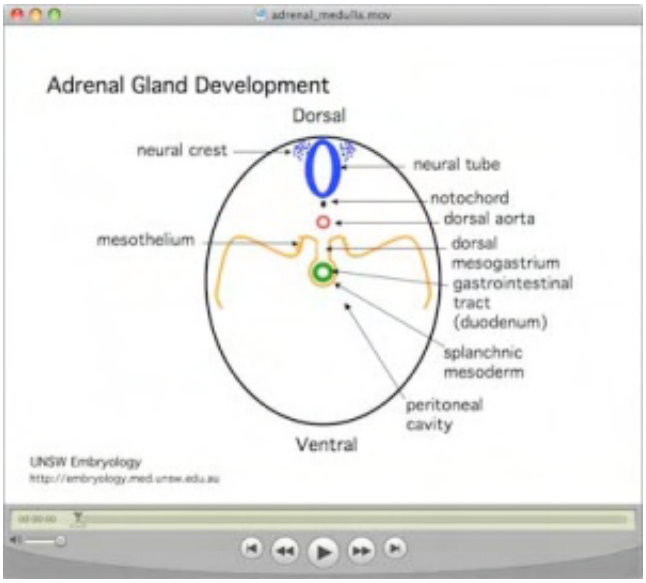
Adrenal cortical hormones - (steroids) Cortisol, Aldosterone, Dehydroepiandrosterone

- zona glomerulosa - regulated by renin-angiotensin-aldosterone system controlled by the juxtaglomerular apparatus of the kidney.
- zona fasciculata - regulated by hypothalamo-pituitary axis with the release of CRH and ACTH respectively.

Adrenal medullary hormones - (amino acid derivatives) Epinephrine, Norepinephrine

Adrenal Development

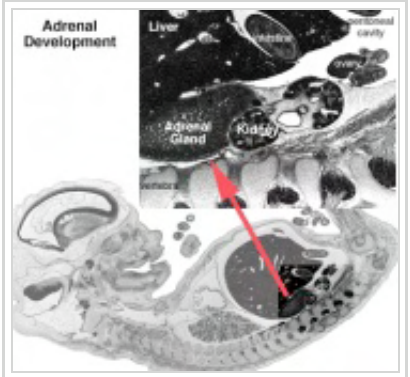
- Fetal Adrenals - fetal cortex later replaced by adult cortex
- Week 6 - fetal cortex, from mesothelium adjacent to dorsal mesentery; Medulla, neural crest cells from adjacent sympathetic ganglia
- Adult cortex - mesothelium mesenchyme encloses fetal cortex



Adrenal Cortex

- Late Fetal Period - differentiates to form cortical zones
- Birth - zona glomerulosa, zona fasiculata present
- Year 3 - zona reticularis present

Endocrinology - Adrenal Cortex Development (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A442&rendertype=box&id=A466)



Week 10 adrenal gland

Adrenal Medulla

- neural crest origin, migrate adjacent to coelomic cavity, initially uncapsulated and not surrounded by fetal cortex, cells have neuron-like morphology
- 2 cell types - secrete epinepherine (adrenaline) 80%; secrete norepinepherine (noradrenaline* 20%

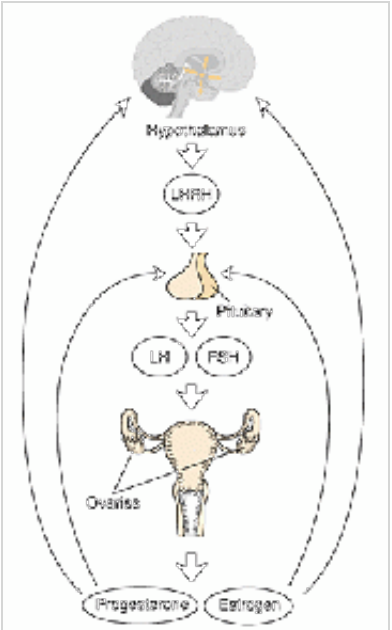
Media:Adrenal_medulla.mov

Gonad

Lecture - Genital Development | UNSW Embryology - Gonads

Lecture - Genital Development | UNSW Embryology - Gonads (http://embryology.med.unsw.edu.au/Notes/endocrine15.htm) see also previous Sexual Differentiation Lecture/Practical

HPG Axis - Endocrinology - Simplified diagram of the actions of gonadotrophins (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972&rendertype=box&id=A1057)



Female HPG axis

Gonad Development

- mesoderm - mesothelium and underlying mesenchyme, primordial germ cells
- Gonadal ridge - mesothelium thickening, medial mesonephros
- Primordial Germ cells - yolk sac, to mesentery of hindgut, to genital ridge of developing kidney

Differentiation

- testis-determining factor (TDF) from Y chromosome: presence (testes), absence (ovaries)

Testis

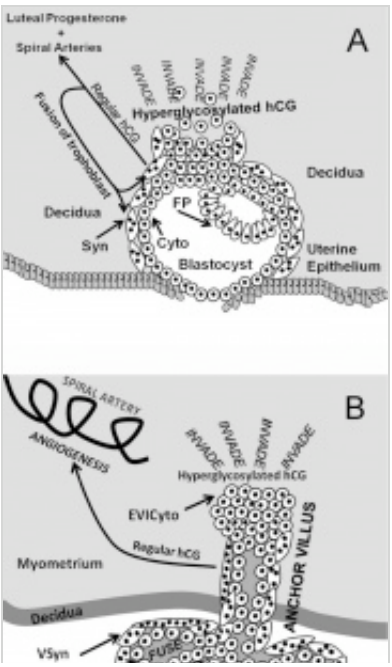
- 8 Weeks, mesenchyme, interstitial cells (of Leydig) secrete testosterone, androstenedione
- 8 to 12 Weeks - hCG stimulates testosterone production
- Sustentacular cells - produce anti-mullerian hormone to puberty

Ovary

- X chromosome genes regulate ovary development

Placenta

Lecture - Placenta Development | UNSW Embryology - Endocrine Placenta (http://embryology.med.unsw.edu.au/Notes/endocrine14.htm)

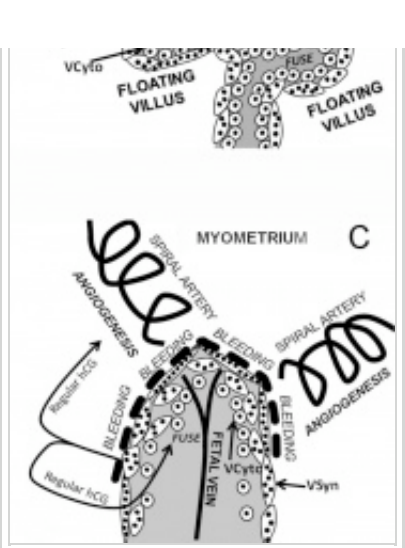


- Human chorionic gonadotrophin (hCG) - like leutenizing hormone, supports corpus luteum in ovary, pregnant state rather than menstrual, maternal urine in some pregnancy testing

- Human chorionic somatommotropin (hCS) - or placental lactogen stimulate (maternal) mammary development
- Human chorionic thyrotropin (hCT)
- Human chorionic corticotropin (hCACTH)
- progesterone and estrogens - support maternal endometrium
- Relaxin

- Placenta - Maternal (decidua) and Fetal (trophoblastic cells, extraembryonic mesoderm) components
- Endocrine function - maternal and fetal precursors, synthesis and secretion
    - Protein Hormones - chorionic gonadotropin (hCG), chorionic somatomammotropin (hCS) or placental lactogen (hPL), chorionic thyrotropin (hCT), chorionic corticotropin

(hCACTH)
    - hCG - up to 20 weeks, fetal adrenal cortex growth and maintenance
    - hCS – rise through pregnancy, stimulates maternal metabolic processes, breast growth
- Steroid Hormones - progesterone (maintains pregnancy), estrogens (fetal adrenal/placenta)



Trophoblast hCG function

Other Endocrine

UNSW Embryology - Other Endocrine Tissues (http://embryology.med.unsw.edu.au/Notes/endocrine19.htm)

Endocrine Heart

- Atrial natriuretic peptide (ANP) - Increase Filtration rate / decrease Na+ reabsorption
- Endothelins - ET-1, ET-2, ET-3, Vasoconstriction / Increase NO
- Nitric oxide (NO) - Vasodilatation

Endocrine Kidney

- Renin - Increase Angiotensin-aldosterone system
- Prostaglandins - decrease Na+ reabsorption
- Erythropoietin - Increase Erythrocyte (rbc) production
- 1,25 (OH)2 vitamin D - calcium homeostasis
- Prekallikreins - Increase Kinin production

GIT Endocrine

Enteric control of digestive function

- Gastrin - Secreted from stomach (G cells), role in control of gastric acid secretion
- Cholecystokinin - small intestine hormone, stimulates secretion of pancreatic enzymes and bile
- Secretin - small intestine hormone (epithelial cells), stimulates secretion of bicarbonate-rich fluids from pancreas and liver

Adipose Tissue

UNSW Embryology - Endocrine Adipose Tissue (http://embryology.med.unsw.edu.au/Notes/endocrine18.htm)

- Leptin - polypeptide hormone produced in adipose and many other tissues with also many different roles
- Adiponectin - regulation of energy homeostasis and glucose and lipid metabolism, as well as acting as an anti-inflammatory on the cellular vascular wall
- Resistin - (for resistance to insulin, RETN) a 108 amino acid polypeptide and the related resistin-like protein-beta (Resistin-like molecule-beta, RELMbeta) stimulate endogenous glucose production

Endocrine Functional Changes

- Puberty- Increased activity
- Menopause- Decreased activity

- Disease (diabetes, thyroid, kidney) suggested trends that genetics, health, nutrition, lifestyle may influence time that these events occur
- Pharmaceutical impact - birth control, steroids, Hormone Replacement Therapy (HRT)

Abnormalities

NIH Genes & Disease Chapter 41 - Glands and Hormones (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd.chapter.41)

Pineal

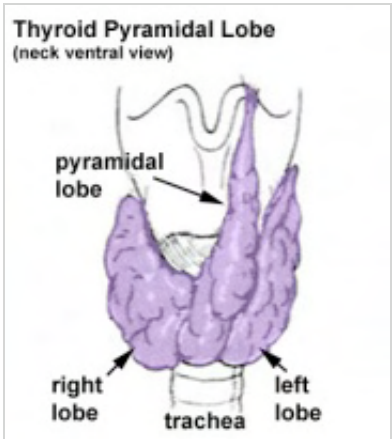
- hypoplasia - associated with retinal disease.
- tumours - in children are associated with abnormal puberty development.

Pituitary

- craniopharyngeal canal - Rathke's pouch abnormality, from the anterior part of the fossa hypophyseos of the sphenoid bone to the under surface of the skull.
- pituitary tumours (adenomas) - several abnormalities associated with abnormal levels of the hormonal output of the pituitary.
    - Growth hormone (GH) adenomas - benign pituitary tumors lead to chronic high GH output levels, that may lead to acromegaly.
- Cushing's disease - caused either by a pituitary adenoma produces excess adrenocorticotropic hormone (ACTH, corticotropin) or due to ectopic tumors secreting ACTH or corticotropin-releasing hormone (CRH).

Thyroid

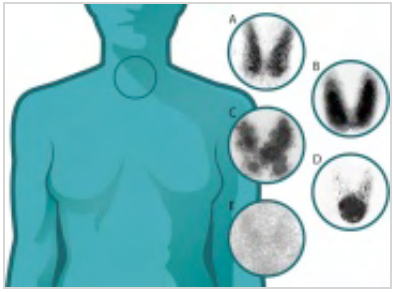
- Pyramidal lobe - from isthmus (50% of people) attached to hyoid bone distal end of thryoglossal duct.
- Congenital hypothyroidism - approximately 1 in 3000 births, associated with neurological abnormalities.
- Lingual thyroid gland - failure of thyroid descent.
- Thyroglossal cyst - persistance of thyroglossal duct. Image - thyroglossal duct (http://www.upstate.edu/cdb/grossanat/imgs/tgdfig2.jpg)
- Thyroglossal fistula - partial degeneration of the thyroglossal duct.
- Abnormal development of the thyroid - incomplete or excessive descent.
- Childhood hypothyroidism delays ossification and bone mineralization.



Thyroid pyramidal lobe

Iodine Deficiency

- A teaspoon of iodine, total lifetime requirement, cannot be stored for long periods by our body, tiny amounts are needed regularly
- Areas of endemic iodine deficiency, where soil and therefore crops and grazing animals do not provide sufficient dietary iodine to the populace
- food fortification and supplementation - Iodized salt programs and iodized oil supplements are the most common tools in fight against IDD


Thyroid uptake scans

Parathyroid

- Usually four glands are present (2 on each side), but three to six glands have been found in human.
- Lower parathyroid glands arise from the third pharyngeal pouch and descend with the thymus. Variable descent can lead to a range of adult locations, from just beneath the mandible to the anterior mediastinum.

Pancreas

- Type 1 Diabetes - juvenile onset diabetes, more severe form of illness, increases risk of blindness, heart disease, kidney failure, neurological disease, T-lymphocyte-dependent autoimmune disease, infiltration and destruction of the islets of Langerhans, Approx 16 million Americans
- Type 2 Diabetes - loosely defined as "adult onset" diabetes, becoming more common cases of type 2 diabetes seen in younger people
- Risk of developing diabetes - environmental factors (food intake and exercise play an important role, either overweight or obese), Inherited factors (genes involved remain poorly defined)

Adrenal

- Congenital Adrenal Hyperplasia (CAH) - family of inherited disorders of adrenal steroidogenesis enzymes which impairs cortisol production by the adrenal cortex. Androgen excess leads newborn females with external genital ambiguity and postnatal progressive virilization in both sexes.
    - Enzymes most commonly affected: 21-hydroxylase (21-OH), 11beta-hydroxylase, 3beta-hydroxysteroid dehydrogenase.
    - Enzymes less commonly affected: 17alpha-hydroxylase/17,20-lyase and cholesterol desmolase.

- Pheochromocytomas (PCC) - Catecholamine-producing (neuro)endocrine tumor located in the adrenal medulla. Similar catecholamine-producing tumors outside the adrenal gland are called paragangliomas (PGL).

Endocrine Disruptors

Exogenous chemicals that interfere with the function of hormones. There are 3 main mechanisms: mimic, block or interfere.

Mimic - effects of natural hormones by binding receptors

- Diethylstilbestrol - (DES or diethylstilbetrol) a drug prescribed to women from 1938-1971 to prevent miscarriage in high-risk pregnancies. Acts as a potent estrogen (mimics natural hormone) and therefore a potential endocrine disruptor. Female fetus, increased risk abnormal reproductive tract and cancer. Male fetus, abnormal genitalia. Banned by USA FDA in 1979 as a teratogen, previously used as livestock growth promoter.

Block - binding of a hormone to receptor or hormone synthesis

- Finasteride - chemical used to prevent male pattern baldness and enlargement of prostate glands. An anti-androgen (blocks synthesis of dihydrotestosterone) and therefore a potential endocrine disruptor, exposed pregnant women can impact on male fetus genetial development.
- Vinclozolin - a dicarboximide fungicide, perinatal exposure in rats inhibits morphological sex differentiation. In adult rats, shown to cause gonad tumours (Leydig cell) and atrophy. Chemical has androgen-antagonist (antiandrogenic) activity, metabolies compete with natural androgen

Interfere - with hormone transport or elimination

- Polychlorinated biphenyl pollutants - (PCBs) Rats exposed to PCBs have low levels of thyroid hormone. Compete for binding sites of thyroid hormone transport protein. Without being bound to this protein, thyroid hormones are excreted from the body (McKinney et al. 1985; Morse et al. 1996)

Links

- **UNSW Embryology:** Stage 13/14 Embryo (http://embryology.med.unsw.edu.au/Notes/endocrine3.htm) | Stage 22 Embryo (http://embryology.med.unsw.edu.au/Notes/endocrine4.htm) | Selected Sections Stage 22 Embryo (http://embryology.med.unsw.edu.au/Notes/endocrine4.htm) | Abnormal Endocrine Development (http://embryology.med.unsw.edu.au/Notes/endocrine2.htm) | Pituitary Development (http://embryology.med.unsw.edu.au/Notes/endocrine7.htm) | Thyroid Development (http://embryology.med.unsw.edu.au/Notes/endocrine8.htm) | Adrenal Development (http://embryology.med.unsw.edu.au/Notes/endocrine9.htm) | Pancreas Development (http://embryology.med.unsw.edu.au/Notes/endocrine10.htm) See also GIT Notes- Pancreas (http://embryology.med.unsw.edu.au/Notes/git9.htm) | Endocrine Placenta (http://embryology.med.unsw.edu.au/Notes/endocrine14.htm) | Hypothalmus (http://embryology.med.unsw.edu.au/Notes/endocrine16.htm) | Parathyroid (http://embryology.med.unsw.edu.au/Notes/endocrine17.htm) | Endocrine Adipose Tissue (http://embryology.med.unsw.edu.au/Notes/endocrine18.htm) | Other Endocrine Tissues (http://embryology.med.unsw.edu.au/Notes/endocrine19.htm)
- Embryo Images: Pituitary Development (http://www.med.unc.edu/embryo_images/unit-nervous/nerv_htms/nerv016.htm)

References

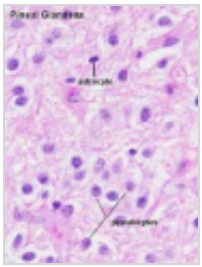
- Endocrinology: An Integrated Approach Nussey, S.S. and Whitehead, S.A. London:Taylor & Francis; c2001 Major hormone types (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A3&rendertype=box&id=A11)
- Genes and Disease, Bethesda (MD): National Library of Medicine (US), NCBI Chapter 41 - Glands and Hormones (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=gnd.chapter.41)

Search

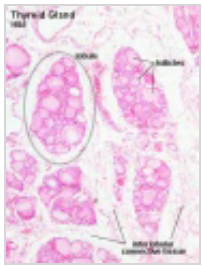
- **Bookshelf** endocrine (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=endocrine) | pineal gland (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=pineal_gland) | hypothalamus (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=hypothalmus) | pituitary gland (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=pituitary_gland) | thyroid gland (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=thyroid_gland) | parathyroid gland (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=parathyroid_gland) | thymus gland (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=thymus_gland) | endocrine pancreas (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=endocrine_pancreas) | adrenal gland (http://www.ncbi.nlm.nih.gov/sites/entrez?db=Books&cmd=search&term=adrenal_gland)
- **Pubmed** endocrine development (http://www.ncbi.nlm.nih.gov/sites/gquery?itool=toolbar&cmd=search&term=endocrine_development)

Histology

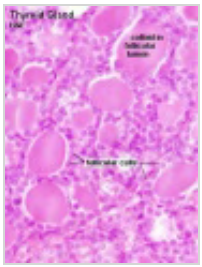
Adult



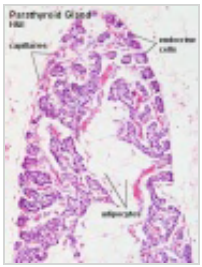
Pineal (high power)



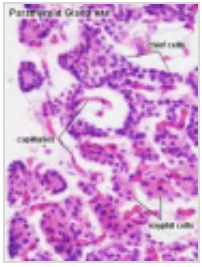
Thyroid (low power)



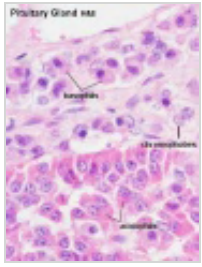
Thyroid (high power)



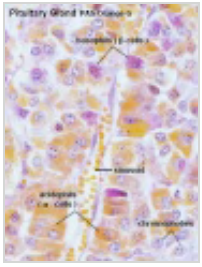
Parathyroid (low power)



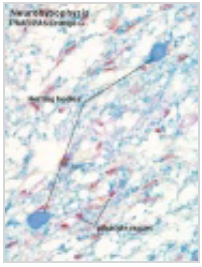
Parathyroid (high power)



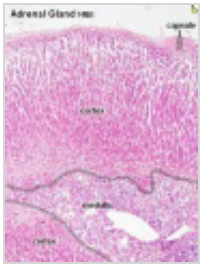
Pituitary - adenohypophysis



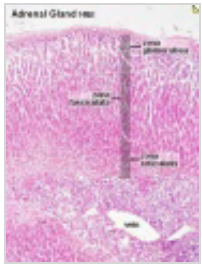
Pituitary - adenohypophysis



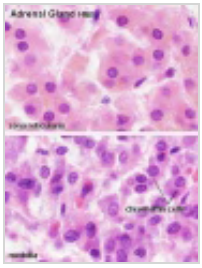
Pituitary - neurohypophysis



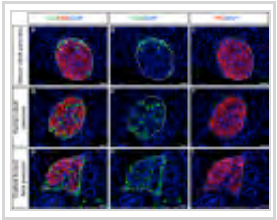
Adrenal - Cortex and Medulla



Adrenal - Cortical Zones

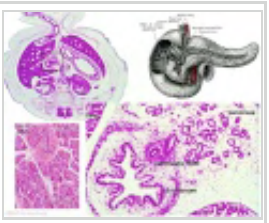


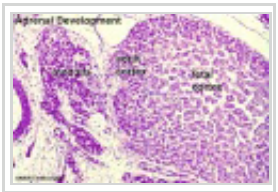
Adrenal - Zona Reticularis and Medulla

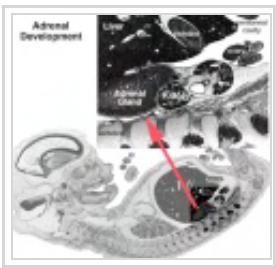


Pancreatic islet

Embryonic







Stage 22 - Pancreatic duct	Stage 22 - Adrenal gland	Week 10 - Adrenal gland

Terms

adrenocorticotropin - (ACTH or corticotropin) anterior pituitary, peptide hormone

antidiuretic hormone - (ADH) hypothalamus, peptide hormone

atrial natriuretic factor - (ANP) heart, , peptide hormone

calcitonin - (CT) C cells of thyroid, peptide hormone

follicle stimulating hormone - (FSH) pituitary, protein hormone

growth hormone - (GH) pituitary, peptide hormone

human chorionic gonadotropin - (hCG) pancreas glycoprotein hormone with 2 subunits (alpha and beta joined non covalently). Similar in structure to luteinizing hormone (LH), hCG exists in multiple hormonal and non-endocrine agents (regular hCG, hyperglycosylated hCG and the free beta-subunit of hyperglycosylated hCG). PMID: 19171054 (http://www.ncbi.nlm.nih.gov/pubmed/19171054)

lutenizing hormone - (LH) pituitary, protein hormone

melaocyte stimulating hormone - (MSH) pituitary, peptide hormone

prolactin - (PRL) pituitary, peptide hormone

parathyroid hormone - (PTH) parathyroid, peptide hormone

thyroid hormone - (TH) thyroid,amino acid derivative

thyroid stimulating hormone - (TSH) pituitary, protein hormone

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Original Glossary (http://embryology.med.unsw.edu.au/Notes/Index/Index.htm)

Course Content 2009

Embryology Introduction | Cell Division/Fertilization | Cell Division/Fertilization | Week 1&2 Development | Week 3 Development | Lab 2 | Mesoderm Development | Ectoderm, Early Neural, Neural Crest | Lab 3 | Early Vascular Development | Placenta | Lab 4 | Endoderm, Early Gastrointestinal | Respiratory Development | Lab 5 | Head Development | Neural Crest Development | Lab 6 | Musculoskeletal Development | Limb Development | Lab 7 | Kidney | Genital | Lab 8 | Sensory - Ear | Integumentary | Lab 9 | Sensory - Eye | **Endocrine** | Lab 10 | Late Vascular Development | Fetal | Lab 11 | Birth, Postnatal | Revision | Lab 12 | Lecture Audio | Course Timetable

2009 Lecture 21

From Embryology

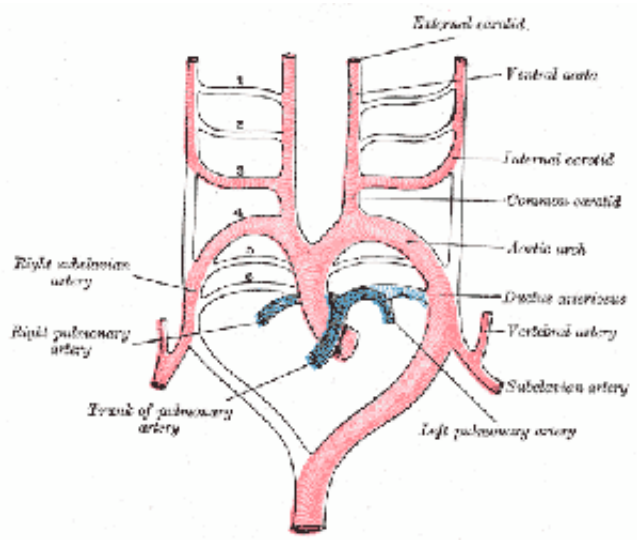
Contents

Late Cardiovascular Development

Introduction

In lecture 7 - Early Vascular Development, there was an introduction to the origins of the cardiovascular system. This second lecture will now focus on the extensive remodeling that occurs in both the heart and vascular system during later development. In addition there will be discussion on the major cardiovascular abnormalities.

The laboratory this week will also give you the opportunity to work through some of these concepts using a new online teaching module.



Lecture Audio Lecture Date: 12-10-2009 Lecture Time: 12:00 Venue: CLB 5 Speaker: Mark Hill
Late Cardiovascular (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48833)

Lecture Objectives

- Describe the development of primary and secondary atrial septa and the ventricular septum.
- Explain the changes occurring in the bulbis cordis and truncus arteriosus in its transformation from a single to a double tube.
- Describe the development of the aortic arches on the right and left sides from the fetus to the adult.
- Describe the development of arteries and veins.
- Describe the major cardiovascular developmental abnormalities.

Textbook references

- Human Embryology (3rd ed.) Larson Chapter 7 p151-188 Heart, Chapter 8 p189-228 Vasculature
- The Developing Human: Clinically Oriented Embryology (6th ed.) Chapter 14: p304-349

Other textbooks

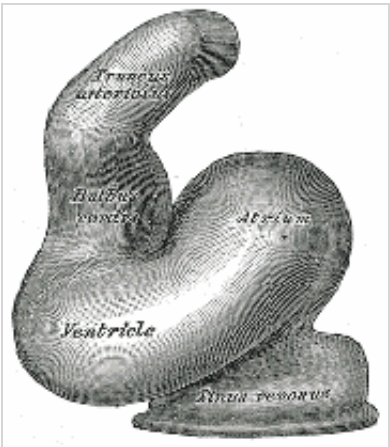
- Before we Are Born (5th ed.) Moore and Persaud Chapter 12; p241-254
- Essentials of Human Embryology Larson Chapter 7 p97-122 Heart, Chapter 8 p123-146 Vasculature
- Human Embryology Fitzgerald and Fitzgerald Chapter 13-17: p77-111

Recent reviews

- Yutzey KE, Kirby ML. Wherefore heart thou? Embryonic origins of cardiogenic mesoderm. Dev Dyn. 2002 Mar;223(3):307-20. Review. PMID: 11891982 (http://www.ncbi.nlm.nih.gov/pubmed/11891982?dopt=Abstract)
- Three-dimensional reconstruction of gene expression patterns during cardiac development. Soufan AT, Ruijter JM, van den Hoff MJ, de Boer PA, Hagoort J, Moorman AF. Physiol Genomics. 2003 May 13;13(3):187-95. Review. PMID: 12746463 (http://www.ncbi.nlm.nih.gov/pubmed/12746463)
- Moorman A, Webb S, Brown NA, Lamers W, Anderson RH. Development of the heart: (1) formation of the cardiac chambers and arterial trunks. Heart. 2003 Jul;89(7):806-14. PMID: 12807866 (http://www.ncbi.nlm.nih.gov/pubmed/12807866?dopt=Abstract)
- Bruneau BG. Transcriptional regulation of vertebrate cardiac morphogenesis. Circ Res. 2002 Mar 22;90(5):509-19. Review. PMID: 11909814 (http://www.ncbi.nlm.nih.gov/pubmed/11909814?dopt=Abstract)

Heart Development

- endocardial tube in pericardial cavity
  - dorsal mesentry (mesocardial) attachment lost
  - attached at cranial (arterial) and caudal (venous) ends
- tube elongation - bending and series of expansions



Day 14 Heart tube

Bulbus Cordis - 3 parts

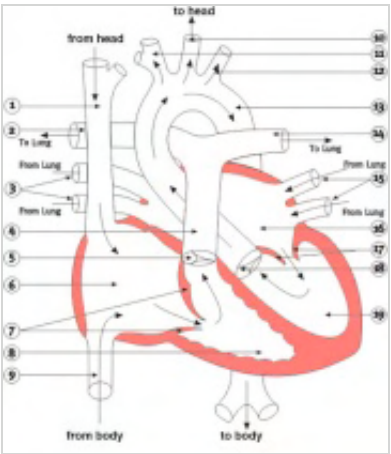
- distal - forms truncus arteriosus (aorta and pulmonary artery)
- middle - conus cordis ventricular outflow tract
- proximal - right ventricle trabeculate part

endocardial cushions

- form initial division of atria and ventricles
- fusion forma a left and right atrioventricular canals

Heart Layers

- **pericardium** - covers the heart, formed by 3 layers consisting of a fibrous pericardium and a double layered serous pericardium (parietal layer and visceral epicardium layer).
- **myocardium** - muscular wall of the heart, thickest layer formed by spirally arranged cardiac muscle cells.
- **endocardium** - lines the heart, epithelial (endothelial) tissue lining the inner surface of heart chambers and valves.



Adult Heart blood flow

Embryonic Heart Rate

- Stage 9-10 2 mm embryo (gestational sac diameter of 20 mm) EHR at least 75 beats / minute
- Stage 11-12 5 mm embryo (gestational sac diameter of 30 mm) EHR at least 100 beats / minute
- Stage 16 10 mm embryo EHR at least 120 beats / minute

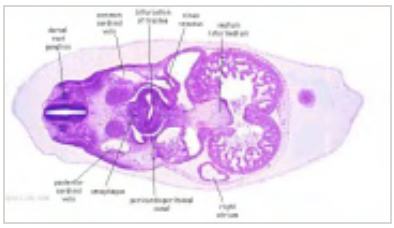
- Stage 18 15 mm embryo EHR at least 130 beats / minute

Week 12 fetal heart rate doppler (http://embryology.med.unsw.edu.au/Movies/usound/Hum12wkFHR.htm)
Week 17 fetal heart rate audio (http://embryology.med.unsw.edu.au/Notes/heart8.htm)

Atrial Septation

Animation - Heart Atrial Septation

Through all development blood shunts from right to left atrium (bypass lungs)


Heart (Carnegie stage 13)

Septum Primum

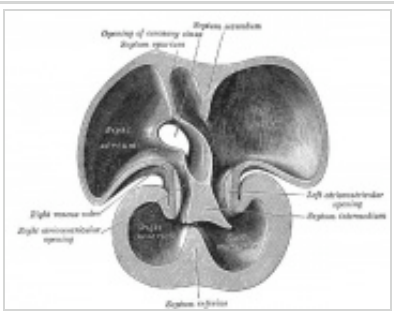
Stage 13 Septum Primum (http://embryology.med.unsw.edu.au/wwwpig/pigc/c11.htm) Stage 22 Septum Primum

(http://embryology.med.unsw.edu.au/wwwhuman/lowpower/HumE/E2L.htm)

- dorso-cranial wall, membranous extension
- grows downward towards endocardial cushions
- opening is **foramen primum** (ostium primum)
- septum primum fuses with endocardial cushion, but cranially had begun to degenerate forming **foramen secundum** (ostium secundum)

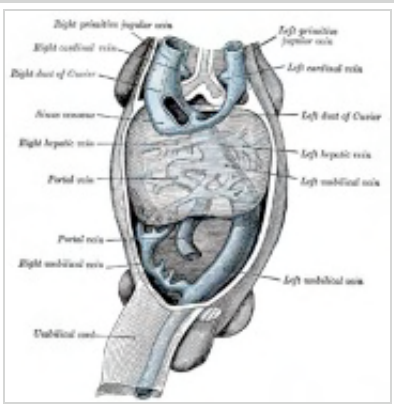
Septum Secundum

- ventro-cranial wall
- grows as septum primum downward, does not fuse with endocardial cushion, opening is **foramen ovale**


Septum Secundum

Right Atrium

- right sinus horn incorporates into dorsal wall sinus venerum
- sinoatrial opening - has 2 flaps, left fuses with septum secundum, right forms valve to inferior vena cava and coronary sinus. Stage 13 - right venous valve (http://embryology.med.unsw.edu.au/wwwpig/pigc/c31.htm) Stage 22 - right venous valve


sinus venosus and tributaries

(http://embryology.med.unsw.edu.au/wwwhuman/lowpower/HumE/E2L.htm)

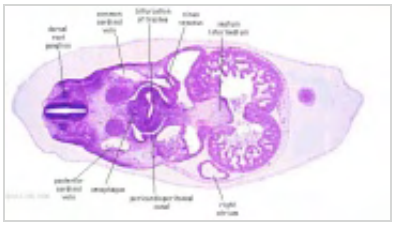
Left Atrium

- posterior wall - outgrowth forms single pulmonary vein, divided into 4 branches
- incorporation into the wall leads to 4 openings in posterior wall
- later moves to the right aligns with atrioventricular canal.

Ventricular Septation

Animation - Heart Realign

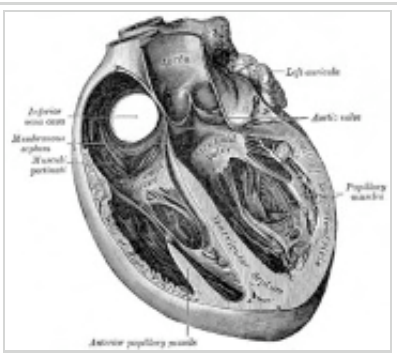
- 2 separate components - superior membranous, inferior muscular



Heart (Carnegie stage 13)

Muscular Septum

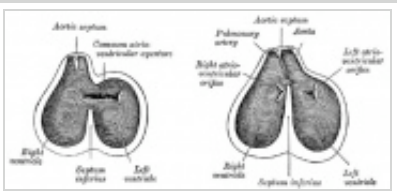
- growth of inferior wall
- fusion of 3 components - right and left bulbar ridges and dorsal endocardial cushion



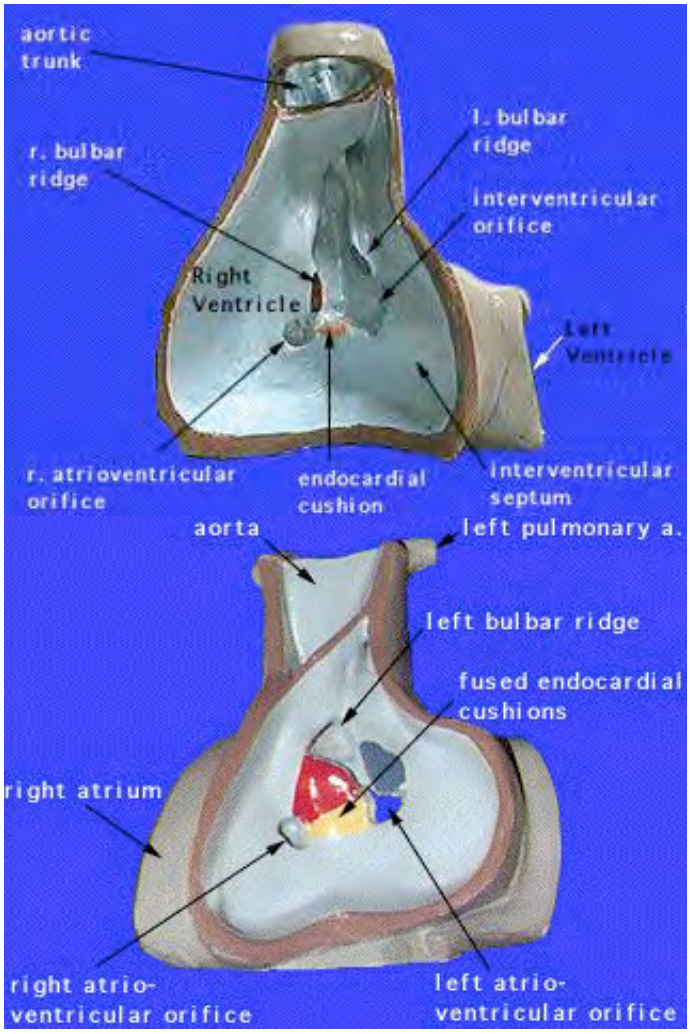
Ventricular septum

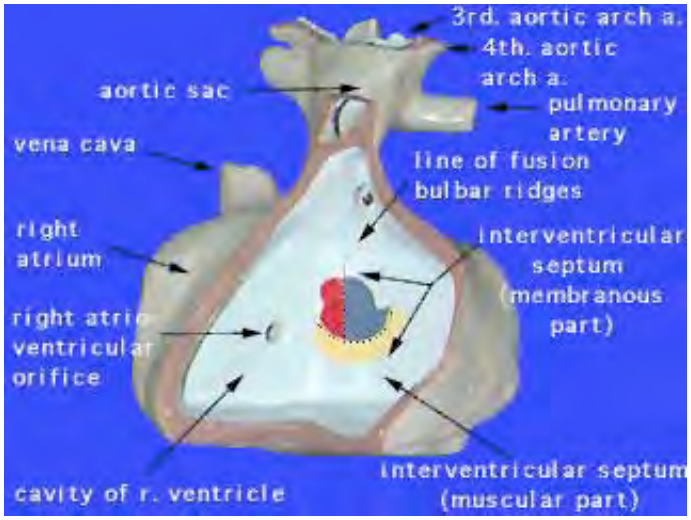
Membranous Septum

- above the muscular septum, fusion continuous with septation of the outflow tract



muscular septum





Outflow Tract Septation

Animation - Heart Outflow Septation

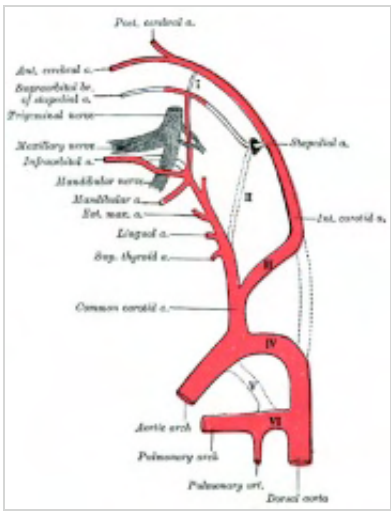
- truncus arteriousus - 2 growths from wall in spiral pattern, inferior upwards Stage 13 truncus arteriousus (http://embryology.med.unsw.edu.au/wwwpig/pigb/b5l.htm)
- mesenchyme and neural crest contribute to this septation process
- fusion of outgrowths separate aortic and pulmonary outflow

Neural crest removal - abnormal cardiac rotation (http://embryology.med.unsw.edu.au/Movies/heart/chickheart.htm)

Vascular Remodeling

Arterial System

- Aortic sac - remodels forming 2 horns, R forms brachiocephalic artery, L forms common carotid artery


pharyngeal arch arteries

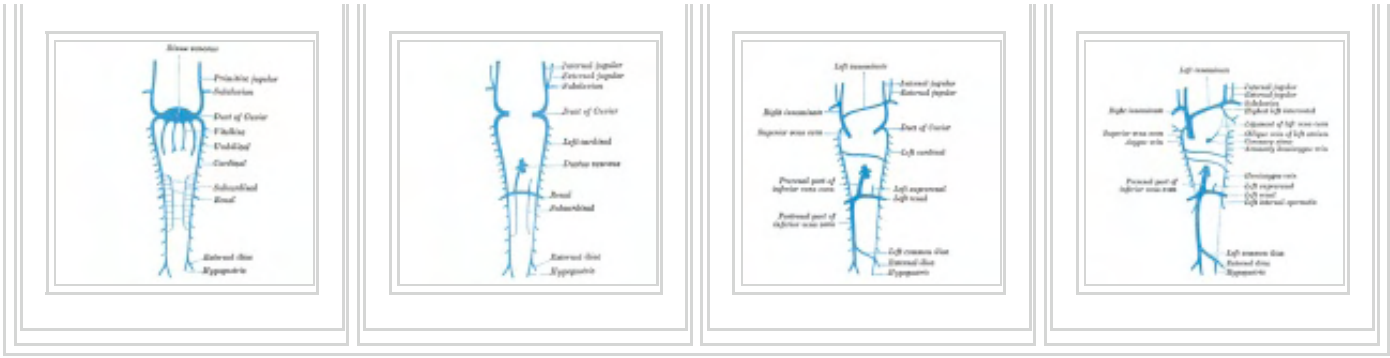
Pharyngeal arch arteries

- pharyngeal arch artery 1 and 2 regress
- pharyngeal arch artery 3 and the associated dorsal aorta form the paired internal carotid arteries, these in turn generate the external carotids
- Left pharyngeal arch artery 4 – forms the aortic arch

- paraxial mesoderm forms paired dorsal aorta
  - head mesenchyme forms aortic arches
  - connecting stalk contains unbilical (placental) arteries
  - dorsal aortas give rise to
  - vitelline arteries which connect to capillaries on yolk sac
  - intersegmental arteries between somites

Venous System

Cardinal veins contribute nearly all systemic venous system.



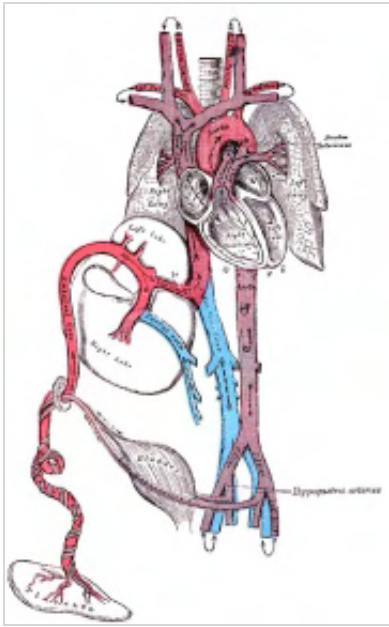
common cardinal veins - ducts of Cuvier

hepatic veins - drain de-oxygenated blood from the liver into the inferior vena cava.

internal iliac vein - hypogastric vein

Birth Changes

Fetal Structure	Adult Structure
foramen ovale	fossa ovalis
umbilical vein (intra-abdominal part)	ligamentum teres
ductus venosus	ligamentum venosum
umbilical arteries and abdominal ligaments	medial umbilical ligaments, superior vesicular artery (supplies bladder)
ductus arteriosum	ligamentum arteriosum



Fetal circulation

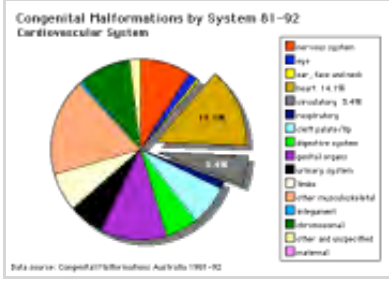
Abnormalities

There are many different cardiac abnormalities, some more common than others, and only a few will be described in this lecture.

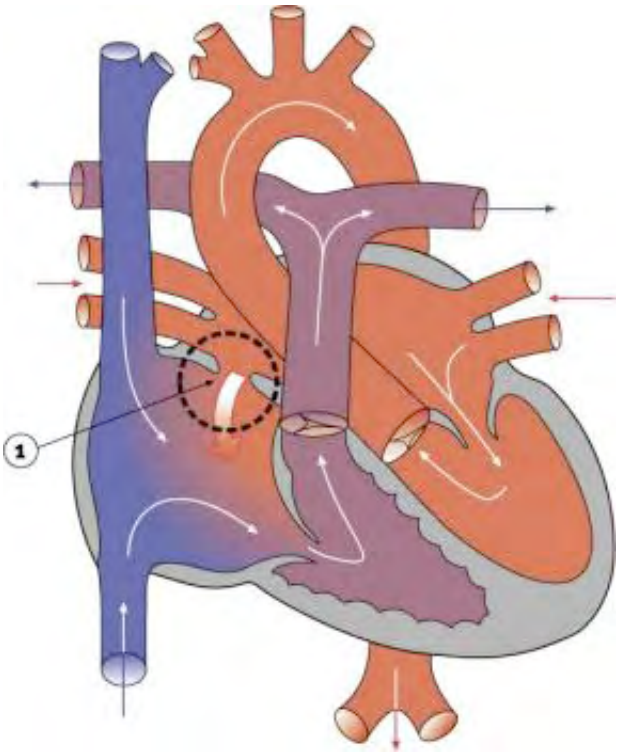
Major Abnormalities: Aortic Stenosis, Atrial Septal Defects, Coarctation of Aorta, Dextrocardia, Hypoplastic Left Heart, Long QT Syndrome, Patent Ductus Arteriosus, Pulmonary Atresia, Pulmonary Stenosis, Tetralogy of Fallot, Transposition of Great Vessels, Tricuspid Atresia, Total Anomalous Pulmonary Venous Connection, Ventricular Septal Defect, Abnormalities of Conducting System.

Links: Cardiovascular Development Abnormalities (http://embryology.med.unsw.edu.au/Notes/heart2.htm)

Atrial Septal Defects

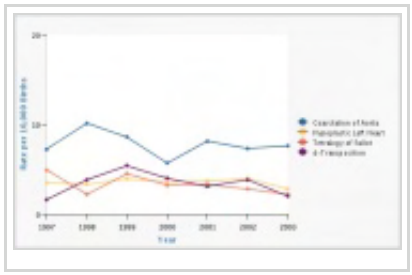


- Atrial Septal Defects (ASD) are a group of common (1% of cardiac) congenital anomolies defects occuring in a number

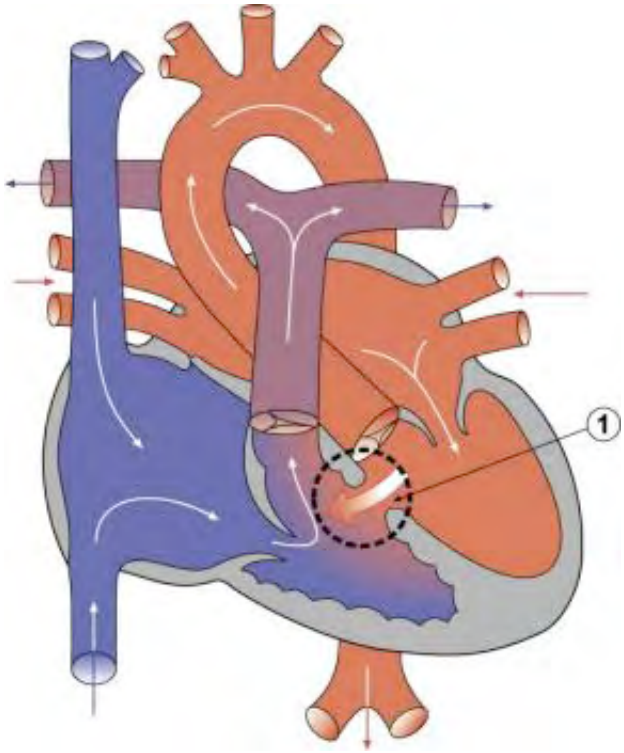


of different forms and more often in females.

- patent foramen ovale - allows a continuation of the atrial shunting of blood, in 25% of people a probe patent foramen ovale (allowing a probe to bepassed from one atria to the other) exists.
- ostium secundum defect
- endocardial cushion defect involving ostium primum
- sinus venosus defect - contributes about 10% of all ASDs and occurs mainly in a common and less common form. Common ("usual type") - in upper atrial septum which is contiguous with the superior vena cava. Less common - at junction of the right atrium and inferior vena cava.
- common atrium



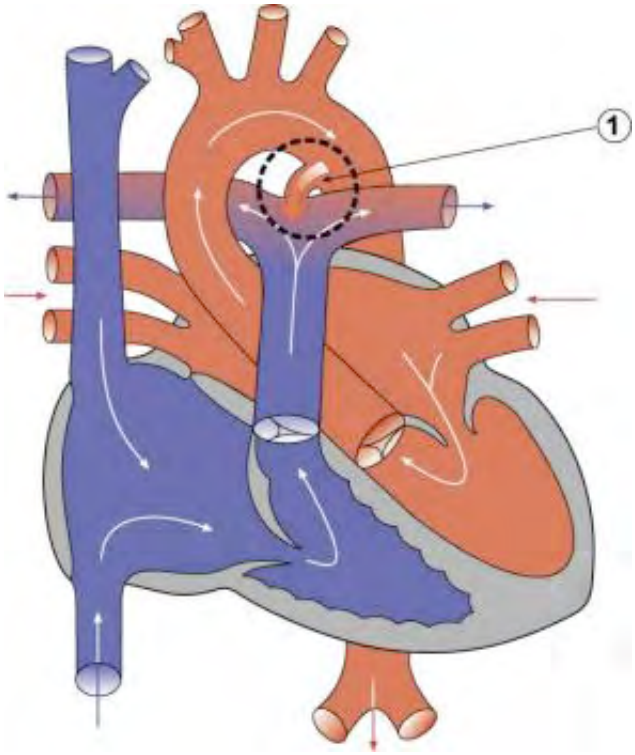
Ventricular Septal Defects



- The Ventricular Septal Defect (VSD) usually occurs in the membranous (perimembranous) rather than muscular interventricular septum, and is more frequent in males that females.
- Perimembranous defects are located close to the aortic and tricuspid valves and adjacent to atrioventricular conduction bundle.
- The defect allows left-right shunting of blood, this shunting depends upon the size of the defect. Small defects may close spontaneously, larger defects result in infant congestive heart failure.
- Clinically repaired by coils or tissue-adapted devices like muscular or perimembranous occluders.

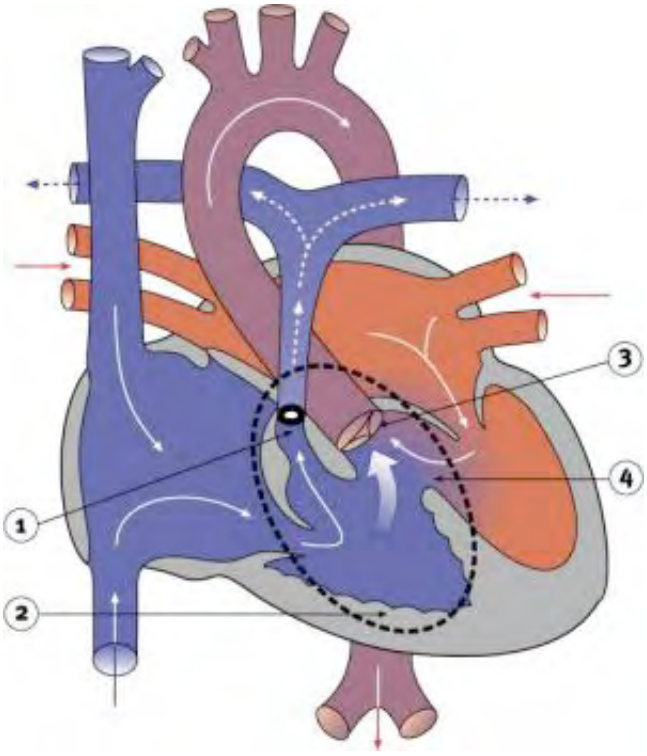
(V.S.D.)

Patent Ductus Arteriosus



- Patent Ductus Arteriosus (P.D.A.) occurs commonly in preterm infants, can close spontaneously (by day three in 60% of normal term neonates) the remainder are ligated simply and with little risk.
- The operation is always recommended even in the absence of cardiac failure and can often be deferred until early childhood.

Tetralogy of Fallot



- Named after Etienne-Louis Arthur Fallot (1888) who described it as "la maladie blue" and is a common developmental cardiac defect.
- The syndrome consists of a number of a number of cardiac defects possibly stemming from abnormal neural crest migration.

Movies




Heart Looping Heart Realign Heart Atrial Septation Heart Outflow Septation

UNSW Embryology - Heart Movies (http://embryology.med.unsw.edu.au/Movies/heart.htm)

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Original Glossary (http://embryology.med.unsw.edu.au/Notes/Index/Index.htm)

Course Content 2009

Embryology Introduction | Cell Division/Fertilization | Cell Division/Fertilization | Week 1&2 Development | Week 3 Development | Lab 2 | Mesoderm Development | Ectoderm, Early Neural, Neural Crest | Lab 3 | Early Vascular Development | Placenta | Lab 4 | Endoderm, Early Gastrointestinal | Respiratory Development | Lab 5 | Head Development | Neural Crest Development | Lab 6 | Musculoskeletal Development | Limb Development | Lab 7 | Kidney | Genital | Lab 8 | Sensory - Ear | Integumentary | Lab 9 | Sensory - Eye | Endocrine | Lab 10 | **Late Vascular Development** | Fetal | Lab 11 | Birth, Postnatal | Revision | Lab 12 | Lecture Audio | Course Timetable

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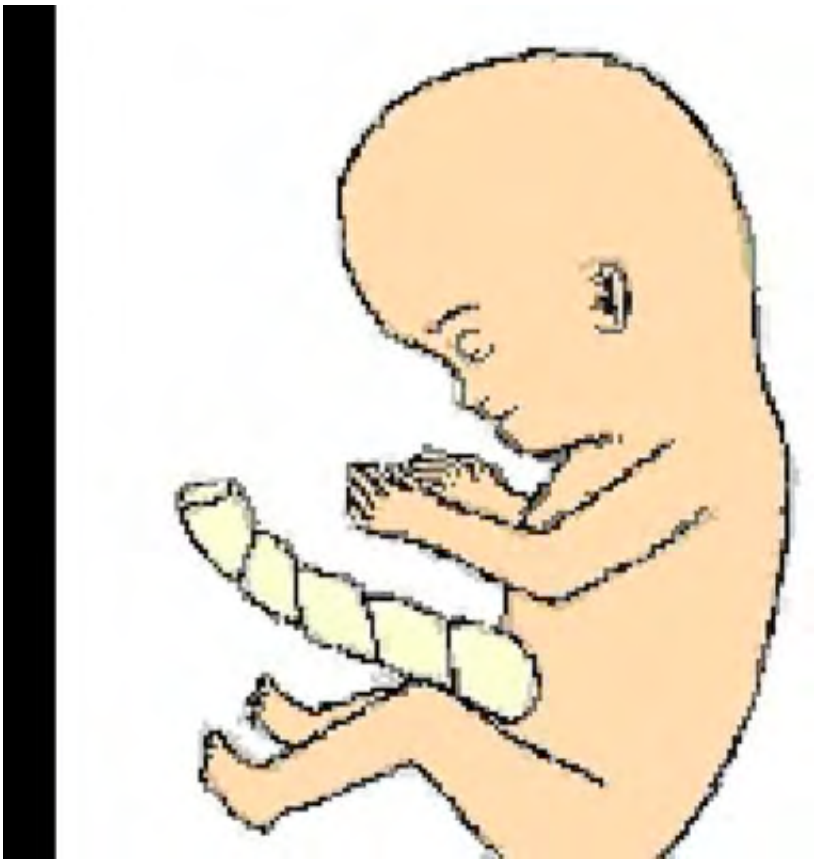
2009 Lecture 22

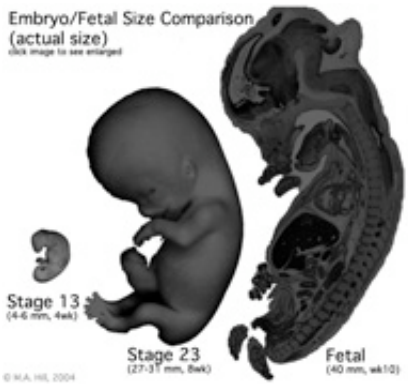
From Embryology

Contents

Fetal Development



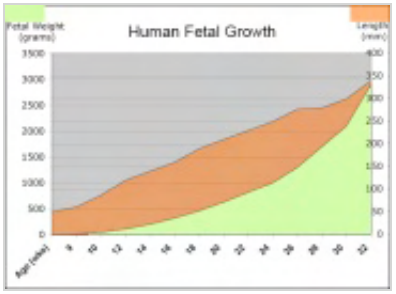
Introduction



The fetal period (9-36 weeks) is about continued differentiation of organs and tissues, most importantly this period is about growth both in size and weight.

The long Fetal period (4x the embryonic period) is a time of extensive growth in size and mass as well as ongoing differentiation of organ systems established in the embryonic period and do so at different times. For example, the brain continues to grow and develop extensively during this period (and postnatally), the respiratory system differentiates (and completes only just before birth), the urogenital system further differentiates between male/female, endocrine and gastrointestinal tract begins to function.

- First Trimester (1 - 12 weeks) - embryonic and early fetal
- Second Trimester (13 - 24 weeks) - organ development and function, growth
- Third Trimester (25 - 40 weeks) - organ function and rapid growth



Fetal length and weight changes

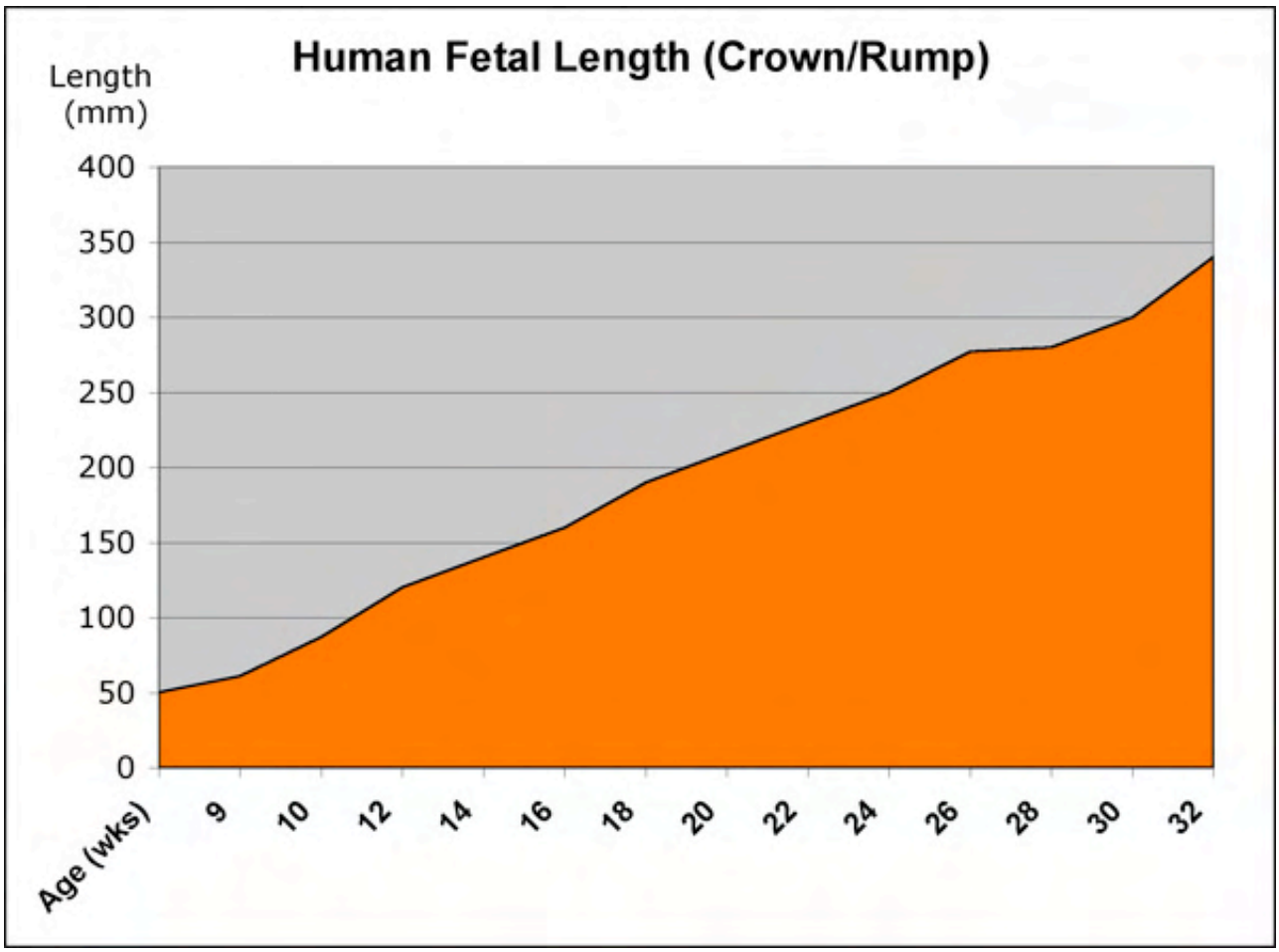
Lecture Audio Lecture Date: 13-10-2009 Lecture Time: 12:00 Venue: BioMed E Speaker: Mark Hill Fetal (http://lectopia.elearning.unsw.edu.au/ilectures/ilectures.lasso?ut=153&id=48845)

Textbooks

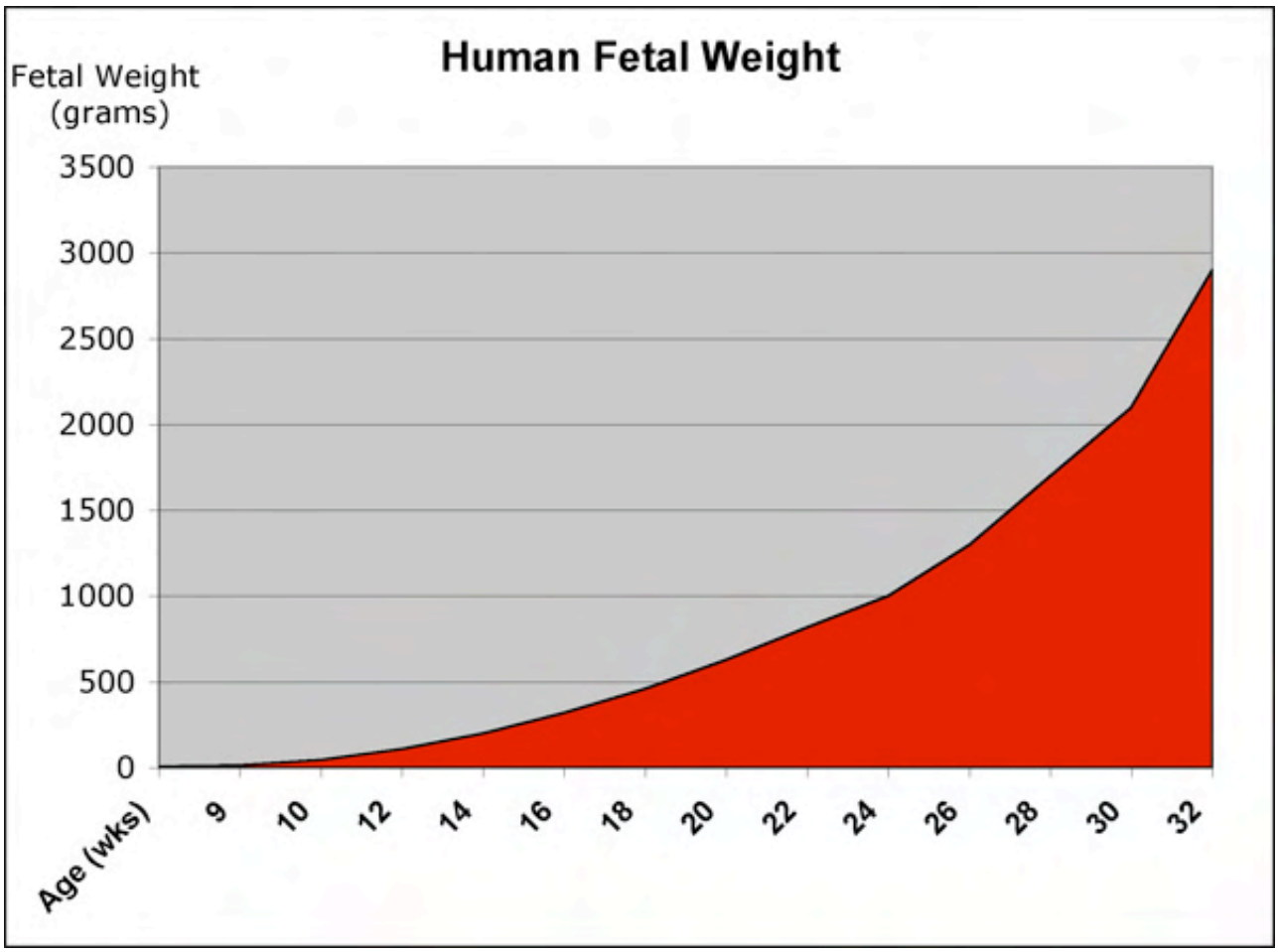
- Human Embryology (3rd ed.) Larson Ch15: Fetal development and the Fetus as Patient p481-499
- The Developing Human: Clinically Oriented Embryology (6th ed.) Moore and Persaud
- Color Atlas of Clinical Embryology (2nd ed.) Moore, Persaud and Shiota Ch3: 9th to 38th weeks of human development p50-68

Fetal Size

Fetal length change is greatest in the middle period (second trimester).



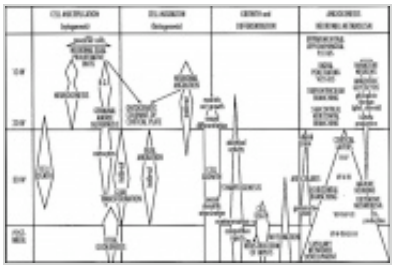
Fetal Weight



See also Fetal origins hypothesis and Normal Development - Birth - Low Birth Weight (http://embryology.med.unsw.edu.au/Child/birthweight.htm)

Fetal Neural

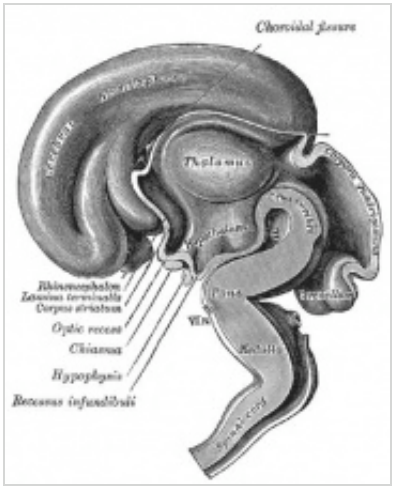
During the fetal period there is ongoing growth in size, weight and surface area of the brain and spinal cord. Microscopically there is ongoing: cell migration, extension of processes, cell death and glial cell development.



Timeline of events in Human Neural Development

Cortical maturation (sulcation and gyration) and vascularization of the lateral surface of the brain starts with the insular cortex (insula, insulary cortex or insular lobe) region during the fetal period. This cerebral cortex region in the adult brain lies deep within the lateral sulcus between the temporal lobe and the parietal lobe.

- **sulcation** - The process of brain growth in the second to third trimester which forms sulci, grooves or folds visible on fetal brain surface as gyri grow (gyration). Abnormalities of these processes can lead to a smooth brain (lissencephaly).
- **gyration** - The development of surface folds on the brain (singular, gyrus)



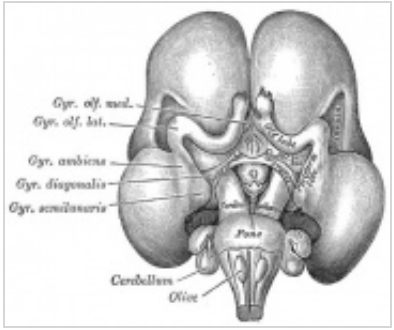
Human brain at three months (median sagittal section)

Insular Gyral and Sulcal Development

- 13-17 gestational weeks - appearance of the first sulcus
- 18-19 gestational weeks - development of the periinsular sulci
- 20-22 gestational weeks - central sulci and opercularization of the insula
- 24-26 gestational weeks - covering of the posterior insula
- 27-28 gestational weeks - closure of the laeteral sulcus (Sylvian fissure or lateral fissure)

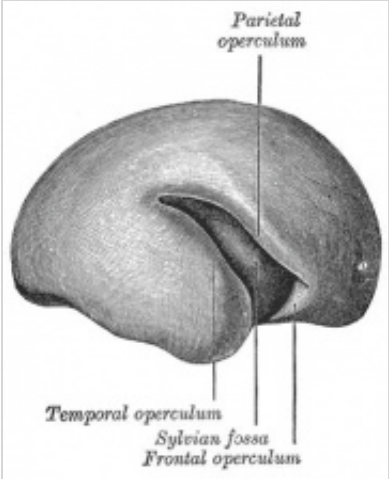
(Data from: Afif A, etal., 2007)

Three-dimensional magnetic resonance imaging and image-processing algorithms have been used to quantitate between 29-41 weeks volumes of: total brain, cerebral gray matter, unmyelinated white matter, myelinated, and cerebrospinal fluid (grey matter- mainly neuronal cell bodies; white matter- mainly neural processes and glia). A study of 78 premature and mature newborns showed that total brain tissue volume increased linearly over this period at a rate of 22 ml/week. Total grey matter also showed a linear increase in relative intracranial volume of approximately 1.4% or 15 ml/week. The rapid increase in total grey matter is mainly due to a fourfold increase in cortical grey matter. Quantification of extracerebral and intraventricular CSF was found to change only minimally.



Human brain at four months (inferior surface)

(Text - modified from Huppi etal., (1998) Quantitative magnetic resonance imaging of brain development in premature and mature newborns. Ann Neurol 43(2):224-235.)



Human brain at five months (outer surface)

Neural development will continue after birth with substantial growth, death and reorganization occuring during the postnatally (**MH** - postnatal not described in this current lecture)

Neural Development - Fetal (http://embryology.med.unsw.edu.au/Notes/neuron8.htm) | Neuroscience - Regional specification of the developing brain (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=neurosci&part=A1465&rendertype=figure&id=A1466)

Fetal Cardiovascular

MH - covered in yesterday's lecture Late Vascular Development.

- fetal neutrophils, monocytes, and macrophages are produced
- mononuclear phagocytes do not mature until after birth

Immune System

- maternal placenta transfer of IgG not other immunoglobulin isotypes.
- fetal lymphocytes (mature T and B cells) produced not activated

MH - see **Postnatal lecture** - maternal milk IgG and IgA antibodies, leukocytes, secretory IgA, lactoferrin, lysozyme, and oligosaccharides and glycoconjugates that are receptor analogs for microbial adhesins and toxins.

Fetal Respiratory

MH - covered in lecture Respiratory Development.

Month 3-6 - lungs appear glandular, end month 6 alveolar cells type 2 appear and begin to secrete surfactant.

Month 7 - respiratory bronchioles proliferate and end in alveolar ducts and sacs.

Lung Stages

- week 4 - 5 embryonic
- week 5 - 17 pseudoglandular
- week 16 - 25 canalicular
- week 24 - 40 terminal sac
- late fetal - 8 years alveolar

Fetal Genital

MH - introduced in the Genital Development lecture.

- ovary and testis development
- external genital development
- testis descent

Fetal Endocrine

Pituitary Hormones

- HPA axis established by week 20
- Pituitary functional throughout fetal development

Thyroid Hormone

- required for metabolic activity, also in the newborn
- important for neural development

Parathyroid Hormone

- newborn has total calcium levels (approx 20 grams) accumulated mainly in the 3rd trimester (weeks 28–40)
- fetal parathyroid hormone (PTH) potentially available from 10–12 weeks and PTH does not cross the placenta
- fetus relatively hypercalcemic, active transplacental transport of Ca2+ to fetus
- maternal serum - calcium ions (Ca2+), inorganic phosphate (Pi) and PTH concentrations are within the non-pregnant normal range throughout pregnancy.
- maternal bone turnover increases in the 3rd trimester.

(Based on Endocrinology - Materno—fetal calcium balance (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A742&rendertype=box&id=A876))

Pancreatic Hormones

- maternal diabetes can affect fetal pancreas development (increase in fetal islet beta cells).

Gonadal Hormones

- testosterone - required during fetal development for external genital development and internal genital tract in male.
- estrogens - secreted inactive precursor converted to active form by placenta.

Endocrinology - Control of steroid production in the fetal gonads (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=endocrin&part=A972#A1056) | Neuroscience - The Effect of Sex Hormones on Neural Circuitry (http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=neurosci&part=A2124)

Abnormalities

UNSW Embryology - Abnormal Development (http://embryology.med.unsw.edu.au/Defect/page1.htm)
Tutorial - Applied Embryology and Teratology
(http://embryology.med.unsw.edu.au/Medicine/BGD2tutorial.htm)

Teratology

How different environmental effects during the pregnancy may influence outcomes. A teratogen (Greek, teraton = monster) is defined as any agent that causes a structural abnormality (congenital abnormalities) following fetal exposure during pregnancy. The overall effect depends on dosage and time of exposure (see critical periods below).

Absolute risk - the rate of occurrence of an abnormal phenotype among individuals exposed to the agent. (e.g. fetal alcohol syndrome)

Relative risk - the ratio of the rate of the condition among the exposed and the nonexposed. (e.g. smokers risk of having a low birth weight baby compared to non-smokers) A high relative risk may indicate a low absolute risk if the condition is rare.

Mutagen - a chemical or agent that can cause permanent damage to the deoxyribonucleic acid (DNA) in a cell. DNA damage in the human egg or sperm may lead to reduced fertility, spontaneous abortion (miscarriage), birth defects and heritable diseases.

Fetotoxicant - is a chemical that adversely affects the developing fetus, resulting in low birth weight, symptoms of poisoning at birth or stillbirth (fetus dies before it is born).

Synergism - when the combined effect of exposure to more than one chemical at one time, or to a chemical in combination with other hazards (heat, radiation, infection) results in effects of such exposure to be greater than the sum of the individual effects of each hazard by itself.

Toxicogenomics - the interaction between the genome, chemicals in the environment, and disease. Cells exposed to a stress, drug or toxicant respond by altering the pattern of expression of genes within their chromosomes. Based on new genetic and microarray technologies.

Critical Periods

Human Critical Periods of development
(http://embryology.med.unsw.edu.au/Medicine/images/hcriticaldev.gif)

Fetal Origins Hypothesis

Fetal Origins Hypothesis (http://embryology.med.unsw.edu.au/Defect/page10.htm)

Maternal derived abnormalities relate to lifestyle, environment and nutrition and while some of these directly effect embryonic development. There is also growing evidence that some effects are more subtle and relate to later life health events. This theory is based on the early statistical analysis carried out by Barker of low birth weight data collected in the early 1900's in the south east of England which he then compared with these same babies later health outcomes. The theory was therefore originally called the "Barker Hypothesis" and has recently been renamed as "fetal origins" or "programming".

Glossary Links

2009 Lecture 23

From Embryology

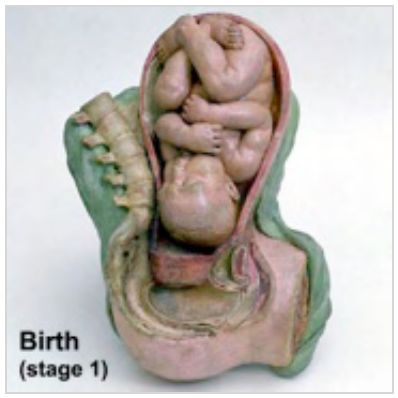
Contents

Birth and Postnatal Development

Introduction

There are a great number of comprehensive, scientific and general, books and articles that cover Parturition, Birth or Childbirth.

Birth or parturition is a critical stage in development, representing in mammals a transition from direct maternal support of fetal development, physical expulsion and establishment of the newborns own respiratory, circulatory and digestive systems.



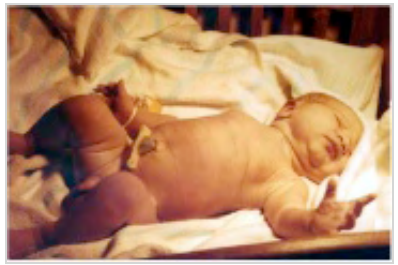
Historic model of birth

Textbooks

- Human Embryology (2nd ed.) Larson Chapter 15 p471-488
- The Developing Human: Clinically Oriented Embryology (6th ed.) Moore and Persaud Chapter 7 p129-167

Gestation Period

The median duration of gestation for first births from assumed ovulation to delivery was **274** days (just over 39 weeks). For multiple births, the median duration of pregnancy was **269** days (38.4 weeks).

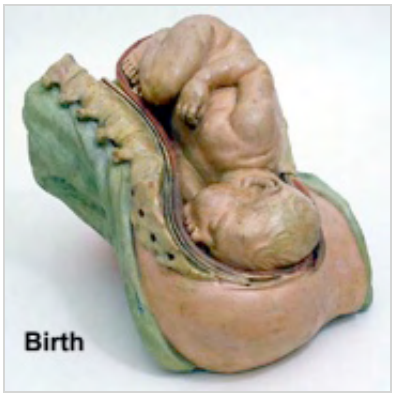

Newborn

> "...one should count back 3 months from the first day of the last menses, then add 15 days for primiparas or 10 days for multiparas, instead of using the common algorithm for Naegele's rule."
> Reference: Mittendorf R, Williams MA, Berkey CS, Cotter PF. (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=16547957&dopt=Abstract) The length of uncomplicated human gestation. Obstet Gynecol. 1990 Jun;75(6):929-32

Historically, Franz Carl Naegele (1777-1851) developed the first scientific rule for estimating length of a pregnany.

Childbirth

- Parturition (Latin, *parturitio* = "childbirth") describes expelling the fetus, placenta and fetal membranes and is probably initiated by fetus not mother.
- Preterm birth - Risks of preterm birth in abnormal low birth weight (intrauterine growth restriction) and high (large for gestational age) categories are 2- to 3-fold greater than the risk among appropriate-for-gestational-age infants.
- Maternal labor - uterine contractions and dilation of cervix, process under endocrine regulation
- Placenta and fetal membranes - (Latin, *secundina* = "following") expelled after neonate birth



Birth Stage 2

Uterine Myometrial Changes

- Smooth muscle fibers - hypertrophy not proliferation
- Stretching of myometrium - stimulates spontaneous muscular contraction, during pregnancy progesterone inhibits contraction
- Stimulating contraction - increased estrogen levels (placental secretion sensitizes smooth muscle), increased oxytocin levels (fetal oxytocin release- force and frequency of contraction), fetal pituitary prostaglandin production (estrogen and oxytocin stimulate endometrial production of prostaglandin)

Progesterone

- maintains pregnancy - initially synthesized by corpus luteum, then levels maintained by placenta
- hyperpolarizes myometrial cells (-65 mV), reduces excitability and conductivity
- Level in plasma may fall just before parturition, definitely decreases following delivery of placenta

Estrogens

- Group of steroidal hormones, peak when parturition begins
- induce increased synthesis of actomyosin and ATP in myometrial cells
- alter membrane potential (-50 Mv) enhances excitation/conduction
- act to directly increase myometrial contraction
- indirectly by increasing oxytocin from pituitary gland
- Estriol - synthesized by fetus and placenta

Oxytocin

- Peptide hormone (8aa) from maternal posterior pituitary, initiation and maintenance of labour (synthetic form labour induction)
- myometrium sensitivity to oxytocin (increased by estrogen, decreased by progesterone)
- stimulus for release - mechanical stimulation of uterus, cervix and vagina (ethanol inhibits release)

Prostaglandins

- hydroxy fatty acids - sythesized by placenta, amniotic fliud contains mainly PGF2 alpha, causes myometrial contraction (also in maternal plasma)
- PGF2 alpha and PGE2 - used to induce labour (intravenous, oral, intravaginal, intraamniotic)
- Aspirin inhibitor of PG synthesis - leads to increased duration of pregnancy

External Environment

- mainly shown in other species parturition occurs in peaceful undisturbed surroundings, stress may have an inhibitory effect on oxytocin release

- Most human births occur at night (peak at 3am) diurnal rhythm influence

Labor Stages

Stage 1 - dilatation

- uterine contractions 10 minutes apart, function to dilate cervix fetal membranes rupture releasing amnion, 7 -12 hours (longer for first child)

Stage 2 - expulsion

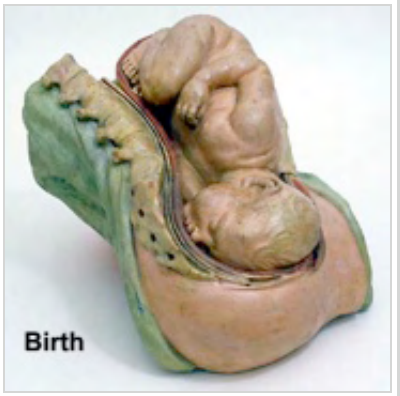
- uterine contractions push fetus through cervix and vagina, contractions 2-3 minutes apart, 20 - 50 minutes

Stage 3 - placental

- following child delivery contractions continue to expel placenta. haematoma separates placenta from uterine wall, separation occurs at spongy layer of decidua basalis, 15 minutes

Stage 4 - recovery

- continued myometrial contraction closes spiral arteries, 2+ hours



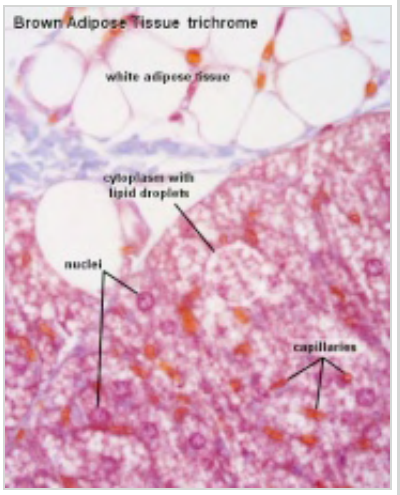
Birth Stage 2

Newborn Homoeostasis

Newborn has to establish new functioning systems in a balanced and regulated manner (homoeostasis).

- lung function
- circulatory changes
- thermoregulation
- endocrine function
- nutrition
- gastrointestinal tract function
- waste
- kidney function

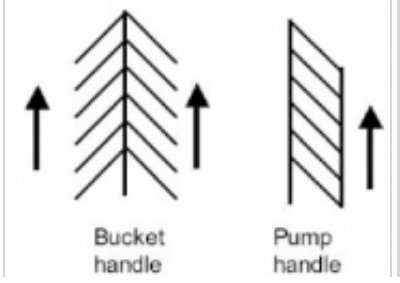
Glucocorticoids - have an important role in the preparation for birth, including involvement in lung and cardiac development, and the maturation of enzymes in a variety of pathways.



Brown adipose tissue

Respiration

- Lungs at birth collapsed and fluid-filled - replaced with air by powerful inspiratory movement and absorption through the alveoli
- Lung epithelia has to rapidly change from its prenatal secretory function to that of fluid absorbtion.
  - initiated by a late fetal change in alveolar epithelial cell (AEC) chloride and fluid secretion to sodium and fluid absorption.
  - absorption requires sodium-potassium ATPase (Na-K-



ATPase) together with apical sodium entry mechanisms (Epithelial Sodium Channels, ENaC)
    - Fetal thyroid hormone is thought to have a hormonal role in this developmental switch

Neonatal rib orientation

- These changes and pressure also lead to the pulmonary sytem becoming activated and changes in the circulatory shunting that existed before birth.
- During the late fetal period regular fetal breathing movements (FBM) also occur preparing both the skeletomuscular sysyem and lungs mechanically for respiration.
- Respiratory Rate is higher than adult (30 breaths/minute).
- Rib Orientation - Infant rib is virtually horizontal, allowing diaphragmatic breathing only. Adult rib orientation is oblique (both anterior and lateral views), allows for pump-handle and bucket handle types of inspiration.

Postnatal Development - Respiratory (http://embryology.med.unsw.edu.au/Child/page5.htm)

Cardiovascular

- **Umbilical Vasculature** - The umbilical blood vessel cavity is lost postnatally over the course of weeks to months after birth. The adult anatomical remnant of the umbilical vein between the umbilicus and liver is the ligamentum teres.
- **Foramen Ovale** - two separate forms of foramen ovale closure; functional and structural. Functional closure begins at the first breath and is rapid. Structural (anatomical) closure is much slower and generally occurs before the end of the first year.
- **Ductus Arteriosus** - a direct connection between the pulmonary trunk and the dorsal aorta. Postnatal closure occurs initially by by smooth muscle contraction and begins at the first breath and is rapid, completed within the first day (about 15 hr after birth). Anatomical closure is much slower occuring by 2–3 weeks after birth (33% of infants), by 2 months (90% of infants) and by 1 year (99% of infants). The adult anatomical remnant of the ductus arteriosus is the ligamentum arteriosum.
- **Ductus Venosus** - connects portal and umbilical blood to the inferior vena cava. Functional closure occurs postnatally within hours. Structural closure commences days after birth and completes by 18 to 20 days. The adult anatomical remnant of the ductus venosus is the ligamentum venosum (a dorsal fissure on the liver).

Neonatal Testing

APGAR

Measured at one and five minutes after birth the Score values are totalled for all indicators: 7-10 is considered normal, 4-7 may require resuscitative measures, 3 and below require immediate resuscitation.

In recent years there has been some controversy of the relevance and accuracy of some of the criteria used in this test, though many feel it is still an invaluable initial assessment tool particularly where medical services are limited.

Indicator	*Score 0*	*Score 1*	*Score 2*
Activity (muscle tone)	Limp; no movement	Some flexion of arms and legs	Active motion
Pulse (heart rate)	No heart rate	Fewer than 100 beats per minute	At least 100 beats per minute

Grimace (reflex response)	No response to airways being suctioned	Grimace during suctioning	Grimace and pull away, cough, or sneeze during suctioning
Appearance (color)	The baby's whole body is completely bluish-gray or pale	Good color in body with bluish hands or feet	Good color all over
Respiration (breathing)	Not breathing	Weak cry; may sound like whimpering, slow or irregular breathing	Good, strong cry; normal rate and effort of breathing

Reference: Apgar, V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg. 1953 Jul-Aug;32(4):260-7. PMID:13083014 (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=13083014)

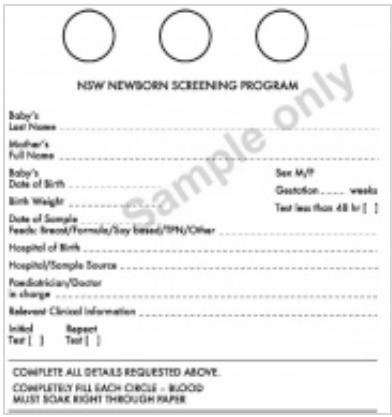
Guthrie Test

- Blood is collected using a heelprick and spotted onto a test sheet to dry for later testing.
- Different countries and medical services have different policies on not only what will be diagnostically tested, but also how long the test card will be kept following analysis.


Robert Guthrie

Routine Screened Disorders

- Biotinidase Deficiency (OMIM (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253260))
- Congenital Adrenal Hyperplasia (CAH) (OMIM (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=201910))
- Congenital Hypothyroidism (CH)
- Congenital Toxoplasmosis
- Cystic Fibrosis (CF) (OMIM (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=219700))
- Galactosemia (GAL) (OMIM (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=230400))
- Homocystinuria (OMIM (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=236200))
- Maple Syrup Urine Disease (MSUD) (OMIM (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=248600))
- Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD) (OMIM (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=201450))



Guthrie card

Heart

- An electrocardiogram (ECG / EKG) is an electrical recording of the heart which may identify electrical disorders including long QT syndrome.

Hip Displasia

- Non-specific hip instability is a common finding in newborns, particularly in females.
- More than 80% of clinically unstable hips at birth resolve spontaneously. Screening newborns for Developmental dysplasia of the hip (DDH) shows an incidence in infants between 1.5 and 20 per 1000 births. This incidence is influenced by several factors (diagnostic criteria, gender, genetic and racial factors, and age of the population).

Links: Musculoskeletal Abnormalities- Congenital Dislocation of the Hip (http://embryology.med.unsw.edu.au/Notes/skmus2.htm#HIPDISLOCATION) | [hipdyssyn.pdf Screening for Developmental Dysplasia of the Hip PDF] | Screening for developmental dysplasia of the hip. Evidence synthesis no. 42. Rockville, Md.: Agency for Healthcare Research and Quality http://www.ahrq.gov/downloads/pub/prevent/pdfser/hipdyssyn.pdf | U.S. Preventive Service Task Force. (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16770931) Screening for developmental dysplasia of the hip: recommendation statement. Am Fam Physician. 2006 Jun 1;73(11):1992-6.

Hearing

- The incidence of significant permanent hearing loss is approximately 1-3/1000 newborns.
- Neonatal hearing screening is carried out in the USA, UK and in Australia (2002 NSW Statewide Infant Screening Hearing Program, SWISH) There is a general guide giving a timetable for a number of simple responses that a neonate should make if hearing has developed normally.
- State Wide Infant Screening Hearing Program (SWISH) a newborn hearing testing program using an automated auditory response technology (AABR). Program was introduced in NSW Australia in 2002 across 17 area health service coordinators. It is thought that in NSW 86,000 births/year = 86-172 babies potentially born with significant permanent hearing loss.
- Automated Auditory Brainstem Response (AABR) uses a stimulus which is delivered through earphones and detected by scalp electrodes. The test takes between 8 to 20 minutes and has a sensitivity 96-99%.

Premature Birth

Year	< 34 weeks %	34-36 weeks %	total preterm %
1990	3.3	7.3	10.6
1995	3.3	7.7	11
2000	3.4	8.2	11.6
2005	3.6	9.1	12.7


Premature infant

Data from: Prevention of preterm birth: a renewed national priority Damus K. Curr Opin Obstet Gynecol. 2008 Dec;20(6):590-6 PMID: 18989136 (http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=18989136&dopt=Abstract)

Australia Recommendations

Perinatal care at the borderlines of viability: a consensus statement based on a NSW and ACT consensus workshop (February 2005) published in The Medical Journal of Australia 2006; 185 (9): 495-500.

- < 23 weeks survival is minimal and the risk of major morbidity is so high that initiation of resuscitation is not appropriate.
- 23 weeks active treatment may be discussed, but would be discouraged in NSW/ACT neonatal

intensive care units.
- 23 to 25 weeks otherwise normal infant, there is an increasing obligation to treat. However, it is acceptable medical practice not to initiate intensive care if parents so wish, following appropriate counselling.
- 24 weeks antenatal transfer to a tertiary centre for fetal reasons is indicated. The option of non-initiation of intensive care/resuscitation should be offered.
- 25 weeks active treatment is usually offered, but the option of non-initiation of intensive care/resuscitation (presence of adverse fetal factors such as twin-to-twin transfusion, intrauterine growth restriction or chorioamnionitis) should also be discussed.
- 26 weeks + otherwise normal infant the obligation to treat is very high, and treatment should generally be initiated unless there are exceptional circumstances.

Abnormalities

There are many birth associated abnormalities, only a few examples are listed below. (More? Abnormal Development (http://embryology.med.unsw.edu.au/Defect/page1.htm))

Labor Abnormalities

- **Premature Labor** - occurs 7 -10% in humans, contributes 75% perinatal mortalities
- **Underdeveloped Systems** - particularly respiratory, surfactant, hyaline membrane disease (see respiratory development lecture)

Placental Abnormalities

- **placenta accreta** - abnormal adherence, with absence of decidua basalis
- **placenta percreta** - villi penetrate myometrium
- **placenta previa** - placenta overlies internal os of uterus, abnormal bleeding, cesarian delivery

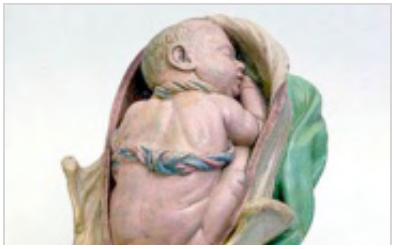
Breech Delivery

- Historically, breech-born children were called *agrippi*, meaning "delivered with difficulty" (aegre parti).
- Breech position - occurs in about 3% of fetuses when buttocks or lower limb are presented to the birth canal rather than normal cephalic (head-first) position (presentation).
- Associated increased - perinatal mortality, perinatal morbidity, recurrence in successive siblings


Breech Birth

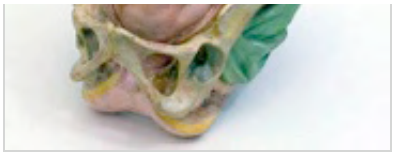
Current research suggests that genetically that both men and women delivered in breech presentation at term could also contribute to an increased risk of breech delivery in their offspring. ([#18369204 Nordtveit TI, etal., 2008])

Meconium aspiration syndrome



- meconium is formed from gut and associated organ secretions as well as cells and debris from the swallowed amniotic fluid.
- Meconium accumulates during the fetal period in the large intestine (bowel). It can be described as being a generally dark colour (green black) , sticky and odourless.

- Normally this meconium is defaecated (passed) postnatally over the first 48 hours and then transitional stools from day 4.
- Abnormally this meconium is defaecated in utero, due to oxygen deprivation and other stresses. Premature discharge into the amniotic sac can lead to mixing with amniotic fluid and be reswallowed by the fetus. This is meconium aspiration syndrome and can damage both the developing lungs and placental vessels.

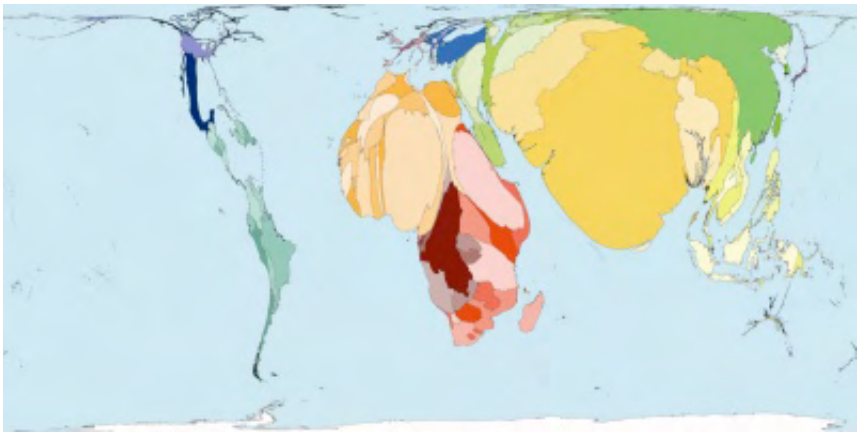


Breech Birth

Necrotizing Enterocolitis

Occurs postnatally in mainly in premature and low birth weight infants (1 in 2,000 - 4,000 births). The underdeveloped gastointestinal tract appears to be susceptible to bacteria, normally found within the tract,to spread widely to other regions where they damage the tract wall and may enter the bloodstream.

Stillbirth and Perinatal Death



Perinatal period is the early postnatal period relating to the birth, statistically it includes the period up to 7 days after birth. Neonatal period is the four weeks/month after birth. Stillbirth and Perinatal Death (http://embryology.med.unsw.edu.au/Child/birth7.htm)

NSW perinatal mortality rate

In New South Wales (2002) 613 perinatal deaths were reported.

- Unexplained antepartum deaths: 26.3% of perinatal deaths (or 39.2% of stillbirths)
- Spontaneous preterm labour: 20.6% (less than 37 weeks gestation)
- Congenital abnormality: 16.8%
- Antepartum haemorrhage: 8.5%
- Specific perinatal conditions: 7.3%, of which twin-twin transfusion accounted for 2.3% of deaths
- Hypertension (high blood pressure): 5.5%
- Perinatal infection: 4.4%
- Maternal disease: 4.4%
- Hypoxic peripartum death: 3.8%

Neonatal deaths (four weeks/month after birth)

- extreme prematurity was most common cause (39.6%)
- congenital abnormality (19.3%)
- neurological disease (13.4%)
- cardio-respiratory conditions (11.9%)
- infection (8.4%)

Data: Report of the New South Wales Chief Health Officer, 2004 accessed 19Oct05

Links

- **UNSW Embryology** Introduction (http://embryology.med.unsw.edu.au/Child/birth1.htm) | Birth Overview (http://embryology.med.unsw.edu.au/Child/birth3.htm) | Abnormalities (http://embryology.med.unsw.edu.au/Child/birth2.htm) | Caesarean (http://embryology.med.unsw.edu.au/Child/birth6.htm) | Apgar (http://embryology.med.unsw.edu.au/Child/apgar.htm) | Premature (http://embryology.med.unsw.edu.au/Child/birthpremature.htm) | Low Birth Weight (http://embryology.med.unsw.edu.au/Child/birthweight.htm) | Placental Cord Clamping (http://embryology.med.unsw.edu.au/Child/birth8.htm) | Cardiovascular (http://embryology.med.unsw.edu.au/Child/birthheart.htm) | Stillbirth and Perinatal Death (http://embryology.med.unsw.edu.au/Child/birth7.htm) | Molecular (http://embryology.med.unsw.edu.au/Child/birth10.htm) Web Links (http://embryology.med.unsw.edu.au/Child/birthlink.htm)
- **Birth Statistics** Australian Birth Statistics (http://embryology.med.unsw.edu.au/Stats/page2.htm) | International and Australian Population Statistics (http://embryology.med.unsw.edu.au/Stats/page1.htm) | WHO Normal Population Statistics (http://embryology.med.unsw.edu.au/Stats/page3.htm) | WHO Fact Sheets (http://www.who.int/inf-fs/en/index_n.html) | Global Perinatal and Maternal Causes of Death (http://embryology.med.unsw.edu.au/Stats/page3a.htm#perinatal) | Population Comparisons between Countries (http://embryology.med.unsw.edu.au/Stats/page4a.htm) | Developed and developing (http://embryology.med.unsw.edu.au/Stats/page4a.htm#Population%20Data) | Australian neighbours (http://embryology.med.unsw.edu.au/Stats/page4a.htm#au1) | Australian Trading Partners (http://embryology.med.unsw.edu.au/Stats/page4a.htm#au2)

Birth Terms

amniotomy - birth medical procedure thought to speed labor, where the amniotic sac is artificially ruptured using a tool (amniohook).

breech - fetal buttocks presented first and can also occur in different forms depending on presentation (complete breech, frank breech, footing breech, knee breech).

decidual activation - increased uterine proteolysis and extracellular matrix degradation.

dilatation - opening of the cervix in preparation for birth (expressed in centimetres).

effacement - shortening or thinning of the cervix, in preparation for birth.

forceps - mechanical "plier-like" tool used on fetal head to aid birth.

fetal macrosomia - clinical description for a fetus that is too large, condition increases steadily with advancing gestational age and defined by a variety of birthweights. In pregnant women anywhere between 2 - 15% have birth weights of greater than 4000 grams (4 Kg, 8 lb 13 oz).

membrane rupture - breaking of the amniotic membrane and release of amniotic fluid (water breaking).

morbidity - (Latin, *morbidus* = "sick" or "unhealthy") refers to a diseased state, disability, or poor health due to any cause.

presentation - how the fetus is situated in the uterus.

presenting part - part of fetus body that is closest to the cervix.

second stage of labour - passage of the baby through the birth canal into the outside world.

Vacuum Extractor - suction cap device used on fetal head to aid birth.

Vertex Presentation (cephalic presentation) where the fetus head is the presenting part, most common and safest birth position.

Glossary Links

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z | Numbers | Original Glossary (http://embryology.med.unsw.edu.au/Notes/Index/Index.htm)

Course Content 2009

Embryology Introduction | Cell Division/Fertilization | Cell Division/Fertilization | Week 1&2 Development | Week 3 Development | Lab 2 | Mesoderm Development | Ectoderm, Early Neural, Neural Crest | Lab 3 | Early Vascular Development | Placenta | Lab 4 | Endoderm, Early Gastrointestinal | Respiratory Development | Lab 5 | Head Development | Neural Crest Development | Lab 6 | Musculoskeletal Development | Limb Development | Lab 7 | Kidney | Genital | Lab 8 | Sensory - Ear | Integumentary | Lab 9 | Sensory - Eye | Endocrine | Lab 10 | Late Vascular Development | Fetal | Lab 11 | **Birth, Postnatal** | Revision | Lab 12 | Lecture Audio | Course Timetable

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