Embryology and Gender Determination *in utero*
• Inheritance, remember, is the passage of hereditary traits from one generation to another.

• It is, likewise, the mechanism by which each individual acquired his or her characteristics from his or her parents and how these individuals will transmit their characteristics to their children.
examples of some traits that have been determined to be dominant or recessive:

<table>
<thead>
<tr>
<th>Dominant</th>
<th>Recessive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curly hair</td>
<td>Straight hair</td>
</tr>
<tr>
<td>Brachydactylism (short fingers)</td>
<td>Normal digits</td>
</tr>
<tr>
<td>Dark brown hair</td>
<td>All other hair colors</td>
</tr>
<tr>
<td>Syndactylism (webbed)</td>
<td>Normal digits</td>
</tr>
<tr>
<td>Coarse body hair</td>
<td>Fine body hair</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Normal blood pressure</td>
</tr>
<tr>
<td>Male pattern baldness</td>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Brachydactylism (short fingers)</td>
<td>Normal ADH/AVP secretion</td>
</tr>
<tr>
<td>Normal skin pigmentation</td>
<td>Normal mentality</td>
</tr>
<tr>
<td>Normal digits</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Brown eyes</td>
<td>Migraines</td>
</tr>
<tr>
<td>Blue or grey eyes</td>
<td>Normal</td>
</tr>
<tr>
<td>Dominant</td>
<td>Recessive</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Near/far sighted</td>
<td>Disease resistance</td>
</tr>
<tr>
<td>Normal hearing</td>
<td>A or B blood factor</td>
</tr>
<tr>
<td>Normal color vision</td>
<td>Rh blood factor</td>
</tr>
<tr>
<td>Broad lips</td>
<td></td>
</tr>
<tr>
<td>Large eyes</td>
<td></td>
</tr>
<tr>
<td>Polydactylism (extra digits)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** columns 1 and 3 pair up.  
**Note:** columns 2 and 4 pair up.  
**Note:** These columns compare dominant *vs.* recessive traits, directly.
• As with any new section, definitions and terms are necessary to navigate one's way through the new information.

• The first set of terms and definitions that follow are terms used in the prenatal period.
• An abortion is the birth of an embryo or fetus before it is viable. All terminations of pregnancy that occur before 20 weeks are called abortions.

• A miscarriage is used colloquially to refer to any interruption of pregnancy that occurs before term. Medically it is most accurate to use spontaneous abortion for the birth of an embryo or fetus to about 20 weeks. Thereafter, the event is termed a premature birth.

• Spontaneous (biologically/genetically driven) abortions end pregnancies in about 15% of recognized pregnancies (usually during the first 12 weeks of gestation).

• Induced abortions are legal, purposeful abortions designed to end the pregnancy.

• Therapeutic abortions are induced due to the mother's health or to prevent the birth of a severely malformed child.

• The abortus is any or all products of an abortion weighing 500 grams.
• An oocyte is the immature ovum or female germ cell.
• The zygote is the beginning of a human being.
• It results from the fertilization of an oocyte by a sperm.
• The expression "fertilized ovum" means zygote and is redundant.
• **Cleavage** is the mitotic division of the zygote. It results in daughter cells called blastomeres. At each successive division, the blastomeres become increasingly smaller.

• A **morula** is a solid ball of cells consisting of 12-16 blastomeres. Morula comes from the Latin "morus" which means mulberry, which is what the morula resembles. It occurs about 3 days after fertilization. The centrally located cells (a.k.a. the inner cell mass) will form the embryo.

• A **blastocyst** is the morula after the morula enters the uterus. After entering the uterus, the morula develops a fluid-filled cavity inside itself.

• The **gastrula** is an embryo going through gastrulation, the period during which the trilaminar disc forms.

• The **neurula** is the embryo in the period during which the neural plate forms and closes to form the neural tube. This period is called neurulation.
• The "embryo" term is not used until the 2d week after the embryonic disc forms. The embryonic period extends until the end of the 8th week, by which time the beginnings of all major structures are present.

• The term "fetus" is used after the end of the 8th week. The fetal period is from the 9th week until birth. Many systems further develop. The rate of body growth is remarkable (particularly during the 3d and 4th months) and weight gain is phenomenal during the terminal months.
• **Conceptus** is a term applied to the embryo (or fetus) and its membranes, i.e., the products of conception. It includes all structures that develop from the zygote, both embryonic and extra-embryonic. Hence, it includes, besides the embryo/fetus, the placenta and membranes.

• The **primordium** is the first trace of, or indication of, an organ or structure, i.e., its earliest stage of development. Primus is Latin for "first"; ordior is Latin for "to begin". A trimester is the three periods of gestation, three months long. Obstetricians commonly divide the nine calendar months of gestation into these periods.
terms and definitions for the postnatal period
• **Infancy** is the first year or so after birth. The body as a whole grows particularly rapidly during infancy. The total length of the baby increases by about half and weight is usually tripled. The neonatal period is the first two weeks after birth.

• **Childhood** is the period from about 15 months to 12 or 13 years of age. Primary teeth appear and are replaced by permanent teeth. Growth just before puberty accelerates and is called the pre-pubertal growth spurt.

• **Puberty** is the period between 12 and 15 for girls and 13 and 16 years in boys. This is the period in development when the secondary sex characteristics develop. (Note: these ages are dropping in today's society. This is probably due to the high level of nutrition we are experiencing and/or to the high levels of fat in our diets that allow the sex hormones to be synthesized sooner.)
• **Adolescence** is the period 3 or 4 years after puberty. It extends from the earliest signs of sexual maturity until the attainment of physical, mental and emotional maturity.

• The general growth rate decelerates, but growth of some structures accelerates, e.g., the female breasts.

• **Adulthood** is the period following adolescence. Ossification and growth are virtually completed during early adulthood (18-25 years of age).

• Thereafter, developmental changes occur very slowly, usually resulting in selective loss of highly specialized cells and tissues.
"Zygogenesis"
• In order to form a zygote, two cells are needed: a sperm and an ovum.
• Anatomically, the sperm resembles a teardrop with a long tail. At the head of the sperm is the acrosome that contains hydrolytic enzymes necessary to permit the sperm to penetrate the ovum.
• Inside the head of the sperm is the DNA that will comprise half of an individual.
• The neck, or midpiece, of the sperm contains the mitochondria that provide the energy to drive the tail so that the sperm will migrate towards/through the female's reproductive system.
• Follicular cells of the corona radiata (radiating halo) surround the secondary oocyte.
• These cells bound on the zona pellucida.
• Farther in and next to the zona pellucida is the perivitelline space, which contains the first polar body and surrounds the secondary oocyte.
Capacitation and Fertilization

- Top Figure illustrates the events that occur after the sperm have migrated into the uterus or fallopian tubes.
- In short, the enzymes in the acrosome make the head membrane "leaky" (capacitation). This process takes around 7 hours.
- Bottom Figure illustrates how the sperm penetrates (fertilizes) the secondary oocyte by passing through the corona radiata so that the leaky head comes into contact with the zona pellucida.
- The enzymes (at least a hyaluronidase) cause the partial destruction of the zona pellucida in such a manner that the sperm may penetrate the zona pellucida, fuse its outer membranes with the cell membrane of the secondary oocyte (Graafian follicle) and "dump" its nuclear/genetic material inside the oocyte.
• Figure A illustrates the presence of the sperm DNA and remnants inside the "secondary oocyte".

• Figure B illustrates that the sperm tail remnants and mitochondrial remnants are degenerating during the formation of a male pro-nucleus.
Figure C shows that the two pronuclei are fusing to form one single nucleus that will initiate by some, as yet unknown, mechanism the process of mitosis (Figure D) in the now-formed zygote.

The period of pronuclei formation to complete zygote formation takes approximately 14 days, i.e., week 0 to week 2 of gestation.

Note also that the illustration in Figure D represents the appearance of the zygote at 24 hours of age.
Under usual conditions, one sperm plus one ovum gives one new zygote. There are times, though, when one sperm and one ovum give multiple births. The example of multiple births here is that of twins.

When one sperm and one ovum unite and produce twins, these twins are monozygotic and identical.

70-75% of the time, they are monochorionic, diamniotic and monoplacental.

Their gender is identical and their genetics are identical. Their fingerprints and retinal scans are different and their hearts may be mirror images of each other, i.e., one twin may exhibit dextro-cardiorotation, or the heart is rotated to the right side of the chest instead of the left.
• 25-30% of the time, identical twins will be dichorionic (mono in graphic, right), diamniotic and diplacental.
• Somewhere around 1% of the time, monozygotic twins may be monochorionic and monoamniotic.
• Fraternal twins are dizygotic twins, i.e., result from the fertilization of two ova by 2 sperm. These twins are dichorionic, diamniotic and diplacental. Their genders are not necessarily identical and their genetics are not identical.
The morula at about 3 days after fertilization. Fertilization generally takes place in the fallopian tube. Once fertilization has occurred, the early zygote migrates down the fallopian tube to the uterine cavity. Once inside the uterine cavity, the morula develops the fluid-filled cavity (blastocyst cavity) and begins the process of implanting into the uterine wall.

This occurs by around day 7 after fertilization (bottom). Note that the outer wall of the blastocyst, the trophoblast, sends cells into the uterine wall that forms the syncytiotrophoblast. This tissue will develop into the placenta over time.
Implantation
• In order to appreciate implantation by the blastocyst, it is important to have a fundamental, working knowledge of the uterine wall anatomy.

• The muscular layer of the uterus, the myometrium (#8) is the outermost region illustrated.

• The endometrium (#10) consists of the basal layer (#7), the spongy layer (#6) and the compact layer (#5).

• The endometrium is sloughed during menstrual bleeding. The inner lining of the endometrium is endometrial endothelium (#1).

• It is this layer that, through differentiation, provides for the development of uterine glands (#4) that will help prepare the uterus for implantation/pregnancy.
ANATOMY OF UTERINE WALL

1. Endometrial endotheium
2. Spiral artery
3. Vein
4. Uterine gland
5. Compact layer
6. Spongy layer
7. Basal layer
8. Functional layer
9. Endometrium
10. Myometrium

Functionals
Basals

Endometrium
Myometrium
Perimetrium
• The blood supply to the endometrium consists of spiral arteries (#2) and veins (#3). The spiral arteries are of utmost importance, as they provide the nutrients for the fetus.
• Their influence is so significant that if even one spiral artery is tied off in pregnant rats, the rat pup dependent upon that spiral artery undergoes a reduction in growth that amounts to more than 10% of his/her litter mates' weights at birth.
• By 9 days after fertilization, the blastocyst is all but implanted, (top). Note the level of invasion of the syncytiotrophoblast into the endometrium.

• The ball of cells, in many ways, resembles a growing tumor. In (top), note that there are two layers of cells that separate the primary yolk sac from the amniotic cavity. The top (green) layer is the hypoblast; the bottom (brown) layer is the epiblast.

• Together, these two layers comprise the bilaminar disc.

• Another view is presented in (bottom) of the bilaminar disc at 13 days after fertilization, i.e., nearing the end of "zygogenesis" and preparing to enter the realm of the embryonic period. Note that the connecting stalk attaches the bilaminar disc to the chorion (the cytотrophoblast, extra-embryonic mesoderm and syncytiotrophoblast).
The concentrations of a hormone called human chorionic gonadotropin (hCG) throughout pregnancy. Where does this hormone come from? It is first released by the trophoblast. hCG stimulates the corpus luteum of ovulation to convert to the corpus luteum (CL) of pregnancy. A portion of the trophoblast eventually differentiates into the syncytiotrophoblast ("pre-placenta") and continues to secrete hCG to continue driving the differentiation of the CL of ovulation to become the CL of pregnancy. The peak hCG levels occur when the cytotrophoblast is at maximum thickness. This typically occurs at about 10-12 weeks of gestation. Interestingly enough, this seems to coincide with the maximal morning sickness effect, on average. hCG is detectable up to two weeks post partum.
• The CL is the remnant tissue left behind in the ovary following ovulation. In real life, this appears much like the "crater" left behind after you pop a zit. After ovulation, the leftover crater differentiates into the "yellow body" (CL). The CL secretes progesterone for about the first 6-8 weeks of pregnancy (some sources say 10 weeks), then the placenta takes over this production. It is not uncommon for a pregnant woman to have a little bit of vaginal bleeding (spotting) 6-10 weeks into her pregnancy as progesterone synthesis switches over from the CL to the placenta.

• At parturition, the CL secretes relaxin to relax the ligaments holding the pelvis in place, allowing it to widen for a normal vaginal delivery.
• The relationship between the "developed" placenta and the maternal and fetal sides of it. Note that the nutrients are brought to the maternal side of the placenta via spiral arteries and that wastes are removed on the maternal side by endometrial veins. The maternal side of the placenta is called the decidua basalis. Nutrients and wastes cross the decidua basalis in blood and bathe the fetal portion of the placenta, the chorionic villi. Nutrients and wastes cross the chorionic villi by diffusion, osmosis and active transport mechanisms.
The vessels in the chorionic villi are backwards to those going through the decidua basalis: wastes are brought to the villi via arterial supplies and nutrients are taken up by venules. The most important welfare factor on the development and health of the fetus is that the chorionic villi are bathed by maternal blood.
<table>
<thead>
<tr>
<th>FETUS</th>
<th>PLACENTA</th>
<th>ADULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth</td>
<td>Nutrients: carbohydrates, amino acids, proteins, lipids, ad nauseum</td>
<td></td>
</tr>
<tr>
<td>Protection from diphtheria, smallpox, measles</td>
<td>IgG</td>
<td></td>
</tr>
<tr>
<td>Bacteria, Heparin, Transferrin, IgM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FETUS</td>
<td>PLACENTA</td>
<td>ADULT</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td>-------</td>
</tr>
<tr>
<td>Waste</td>
<td>Lungs and Kidneys</td>
<td></td>
</tr>
<tr>
<td>Fetal chicken pox</td>
<td>Varicella zoster virus</td>
<td></td>
</tr>
<tr>
<td>Cat scratch fever*</td>
<td><em>T. gondii</em></td>
<td></td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>CO</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>$^{90}$Sr</em></td>
<td></td>
</tr>
</tbody>
</table>
Cart Scratch Fever

• For decades, attempts to identify the causative organism were fruitless. In 1983, Dr Daniel Wear of the Armed Forces Institute of Pathology demonstrated pleomorphic coccobacilli using the Warthin-Starry silver stain. As reported in the Journal of the American Medical Association (JAMA) in 1988, the organism finally was grown in a laboratory and fulfilled Koch's postulates. In 1991, the bacterium was named *Afipia felis*.

• In 1992, Regnery and others studied serologic responses of patients with CSD against *Rochalimaea henselae*, which is known to cause bacillary angiomatosis among patients with AIDS. A high rate of seropositivity against *R henselae* among patients with CSD but a low rate of positivity against *A felis* existed, causing another modification of theories regarding causative agents.

• In 1993, a proposal for nomenclature change based on genetic similarity converted *Rochalimaea* to *Bartonella*. Accordingly, current theories postulate that CSD is caused by *Bartonella henselae*, with flea-borne transmission to kittens and a feline reservoir for the disease.

• Verbatim Source: [http://www.emedicine.com/emerg/topic84.htm](http://www.emedicine.com/emerg/topic84.htm)
Pre-Embryonic Period
• The pre-embryonic period runs from week 2 to 4 weeks of gestation. During the third week of gestation, the trilaminar disc forms from the bilaminar disc. The three layers (laminates) of the trilaminar disc are the ectoderm, the endoderm and the mesoderm.
• The ectoderm gives rise, following differentiation and development, to the epidermis, hair, the anterior pituitary gland and the inner ear.

• Neuroectoderm gives rise to the cranial nerves, the posterior pituitary gland and the central nervous system and pineal gland.

• The endoderm gives rise to the epithelium of the lower respiratory tract, GI tract, urinary bladder, urachus, pharynx, thyroid gland, Eustachian tubes and parathyroid glands.

• The mesoderm gives rise to the skull and muscles, trunk muscles, genitourinary system, gonads, serous mesothelium, cardiovascular and lymphatic systems, spleen and adrenal cortices.
Embryonic Period

Week 4 to week 8 is the embryonic period.
• The appearance of the embryo at 28 days of gestation.
• The arrow at the lower right of the embryo gives an idea of the actual size of this embryo. Per my original, this is actual size. Per your print out, it is not actual size.
• Note that you can see a lens placode for eye placement; an otic pit for ear placement.
• You can also see 4 branchial arches. These will be discussed in shortly. Note the presence of limb buds, both upper and lower.
• Somites are present, as well.
• Somites differentiate as follows:
  – myotomes, which become skeletal muscle;
  – dermatomes, which become connective tissues and
  – sclerotomes which form vertebra.
embryos at 32, 36 and 41 days of gestation.
• Note that between days 32 and 41 that the lens of the eye is pigmented.
• Note that the upper limbs are developing, stage by stage, ahead of the lower limbs.
• Interestingly enough, as we heal (abrasions, lacerations, avulsions, *ad nauseum*), we heal fastest on top of our bodies and slowest on the bottom of our bodies -- identically to how we developed in the womb.
• Note, too, that the external ear is rapidly developing in the 9 day span illustrated.
days 48, 51, 52 and 56 of gestation/development

• Note that within a 3-day period, the embryo goes from something not necessarily recognizable as a human to something easily recognizable as a human. By day 51, eyelids are noticeable. By 56 days of gestation, the fingers and toes are separated and the embryo is unmistakably human.
Chorionic Villus Sampling

• By 8 weeks of gestation, the conceptus is now referred to as a fetus -- as well as for the rest of gestation.

• Between 8-12 weeks of gestation, testing for genetic disorders may begin with chorionic villus sampling.
• In a nutshell, an endoscope is passed through the vagina and cervix. An aspiration needle takes a sample of extra-placental villi from the chorion. The cells thus obtained are immediately karyotyped. This technique, while may be done sooner than amniocentesis, poses more risks to the fetus than does amniocentesis.
Amniocentesis

- Amniocentesis is generally done after 16 weeks of gestation, although some sources indicate that it may be performed as early as 14 weeks.

- In general, a needle is passed through the abdominal wall of the pregnant mother into the amniotic sac. The needle is held at 90 to the abdominal wall. The needle is guided by ultra-sound so that the needle does not nick the placenta, causing fetal problems.

- Samples of amniotic fluid are drawn off and centrifuged. The supernatant will be used for laboratory/diagnostic tests and the precipitate (pellet), which contains amniotic cells, will be cultured for several weeks, then karyotyped.

crudely illustrates relative changes in size throughout gestation
Weight, size and numerous other characteristics (table, below) may approximate fetal age

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Intestine in abdomen; early fingernail development</td>
</tr>
<tr>
<td>12</td>
<td>Sex distinguishable</td>
</tr>
<tr>
<td>16</td>
<td>Ears stand out</td>
</tr>
<tr>
<td>18</td>
<td>Vernix caseosa present; early toenail development</td>
</tr>
<tr>
<td>22</td>
<td>Skin wrinkled and red</td>
</tr>
<tr>
<td>28</td>
<td>Eyes open; good head of hair; testes at level of deep inguinal rings</td>
</tr>
<tr>
<td>32</td>
<td>Fingernails reach finger tips; skin pink and smooth; testes enter scrotum</td>
</tr>
<tr>
<td>36</td>
<td>Body plump; toenails reach toe tips; firm grasp</td>
</tr>
<tr>
<td>38</td>
<td>Prominent chest; breasts protrude; testes in scrotum fingernails are beyond finger tips</td>
</tr>
</tbody>
</table>
the adverse effects of smoking and poor nutrition on fetal weight throughout gestation

• It seems that if a mother smokes or has poor nutrition during her pregnancy, her fetus runs about the same risk of being born with below adequate birth weight. Smoking, we now know, presents numerous other risks to the unborn fetus including, but not limited to, increased risk to pulmonary problems, increase risks of ear infections, increased risk of neurological problems.

• Mothers carrying twins under the best of circumstances still have fetuses that are less than their singleton birth peers' weight. Multiple-birth fetuses are generally smaller than their singleton counterparts.
# Critical Periods in Human Development

<table>
<thead>
<tr>
<th>Week of gestation</th>
<th>Stage</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>Zygote to bilaminar disc</td>
<td>Usually NOT susceptible to teratogens; if are, the zygote dies</td>
</tr>
<tr>
<td>3-8</td>
<td>[Pre]embryonic*</td>
<td>Major morphological malformations occur during this stage</td>
</tr>
<tr>
<td>9-term</td>
<td>Fetal</td>
<td>Physiological defects and MINOR morphological malformations occur during this stage</td>
</tr>
</tbody>
</table>

* This period is a "biggee" in terms of problems due to teratogens. During weeks 3-6, the whole of the central nervous system may be effected. During weeks 3-7, the heart may be effected. During weeks 4-8, the upper/lower limbs and eyes may be effected. During weeks 4-8, the teeth, palate and external genitalia may be effected. During weeks 7-9, the external genitalia may be effected. During weeks 4-9, the ear may be effected. Items in red denote those systems that remain susceptible to effects of teratogens through out gestation.
a few of the common teratogens and the effects they have on developing embryos/fetuses

<table>
<thead>
<tr>
<th>Teratogen</th>
<th>Effect</th>
<th>Teratogen</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td>Masculinize female fetuses</td>
<td>Cytomegalovirus (CMV)</td>
<td>Microcephalus; hydrocephalus; retardation</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Fetal alcohol syndrome; intrauterine growth retardation; retardation</td>
<td>Herpes simplex viruses</td>
<td>Microcephaly; microphthalmia</td>
</tr>
<tr>
<td>Lithium carbonate</td>
<td>Cardiovascular malformations</td>
<td>T. gondii</td>
<td>Microcephaly; cerebral calcifications; microphthalmia</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Skeletal abnormalities: facial, skull, spine, extremities</td>
<td>Treponema pallidum</td>
<td>Congenital deafness; retardation; hydrocephalus</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Nasal hypoplasia; retardation; microcephaly</td>
<td>High radiation</td>
<td>Skeletal malformations; retardation</td>
</tr>
</tbody>
</table>
Brief Overview of Selected Organ [System] Development
structures that develop from the branchial arches

- Note that the 5th arch is not mentioned in this graphic. The reason for that is because the 5th arch is not consistently present, making it similar in presence to the anconeus muscle in the elbow or the peroneus tertius muscle in the ankle.

- Structures that arise from the 1st arch include the temporalis muscle, the masseter muscle and the anterior digastricus muscle. The fifth cranial nerve (trigeminal or V) also arises from the 1st arch.
structures that develop from the branchial arches

- Structures that arise from the 2d arch include the following muscles: orbicularis oculi, orbicularis oris, frontalis, the three auriculari (attrahens, attollens and retrahens auriculam) muscles about the external ear, the occipitalis, the platysma and the risorius/buccinator pair. The seventh cranial nerve (facial or VII) is also derived from this arch.
structures that develop from the branchial arches

- Structures that arise from the 3rd arch are the stylopharyngeus muscle and the ninth cranial nerve (IX or glossopharyngeal).
- Structures that arise from the 4th and 6th arches are the pharyngeal muscles. The tenth cranial nerve (X or vagus nerve) arises from the 4th arch, ONLY.
A primitive version of the developing cardiovascular system

• Of interest is that our hearts begin, if you will, as two distinct heart tubes that, eventually, must fuse into simultaneously acting chambers. The anterior cardinal veins will eventually develop into the superior vena cava (SVC), draining the superior portion of the body into the right side of the heart. Note also (#9 in the figure) the presence of two (2) umbilical arteries and one (1) umbilical vein. Note that the arteries are colored blue and the vein is colored red. They are not mis-colored. These vessels carry blood in composition opposite that of the other arteries and veins with the exception of the pulmonary arteries and veins which, likewise, carry blood in opposite composition of the other arteries and veins in the body. Note, likewise, the relation between the cord vessels and the chorionic villi. This diagram is from a section of an embryo at 20 days of gestation.
the heart 8 days later

• Note that at 28 days of gestation that the heart already has the rudimentary "fixin's" of the adult heart. Of particular interest is #5 in the top 2 illustrations. These are called endocardial cushions. The cushions normally fuse in such a manner that they provide for a "seal" between the four chambers of the heart.

• In some instances, these cushions do not fuse, leaving a hole in the center of the heart. This is called atrioventricularis communis or endocardial cushion defect of the complete type.

• It is not very common in most individuals, however, in approximately 1 out of 5 births of babies with Down Syndrome, a baby will have this defect.
development of the heart is incredibly rapid

- from a rudimentary heart at 28 days to a fully functioning fetal heart by 56 days of gestation. In the lower right graphic, the red arrow denotes the flow of blood through the foramen ovale, bypassing flow to the "non-functioning" lungs in utero.
illustratively summarized neurulation

- The neural plate pushes towards the mesoderm as the neural crests press up and over the neural plate to form the neural groove by day 18 of gestation. The lateral edges of the neural crests converge above this development to form epidermis and the neural tube. The neural crests eventually give rise to developing spinal ganglia, sympathetic trunk ganglia, melanocytes, to name a few. The neural tube goes on to become the placement site for the central nervous system, i.e., the brain and spinal cord. The neural tube is formed by day 28 of gestation.
the development of the brain from 13 weeks of gestation to the newborn brain.

• Per your print out, these are approximately 64% of actual size. Note how smooth the brain starts out and wrinkles with development.
the development of the mammary glands

• At 28 days of gestation, note that humans have a mammary ridge. This is common to mammals. In humans, if this ridge does not degenerate, polymastia (multiple breasts) and/or polythelia (multiple nipples) occur.

• Within 14 days, though, the ridge degenerates to mammary remnants, which will become the breasts in humans. The lower graphics walk us through sections of developing breasts, *in utero*.

• Note that at birth the lactiferous ducts are in place in both sexes. Indeed, it has been postulated that if a man were placed under appropriate endocrine regulation, he would be able to lactate. This "ability" seems to disappear somewhere in a man's mid-20's, or so, as the underlying architecture degenerates.
the development of the mammary glands

- It is not uncommon for female babies to appear to lactate at or shortly after birth.
- Female babies have the highest levels of prolactin in their blood they will ever have in their lives -- even higher than when they have their own babies. This hormone drives milk synthesis. In the newborn breast, though, milk is not released, rather a waxy "witches' milk" is secreted.
- Estrogens, likewise, play a role in the secretion of witches' milk and may cause the newborn to have a tiny amount of bloody discharge from the infant's vagina. Both spontaneously cease after the effects of the maternal estrogens wear off.
Gender Determination *In Utero*
• A simple Punnett square showing the two possible combinations of a sperm and an egg, insofar as the determination of the sex of the offspring is/are concerned.
• Y-linked genes are called holandric genes. These are inherited only through the males and are involved in male sexual development. One of these genes (or groups of genes) is called the H-Y genes.

• The H means histocompatibility from mice studies. Female mice will not accept male mice skin grafts from the same INBRED strain. Truly, then the "H" probably ought to stand for histoincompatibility.

• H-Y genes are located near the centromere in an indistinguishable region of the Y chromosome OR on the short arm adjacent to the centromere (more likely). The short arm is identified as "Yp", where the "p" is still for petite. "Yq", then, would be the long arm of the Y chromosome. H-Y genes code for the H-Y antigen which plays a significant role in the sexual differentiation of the undifferentiated gonad that causes the external genitalia of the male to be synthesized. Yq contains genes for spermatogenesis and for outer ear hair growth of an excessive nature.
• The H-Y antigen is also a cell surface antigen, also known as testis-determining substance. The H-Y antigen appears in MICE in the 8-cell stage. The H-Y antigen is a SWITCH that over-rides female differentiation and causes male differentiation, i.e., all of us start out after conception as "females". The H-Y antigen also stimulates the immature testis to develop by 43-50 days of gestation (about 16-30 mm Crown-Rump [CR] length), which stimulates Sertoli cells to begin spermatogenesis (as opposed to the XX genotype: ovarian development is not positively identifiable until the tenth week, making testicular development a faster process than ovarian development). Once the testes and spermatogonia are produced, this function of the Y chromosome is complete.
• In addition, hCG of placental origin has leutinizing hormone-like activity. This suggests that perhaps it might travel to the male fetus and maybe stimulate Leydig cells to produce testosterone.

• The H-Y antigen was thought for many years to be the end-all for male sexual development. It may not, however, be the whole story.

• The Y chromosome also codes for a testis-determining factor (not to be confused with testis-determining substance; a protein called TDF), that causes testicular synthesis.

• There is a possibility that TDF is located on the X chromosome, as well.
the effect of the genotype based upon the presence or lack thereof, of TDF

<table>
<thead>
<tr>
<th>Genotype</th>
<th>→</th>
<th># of &quot;doses&quot; of TDF gene</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>XY</td>
<td>→</td>
<td>2</td>
<td>testis</td>
</tr>
<tr>
<td>XX*</td>
<td>→</td>
<td>1</td>
<td>Ovaries</td>
</tr>
</tbody>
</table>

*NOTE: remember 1 of the X-chromosomes is inactivated in the female.*
• It is still theoretical, as the protein, TDF, has NOT been isolated and sequenced, although strong evidence for its presence exists.
• Perhaps it occurs too early in/during development and with such a short half-life that current technology is incapable of isolating it?
• Maybe if there are potential candidates for TDF they might be best cloned and inserted into the gene sequences and studied?
• TDF codes for the regulatory protein that seems to be a finger protein (Zn-finger protein?) that binds in a regulatory manner with/to DNA.
• With more research, these bits and pieces may help establish the identity of TDF.
In terms of limited recombinant studies, the information in the following table has been established:

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>XY</th>
<th>XY</th>
<th>XX</th>
<th>XX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comment</td>
<td>Has TDF (Y)</td>
<td>No TDF (Y)</td>
<td>Has TDF (X)</td>
<td>No TDF</td>
</tr>
<tr>
<td>Phenotypes</td>
<td>male</td>
<td>female</td>
<td>male</td>
<td>Female</td>
</tr>
</tbody>
</table>
• Hence, it seems that just because a person has the genotype XX, they won't necessarily have the female phenotype. These sorts of studies suggest that H-Y antigen may be less important than once thought. It does seem, however, that the H-Y antigen establishes the GONADAL gender of the fetus.
All fetuses at this stage (7 and 9 weeks of gestational age in graphic) have a dual set of "pre-genitals". The male "parts" are of the mesonephric ducts and the female "parts" are the paramesonephric ducts.

The mesonephric ducts form the epididymis, the ductus deferens, seminal vesicle and the ejaculatory ducts; these ducts virtually disappear in the developing female.

The paramesonephric ducts give rise to the uterus and the fibromuscular wall of the vagina and are virtually dissipated in the male.

The urogenital sinus (lower third of the developing bladder) gives rise to the urinary bladder, most of the urethra, the prostate gland and Cowper's glands in the male. In the female, the same tissue gives rise to the urinary bladder, the urethra, the vagina, Bartholin's glands and Skene's glands/ducts.
the ambiguity of the external genitalia from 4 weeks through 7 weeks of gestation.

• Note that the phallus is derived from the genital tubercle and that there is an anal membrane present by 7 weeks of gestation.

• Note also that the urogenital folds, which are, in turn, surrounded by the labioscrotal swellings, surround the cloacal membrane. The cloaca gives rise to, among other structures, the rectum.
the effects of testosterone (to form the male external genitalia) and estrogens/progesterone (to form the female external genitalia)

• Many organs have identical origins between the sexes: the glans penis and glans clitoris are of identical embryological origin as are the labia majora and the scrotum; the labia minora and the penile shaft, as well. Note that this process, i.e., from ambiguous genitalia to obvious external genitalia, only takes 3 weeks or so.
• Testosterone from Leydig cells and Mullerian-inhibiting hormone (could this be the TDF?????), which inhibits female differentiation and stimulates male differentiation, from Sertoli cells cause somatic sex: external bodily changes that cause the male genital appearance.
In addition, 5-α-reductase reduces testosterone to 5-DHT (5-dihydrotestosterone), which is a more potent androgen and increases differentiation.
• Thus ends discussion on a brief overview of gender determination of humans whilst they are in the womb.