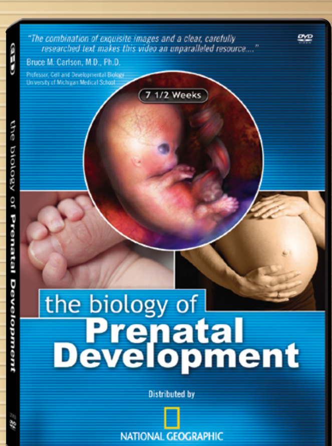
THE ENDOWMENT FOR HUMAN DEVELOPMENT

presents

the biology of Prenatal Development

Program Script, Footnotes, Appendices, Bibliography, and Index



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Program Notes

All embryonic and fetal ages in this program refer to the time since fertilization.

Ages from 4 through 8 weeks are estimated to ±3 days.

Ages from 8 through 12 weeks are estimated to ±5 days.

Ages from 12 weeks through birth are generally estimated to ±1 week.

To simplify age calculations, the term “month” assumes a 4-week period.

Age and stage conventions adopted during the embryonic period are listed in Appendix B.

The Biology of Prenatal Development

Chapter 1 – Introduction

The dynamic process by which the single-cell human **zygote** (zī'gōt)[1] becomes a 100 trillion (10^{14}) cell adult[2] is perhaps the most remarkable phenomenon in all of nature.

Researchers now know that many of the routine functions performed by the adult body become established during pregnancy – often long *before* birth.[3] The developmental period *before* birth is increasingly understood as a time of preparation during which the developing human acquires the many structures, and practices the many skills, needed for survival *after* birth.

Chapter 2 – Terminology

Pregnancy in humans normally lasts approximately 38 weeks[4] as measured from the time of **fertilization**,[5] or **conception,**[6] until birth.

During the first 8 weeks following fertilization, the developing human is called an **embryo,**[7] which means "growing within."[8] This time, called the **embryonic period**,[9] is characterized by the formation of most major body systems.[10]

From the completion of 8 weeks until the end of pregnancy, "the developing human is called a **fetus**," which means "unborn offspring." During this time, called the **fetal period**, the body grows larger and its systems begin to function.[11]

All embryonic and fetal ages in this program refer to the time since fertilization.[12]

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[1] Gasser, 1975, 1.
[2] Guyton and Hall, 2000, 2; Lodish et al., 2000, 12.
[3] Vindla and James, 1995, 598.
[4] Cunningham et al., 2001, 226; O'Rahilly and Müller, 2001, 92.
[5] O'Rahilly and Müller, 1987, 9.
[6] Spraycar, 1995, 377 & 637.
[7] O'Rahilly and Müller, 2001, 87.
[8] Quote from Ayto, 1990, 199.
[9] Human development during the 8-week embryonic period has been divided into a series of 23 stages called Carnegie Stages. These stages are well described in O'Rahilly and Müller, 1987. Because human growth is unique and dependent on multiple factors, different embryos may reach a certain developmental milestone or a certain size at slightly different ages. This internationally-accepted staging system provides a way to describe development independent of age and size. Each of the 23 Carnegie Stages has specific structural features. As we describe various milestones of development, the Carnegie Stage at which they occur will be noted by a designation such as: [Carnegie Stage 2]. See Appendix B for additional information relating embryonic staging and age assignments.
[10] Moore and Persaud, 2003, 3.
[11] Quotes from Moore and Persaud, 2003, 3: "After the embryonic period (eight weeks), the developing human is called a fetus." Also see O'Rahilly and Müller, 2001, 87.
[12] This convention, termed "postfertilization age" by O'Rahilly, has been long preferred by embryologists. [see Mall, 1918, 400; O'Rahilly and Müller, 1999b, 39; O'Rahilly and Müller, 2001, 88 & 91.] Obstetricians and radiologists typically assign age based on the time elapsed since the first day of the last menstrual period prior to fertilization. This is correctly termed "postmenstrual age" and begins 2 weeks *before* fertilization occurs. To summarize: postmenstrual age = postfertilization age + 2 weeks. Therefore, postmenstrual age equals approximately 2 weeks at the time of

The Embryonic Period (The First 8 Weeks)

Embryonic Development: The First 4 Weeks

Chapter 3 – Fertilization

Biologically speaking, “human development begins at fertilization,”[13] when a woman and a man each combine 23 of their own chromosomes through the union of their reproductive cells. A woman's reproductive cell is commonly called an “egg” but the correct term is **oocyte** (ō´ō-sīt).[14] Likewise, a man’s reproductive cell is widely known as a “sperm,” but the preferred term is **spermatozoon** (sper´mă-tō-zō´on).[15] Following the release of an oocyte from a woman’s ovary in a process called **ovulation** (ov´yū-lā´shŭn),[16] the oocyte and spermatozoon join within one of the **uterine tubes,**[17] which are often referred to as **Fallopian tubes**. The uterine tubes link a woman’s ovaries to her **uterus** or **womb.** The resulting single-celled embryo is called a zygote,[18] meaning “yoked or joined together.”[19]

Chapter 4 – DNA, Cell Division, and Early Pregnancy Factor (EPF)

DNA

The zygote’s 46 chromosomes[20] represent the unique first edition of a new individual's complete genetic blueprint. This master plan resides in tightly coiled molecules called **DNA.** They contain the instructions for the development of the entire body. DNA molecules resemble a twisted ladder known as a double helix.[21]

The rungs of the ladder are made up of paired molecules, or bases, called guanine, cytosine, adenine, and thymine. Guanine pairs only with cytosine, and adenine with thymine.[22]

Each human cell contains approximately 3 billion (3×10^9) of these base pairs.[23]

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fertilization. The commonly used term “gestational age” has been used with both age conventions and is best either avoided or carefully defined with each use.

[13] Quote from Moore and Persaud, 2003, 16; From O’Rahilly and Müller, 1987, 9: “Fertilization is the procession of events that begins when a spermatozoon makes contact with an oocyte or its investments and ends with the intermingling of maternal and paternal chromosomes at metaphase of the first mitotic division of the zygote.” See Carlson, 2004, 3; O’Rahilly and Müller, 2001, 8. [Carnegie Stage 1]

[14] O’Rahilly and Müller, 2001, 25: “The term ‘egg’ should be discarded from human embryology.” From O’Rahilly and Müller, 1987, 9: “The term ‘egg’ is best reserved for a nutritive object frequently seen on the breakfast table.”

[15] O’Rahilly and Müller, 2001, 23-24.

[16] O’Rahilly and Müller, 2001, 30.

[17] Dorland and Bartelmez, 1922, 372; Gasser, 1975, 1; Mall, 1918, 421; O’Rahilly and Müller, 2001, 31.

[18] Gasser, 1975, 1; O’Rahilly and Müller, 2001, 33.

[19] Quote from Saunders, 1970, 1; Spraycar, 1995, 1976.

[20] Guyton and Hall, 2000, 34.

[21] Guyton and Hall, 2000, 24; Watson and Crick, 1953, 737.

[22] Guyton and Hall, 2000, 24; Lodish et al., 2000, 103; Watson and Crick, 1953, 737.

[23] Lodish et al., 2000, 456.

The DNA of a *single* cell contains so much information that if it were represented in printed words, simply listing the first letter of each base would require over 1.5 million (1.5×10^6) pages of text![24] If laid end to end, the DNA in a single human cell measures 3⅓ feet or 1 meter.[25] If we could uncoil all of the DNA within an adult's 100 trillion (10^{14}) cells, it would extend over 63 billion (6.3×10^{10}) miles. This distance reaches from the earth to the sun and back 340 times.[26]

Cell Division
Approximately 24 to 30 hours after fertilization, the zygote completes its first cell division.[27] Through the process of **mitosis**, one cell splits into two, two into four, and so on.[28]

Early Pregnancy Factor (EPF)
As early as 24 to 48 hours after fertilization begins, pregnancy can be confirmed by detecting a hormone called "**early pregnancy factor**" in the mother's blood.[29]

Chapter 5 – Early Stages (Morula and Blastocyst) and Stem Cells

By 3 to 4 days after fertilization, the dividing cells of the embryo assume a spherical shape and the embryo is called a **morula** (mōr´ū-lă).[30] By 4 to 5 days, a cavity forms within this ball of cells and the embryo is then called a **blastocyst**.[31] The cells inside the blastocyst are called the **inner cell mass** and give rise to the head, body, and other structures vital to the developing human.[32] Cells within the inner cell mass are called **embryonic stem cells** because they have the ability to form each of the more than 200 cell types contained in the human body.[33]

Chapter 6 – 1 to 1½ Weeks: Implantation and Human Chorionic Gonadotropin (HCG)

After traveling down the uterine tube, the early embryo embeds itself into the inner wall of the mother's uterus. This process, called **implantation**, begins 6 days and ends 10 to 12 days after fertilization.[34] Cells from the growing embryo begin to produce a hormone called **human chorionic gonadotropin** (human kō-rē-on'ik gō'nad-ō-trō'pin), or **hCG**,

[24] See Appendix A.
[25] See Appendix A; Alberts et al., 1998, 189.
[26] See Appendix A.
[27] Hertig, 1968, 26; Hertig and Rock, 1973, 130; (cited by O'Rahilly and Müller, 1987, 12); Shettles, 1958, 400.
[28] Guyton and Hall, 2000, 34.
[29] Moore and Persaud, 2003, 33 & 60; Morton et al., 1992, 72; Nahhas and Barnea, 1990, 105.
[30] Gasser, 1975, 1; O'Rahilly and Müller, 2001, 37; Spraycar, 1995, 1130: "Morula" is derived from the Latin word *morus* meaning "mulberry." [Carnegie Stage 2]
[31] O'Rahilly and Müller, 2001, 39. [Carnegie Stage 3]
[32] Gasser, 1975, 1; O'Rahilly and Müller, 2001, 39; Sadler, 2005, 6.
[33] Alberts et al., 1998, 32. For a definition and discussion of embryonic stem cells see the website of the National Institutes of Health: http://stemcells.nih.gov/infoCenter/stemCellBasics.asp#3
[34] O'Rahilly and Müller, 2001, 40; Implantation begins with attachment of the blastocyst at about 6 days after fertilization. [Attachment of the blastocyst to the inner wall of the uterus is a transient event and is the hallmark of Carnegie Stage 4.] See also Adams, 1960, 13-14; Cunningham et al., 2001, 20; Hamilton, 1949, 285-286; Hertig, 1968, 41; Hertig and Rock, 1944, 182; Hertig and Rock, 1945, 81 & 83; Hertig and Rock, 1949, 183; Hertig et al., 1956, 444. [Carnegie Stage 5]

the substance detected by most pregnancy tests.[35] HCG directs maternal hormones to interrupt the normal menstrual cycle, allowing pregnancy to continue.[36]

Chapter 7 – The Placenta and Umbilical Cord

Following implantation, cells on the periphery of the blastocyst give rise to part of a structure called the **placenta** (plă-sen'tă), which serves as an interface between the maternal and embryonic circulatory systems. The placenta delivers maternal oxygen, nutrients, hormones, and medications to the developing human; removes all waste products; and prevents maternal blood from mixing with the blood of the embryo and fetus.[37] The placenta also produces hormones and maintains embryonic and fetal body temperature slightly above that of the mother's.[38] The placenta communicates with the developing human through the vessels of the **umbilical** (ŭm-bil'i-kăl) **cord**.[39] The life support capabilities of the placenta rival those of intensive care units found in modern hospitals.

Chapter 8 – Nutrition and Protection

By 1 week, cells of the inner cell mass form two layers called the **hypoblast** and **epiblast**.[40] The hypoblast gives rise to the **yolk sac**,[41] which is one of the structures through which the mother supplies nutrients to the early embryo.[42] Cells from the epiblast form a membrane called the **amnion** (am-nē-on),[43] within which the embryo and later the fetus develop until birth.

Chapter 9 – 2 to 4 Weeks: Germ Layers and Organ Formation

By approximately 2½ weeks, the epiblast has formed three specialized tissues, or **germ layers,** called **ectoderm**, **endoderm,** and **mesoderm.**[44] Ectoderm gives rise to numerous structures including the brain, spinal cord, nerves, skin, nails, and hair. Endoderm produces the lining of the respiratory system and digestive tract and generates portions of major organs such as the liver and pancreas. Mesoderm forms the heart, kidneys, bones, cartilage, muscles, blood cells, and other structures.[45]

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[35] Chartier et al., 1979, 134; Cunningham et al., 2001, 27; O'Rahilly and Müller, 2001, 43.
[36] Cunningham et al., 2001, 20 & 26-27; O'Rahilly and Müller, 2001, 31.
[37] Hertig, 1968, 16; Cunningham et al., 2001, 86 & 136; For a detailed description of the placenta see Hamilton and Boyd, 1960. For a detailed description of the placenta vasculature see Harris and Ramsey, 1966. This separation of maternal and fetal blood is almost but not quite perfect as a small number of fetal cells may be found in the maternal circulation and vice-versa. See Cunningham et al., 2001, 96 & 136.
[38] Liley, 1972, 101; O'Rahilly and Müller, 2001, 78-79.
[39] For a detailed description of umbilical cord formation see Florian, 1930.
[40] O'Rahilly and Müller, 2001, 39.
[41] Moore and Persaud, 2003, 50; O'Rahilly and Müller, 2001, 82. [Carnegie Stages 5 & 6]; In humans, the term "yolk sac" has fallen out of favor among some embryologists (including O'Rahilly and Müller) because it is not a nutrient reservoir and does not contain yolk. The technically preferred term is umbilical vesicle. This structure plays a vital role in the transfer of nutrients from mother to embryo before placental circulation becomes fully functional.
[42] Campbell et al., 1993, 756; Kurjak et al., 1994, 437; O'Rahilly and Müller, 2001, 82.
[43] O'Rahilly and Müller, 1987, 29; O'Rahilly and Müller, 2001, 43. [Carnegie Stages 4-5]
[44] O'Rahilly and Müller, 2001, 14 & 135. [Carnegie Stage 7]; It should be noted there are many examples of organs derived from multiple germ layers. For instance, the liver is largely derived from endoderm but contains blood vessels and blood cells derived from mesoderm and nerves of ectodermal origin.
[45] Moore and Persaud, 2003, 80 & 83; Sadler, 2005, 9.

By 3 weeks the brain is dividing into three primary sections called the **forebrain**, **midbrain,** and **hindbrain.**[46]

Development of the respiratory and digestive systems is also underway.[47]

As the first blood cells appear in the yolk sac,[48] blood vessels form throughout the embryo and the tubular heart emerges.[49] Almost immediately, the rapidly growing heart folds in upon itself as separate chambers begin to develop.[50]

The heart begins beating 3 weeks and 1 day following fertilization.[51] The circulatory system is the first body system, or group of related organs, to achieve a functional state.[52]

Chapter 10 – 3 to 4 Weeks: The Folding of the Embryo

Between 3 and 4 weeks, the body plan emerges as the brain, spinal cord, and heart of the embryo are easily identified alongside the yolk sac. Rapid growth causes folding of the relatively flat embryo.[53] This process incorporates part of the yolk sac into the lining of the digestive system and forms the chest and abdominal cavities of the developing human.[54]

Embryonic Development: 4 to 6 Weeks

Chapter 11 – 4 Weeks: Amniotic Fluid

By 4 weeks the clear amnion surrounds the embryo in a fluid-filled sac.[55] This sterile liquid, called **amniotic** (am-nē-ot'ik) **fluid**, provides the embryo with protection from injury.[56]

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[46] Bartelmez, 1923, 236; Müller and O'Rahilly, 1983, 419-420 & 429; O'Rahilly and Gardner, 1979, 123 & 129; O'Rahilly and Müller, 1984, 422; O'Rahilly and Müller, 1987, 90; O'Rahilly and Müller, 1999a, 47 & 52. [Carnegie Stage 9]
[47] DiFiore and Wilson, 1994, 221; Fowler et al., 1988, 793; Grand et al., 1976, 793-794 & 796 & 798; O'Rahilly, 1978, 125; O'Rahilly and Boyden, 1973, 238-239; O'Rahilly and Müller, 1984, 421; O'Rahilly and Tucker, 1973, 6 & 8 & 23; Streeter, 1942, 232 & 235.
[48] Carlson, 2004, 117.
[49] Gilmour, 1941, 28; O'Rahilly and Müller, 1987, 86. [Carnegie Stage 9]
[50] Carlson, 2004, 116 & 446; Navaratnam, 1991, 147-148; O'Rahilly and Müller, 1987, 99. [Carnegie Stage 10]
[51] Campbell, 2004, 14; Carlson, 2004, 430; De Vries and Saunders, 1962, 96; Gardner and O'Rahilly, 1976, 583; Gilbert-Barness and Debich-Spicer, 1997, 650; Gittenger-de Groot et al., 2000, 17; van Heeswijk et al., 1990, 151; Kurjak and Chervenak, 1994, 439; Navaratnam, 1991, 147-148; O'Rahilly and Müller, 1987, 99; Wisser and Dirschedl, 1994, 108. [Carnegie Stage 10, possibly late Stage 9]
[52] Moore and Persaud, 2003, 70: "The cardiovascular system is the first organ system to reach a functional state."
[53] Moore and Persaud, 2003, 78.
[54] Gasser, 1975, 26; Moore and Persaud, 2003, 78.
[55] Gasser, 1975, 30; O'Rahilly and Müller, 2001, 80.
[56] O'Rahilly and Müller, 2001, 81.

Chapter 12 – The Heart in Action

The heart typically beats about 113 times per minute.[57] Note how the heart changes color as blood enters and leaves its chambers with each beat.

The heart will beat approximately 54 million (5.4×10^7) times before birth and over 3.2 billion (3.2×10^9) times over the course of an 80-year lifespan.[58]

Chapter 13 – Brain Growth

Rapid brain growth is evidenced by the changing appearance of the forebrain, midbrain, and hindbrain.

Chapter 14 – Limb Buds and Skin

Upper and lower limb development begins with the appearance of the limb buds by 4 weeks.[59]

The skin is transparent at this point because it is only one cell thick. As the skin thickens, it will lose this transparency, which means that we will only be able to watch internal organs develop for about another month.[60]

Chapter 15 – 5 Weeks: Cerebral Hemispheres

Between 4 and 5 weeks, the brain continues its rapid growth and divides into five distinct sections.[61] The head comprises about one-third of the embryo's total size.[62] The **cerebral** (ser'ĕ-brăl) **hemispheres** appear,[63] gradually becoming the largest parts of the brain.[64] Functions eventually controlled by the cerebral hemispheres include thought, learning, memory, speech, vision, hearing, voluntary movement, and problem-solving.[65]

Chapter 16 – Major Airways

In the respiratory system, the right and left **main stem bronchi** (brong'kī) are present[66] and will eventually connect the trachea (trā´kē-ă), or windpipe, with the lungs.

[57] van Heeswijk et al., 1990, 153.
[58] See Appendix A.
[59] Gasser, 1975, 49 & 59; O'Rahilly and Gardner, 1975, 11; O'Rahilly and Müller, 1985, 148 & 151; O'Rahilly and Müller, 1987, 143; Streeter, 1945, 30; Uhthoff, 1990, 7 & 141. [upper & lower limb buds: Carnegie Stages 12 & 13.]
[60] Moore and Persaud, 2003, 486; O'Rahilly, 1957, 459; O'Rahilly and Müller, 2001, 165; For information about the first-trimester direct-imaging technique used in this program (called embryoscopy), see Cullen et al., 1990.
[61] O'Rahilly and Müller, 1999a, 134; Sadler, 2005, 106. [Carnegie Stage 15]
[62] Laffont, 1982, 5.
[63] Bartelmez and Dekaban, 1962, 25; Campbell, 2004, 17; O'Rahilly and Gardner, 1979, 130; O'Rahilly et al., 1984, 249; O'Rahilly and Müller, 1999a, 115; van Dongen and Goudie, 1980, 193. [Carnegie Stage 14]
[64] Moore, 1980, 938.
[65] Guyton and Hall, 2000, 663-677.
[66] Moore and Persaud, 2003, 245; O'Rahilly and Boyden, 1973, 239; O'Rahilly and Müller, 2001, 291; Sparrow et al., 1999, 550.

Chapter 17 – Liver and Kidneys

Note the massive liver filling the abdomen adjacent to the beating heart**.**

The permanent **kidneys** appear by 5 weeks.[67]

Chapter 18 – Yolk Sac and Germ Cells

The yolk sac contains early reproductive cells called **germ cells.** By 5 weeks these germ cells migrate to the reproductive organs adjacent to the kidneys.[68]

Chapter 19 – Hand Plates and Cartilage

Also by 5 weeks, the embryo develops hand plates,[69] and cartilage formation begins by 5½ weeks.[70] Here we see the left hand plate and wrist at 5 weeks and 6 days.

Embryonic Development: 6 to 8 Weeks

Chapter 20 – 6 Weeks: Motion and Sensation

By 6 weeks the cerebral hemispheres are growing disproportionately faster than other sections of the brain.

The embryo begins to make spontaneous and reflexive movements.[71] Such movement is necessary to promote normal neuromuscular development.

A touch to the mouth area causes the embryo to reflexively withdraw its head.[72]

Chapter 21 – The External Ear and Blood Cell Formation

The external ear is beginning to take shape.[73]

By 6 weeks, blood cell formation is underway in the liver where **lymphocytes** are now present.[74] This type of white blood cell is a key part of the developing immune system.

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[67] Angtuaco et al., 1999, 13; Lipschutz, 1998, 384; Moore and Persaud, 2003, 288; O'Rahilly and Müller, 1987, 167 & 182; O'Rahilly and Müller, 2001, 301; Sadler, 2005, 72. [Carnegie Stage 14]
[68] O'Rahilly and Müller, 2001, 23; Waters and Trainer, 1996, 16; Witschi, 1948, 70, 77 & 79.
[69] O'Rahilly and Müller, 1987, 175; Streeter, 1948, 139. [Carnegie Stage 15]
[70] O'Rahilly and Gardner, 1975, 4. [Carnegie Stages 16 and 17]
[71] Birnholz et al., 1978, 539; de Vries et al., 1982, 301 & 304: "The first movements were observed at 7.5 weeks postmenstrual age." [or 5½ weeks postfertilization age]; Humphrey, 1964, 99: earliest reflex 5½ weeks; Humphrey, 1970, 12; Humphrey and Hooker, 1959, 76; Humphrey and Hooker, 1961, 147; Kurjak and Chervenak, 1994, 48; Visser et al., 1992, 175-176: "Endogenously generated fetal movements can first be observed after 7 weeks postmenstrual age (i.e. 5 weeks after conception);" Natsuyama, 1991, 13; O'Rahilly and Müller, 1999a, 336: 5½ weeks postfertilization; Sorokin, and Dierker, 1982, 723 & 726; Visser et al., 1992, 175-176; Natsuyama, 1991, 13: Spontaneous movement observed by "Carnegie stage 15" (about 33 days postfertilization); Hogg, 1941, 373: Reflex activity begins at 6½ weeks [adjusted to postfertilization age].
[72] Goodlin, 1979, D-128.
[73] Karmody and Annino, 1995, 251; O'Rahilly and Müller, 2001, 480; Streeter, 1948, 190.
[74] Kurjak and Chervenak, 1994, 19.

Chapter 22 – The Diaphragm and Intestines

The **diaphragm** (dī'ă-fram), the primary muscle used in breathing, is largely formed by 6 weeks.[75]

A portion of the intestine now protrudes temporarily into the umbilical cord. This normal process, called **physiologic herniation** (fiz-ē-ō-loj'ik her-nē-ā'shŭn), makes room for other developing organs in the abdomen.[76]

Chapter 23 – Hand Plates and Brainwaves

At 6 weeks the hand plates develop a subtle flattening.[77]

Primitive brainwaves have been recorded as early as 6 weeks and 2 days.[78]

Chapter 24 – Nipple Formation

Nipples appear along the sides of the trunk shortly before reaching their final location on the front of the chest.[79]

Chapter 25 – Limb Development

By 6½ weeks, the elbows are distinct, the fingers are beginning to separate,[80] and hand movement can be seen.

Bone formation**,** called **ossification** (os'i-fi-kā'shŭn), begins within the clavicle, or collar bone, and the bones of the upper and lower jaw.[81]

Chapter 26 – 7 Weeks: Hiccups and Startle Response

Hiccups have been observed by 7 weeks.[82]

Leg movements can now be seen, along with a startle response.[83]

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[75] de Vries et al., 1982, 320.
[76] Gilbert-Barness and Debich-Spicer, 1997, 774; Grand et al., 1976, 798; O'Rahilly and Müller, 1987, 213; Sadler, 2005, 66; Spencer, 1960, 9; Timor-Tritsch et al., 1990, 287.
[77] O'Rahilly and Müller, 1987, 202-203.
[78] Borkowski and Bernstine, 1955, 363 (cited by Bernstine, 1961, 63 & 66; O'Rahilly and Müller, 1999a, 195; van Dongen and Goudie, 1980, 193.); Hamlin, 1964, 113. For a summary of in-utero fetal encephalography (measuring brainwaves) in the near-term fetus using abdominal and vaginal electrodes see Bernstine et al., 1955.
[79] O'Rahilly and Müller, 1985, 155: "The nipple appears at stages 17 and 18." [41-44 days postfertilization]; Wells, 1954, 126.
[80] O'Rahilly and Müller, 2001, 221; Streeter, 1948, 187.
[81] Carlson, 2004, 189; O'Rahilly and Gardner, 1972, 293; O'Rahilly and Gardner, 1975, 19; O'Rahilly and Müller, 2001, 385; Sperber, 1989, 122 & 147. [Carnegie Stage 19]
[82] de Vries et al., 1982, 305 & 311; Visser et al., 1992, 176.
[83] de Vries et al., 1988, 96; Visser et al., 1992, 176.

Chapter 27 – The Maturing Heart

The four-chambered heart is largely complete.[84] On average, the heart now beats 167 times per minute.[85] Electrical activity of the heart recorded at 7½ weeks reveals a wave pattern similar to the adult's.[86]

Chapter 28 – Ovaries and Eyes

In females, the ovaries are identifiable by 7 weeks.[87]

By 7½ weeks, the pigmented retina of the eye is easily seen and the eyelids are beginning a period of rapid growth.[88]

Chapter 29 – Fingers and Toes

Fingers are separate and toes are joined only at the bases. The hands can now come together, as can the feet.[89] Knee joints are also present.[90]

The 8-Week Embryo

Chapter 30 – 8 Weeks: Brain Development

At 8 weeks the brain is highly complex[91] and constitutes almost half of the embryo's total body weight.[92] Growth continues at an extraordinary rate.

Chapter 31 – Right- and Left-Handedness

By 8 weeks, 75 percent of embryos exhibit right-hand dominance. The remainder is equally divided between left-handed dominance and no preference. This is the earliest evidence of right- or left-handed behavior.[93]

Chapter 32 – Rolling Over

Pediatric textbooks describe the ability to "roll over" as appearing 10 to 20 weeks *after birth.*[94] However, this impressive coordination is displayed much earlier in the low-

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[84] Cooper and O'Rahilly, 1971, 292; James, 1970, 214; Jordaan, 1979, 214; Streeter, 1948, 192; Vernall, 1962, 23: "The four chambers of the heart and the associated major vessels are externally apparent in a close approximation to their adult positions." [Carnegie Stage 18]
[85] van Heeswijk et al., 1990, 153.
[86] Straus et al., 1961, 446 (cited by Gardner and O'Rahilly, 1976, 571.): "…an electrocardiogram with the classical P, QRS, and T configuration has been obtained from a 23mm human embryo (Straus, Walker, and Cohen, 1961)."
[87] O'Rahilly and Müller, 2001, 320. [Carnegie Stage 20]
[88] Andersen et al., 1965, 646; O'Rahilly, 1966, 35; O'Rahilly and Müller, 1987, 259; Pearson, 1980, 39; Streeter, 1951, 193. [Carnegie Stage 22] Pigment within the retina is present from about 37 days postfertilization per O'Rahilly, 1966, 25. [Carnegie Stage 16]
[89] Streeter, 1951, 191; reiterated by O'Rahilly and Muller, 1987, 257.
[90] O'Rahilly and Gardner, 1975, 11; O'Rahilly and Müller, 1987, 262.
[91] O'Rahilly and Müller, 1999a, 288: "The brain at [Carnegie] Stage 23 is far more advanced morphologically than is generally appreciated, to such an extent that functional considerations are imperative."
[92] Jordaan, 1979, 149.
[93] Hepper et al., 1998, 531; McCartney and Hepper, 1999, 86.
[94] Bates, 1987, 534.

gravity environment of the fluid-filled amniotic sac.[95] Only the lack of strength required to overcome the higher gravitational force outside the uterus prevents newborns from rolling over.[96]

The embryo is becoming more physically active during this time. Motions may be slow or rapid, single or repetitive, spontaneous or reflexive. Head rotation, neck extension, and hand-to-face contact occur more often.[97] Touching the embryo elicits squinting, jaw movement, grasping motions, and toe pointing.[98]

Chapter 33 – Eyelid Fusion

Between 7 and 8 weeks, the upper and lower eyelids rapidly grow over the eyes and partially fuse together.[99]

Chapter 34 – "Breathing" Motion and Urination

Although there is no air in the uterus, the embryo displays intermittent breathing motions by 8 weeks.[100]

By this time, kidneys produce urine which is released into the amniotic fluid.[101]

In male embryos, the developing testes begin to produce and release testosterone (tes-tos´tĕ-rōn).[102]

Chapter 35 – The Limbs and Skin

The bones, joints, muscles, nerves, and blood vessels of the limbs closely resemble those in adults.[103]

By 8 weeks the epidermis, or outer skin, becomes a multi-layered membrane,[104] losing much of its transparency.

Eyebrows grow as hair appears around the mouth.[105]

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[95] de Vries et al., 1982, 320; Goodlin and Lowe, 1974, 348; Humphrey, 1970, 8.
[96] Liley, 1972, 101.
[97] de Vries et al., 1982, 311.
[98] Humphrey, 1964, 102; Humphrey, 1970, 19.
[99] Process described by Andersen et al., 1965, 648-649; O'Rahilly, 1966, 36-37; O'Rahilly and Müller, 1987, 261. [Carnegie Stage 23]
[100] Connors et al., 1989, 932; de Vries et al., 1982, 311; McCray, 1993, 579; Visser et al.,1992, 177.
[101] O'Rahilly and Müller, 2001, 304; Windle, 1940, 118; (Windle reports urine formation begins at nine weeks.)
[102] Moore and Persaud, 2003, 307; Waters and Trainer, 1996, 16-17.
[103] O'Rahilly and Gardner, 1975, 15: "By the end of the embryonic proper (Stage 23, 8 postovulatory weeks), all of the major skeletal, articular, muscular, neural, and vascular elements of the limbs are present in a form and arrangement closely resembling those of the adult." See O'Rahilly, 1957, for a summary of joint types and a description of limb joint development during the embryonic period. See Gray et al., 1957, for a detailed examination of the bones and joints of the hand throughout the embryonic and fetal periods.
[104] Hogg, 1941, 407; Pringle, 1988, 178.
[105] Hogg, 1941, 387; O'Rahilly and Müller, 2001, 169.

Chapter 36 – Summary of the First 8 Weeks

Eight weeks marks the end of the embryonic period. During this time, the human embryo has grown from a single cell into the nearly 1 billion (10^9) cells[106] which form over 4,000 (4×10^3) distinct anatomic structures. The embryo now possesses more than 90 percent of the structures found in adults.[107]

The Fetal Period (8 Weeks through Birth)

Chapter 37 – 9 Weeks: Swallows, Sighs, and Stretches

The fetal period continues until birth.

By 9 weeks, thumb sucking begins[108] and the fetus can swallow amniotic fluid.[109] The fetus can also grasp an object,[110] move the head forward and back, open and close the jaw, move the tongue, sigh,[111] and stretch.[112] Nerve receptors in the face, the palms of the hands, and the soles of the feet can sense light touch.[113] "In response to a light touch on the sole of the foot," the fetus will bend the hip and knee and may curl the toes.[114]

The eyelids are now completely closed.[115]

In the larynx, the appearance of vocal ligaments signals the onset of vocal cord development.[116]

In female fetuses, the uterus is identifiable[117] and immature reproductive cells, called **oogonia** (ō-ō-gō′nē-ă), are replicating within the ovary.[118] External genitalia begin to distinguish themselves as either male or female.[119]

Chapter 38 – 10 Weeks: Rolls Eyes and Yawns, Fingernails and Fingerprints

A burst of growth between 9 and 10 weeks increases body weight by over 75 percent.[120]

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[106] Pringle, 1988, 176.
[107] O'Rahilly and Müller, 2001, 87: "It has been estimated that more than 90% of the more than 4500 named structures of the adult body become apparent during the embryonic period (O'Rahilly)."
[108] Liley, 1972, 103.
[109] Campbell, 2004, 24; de Vries, 1982, 311; Petrikovsky et al., 1995, 605.
[110] Robinson and Tizard, 1966, 52; Valman and Pearson, 1980, 234.
[111] de Vries et al., 1982, 305-307.
[112] de Vries et al., 1982, 311.
[113] Humphrey, 1964, 96; Humphrey, 1970, 16-17 (cited by Reinis and Goldman, 1980, 232); Humphrey and Hooker, 1959, 77-78.
[114] Robinson and Tizard, 1966, 52; Quote from Valman and Pearson, 1980, 234.
[115] Andersen et al., 1965, 648-649; O'Rahilly and Müller, 2001, 465; Pearson, 1980, 39-41.
[116] O'Rahilly and Müller, 1984, 425; See also Campbell, 2004, 29.
[117] O'Rahilly, 1977a, 128; O'Rahilly, 1977b, 53; O'Rahilly and Müller, 2001, 327.
[118] O'Rahilly and Müller, 2001, 25 & 322.
[119] Campbell, 2004, 28 & 35; O'Rahilly and Müller, 2001, 336.
[120] Brenner et al., 1976, 561.

By 10 weeks, stimulation of the upper eyelid causes a downward rolling of the eye.[121] The fetus yawns and often opens and closes the mouth.[122] Most fetuses suck the right thumb.[123]

Sections of intestine within the umbilical cord are returning to the abdominal cavity.[124]

Ossification is underway in most bones.[125] Fingernails and toenails begin to develop.[126]

Unique fingerprints appear 10 weeks after fertilization. These patterns can be used for identification throughout life.[127]

Chapter 39 – 11 Weeks: Absorbs Glucose and Water

By 11 weeks the nose and lips are completely formed.[128] As with every other body part, their appearance will change at each stage of the human life cycle.

The intestine starts to absorb glucose and water swallowed by the fetus.[129]

Though sex is determined at fertilization, external genitalia can now be distinguished as male or female.[130]

Chapter 40 – 3 to 4 Months (12 to 16 Weeks): Taste Buds, Jaw Motion, Rooting Reflex, Quickening

Between 11 and 12 weeks, fetal weight increases nearly 60 percent.[131]

Twelve weeks marks the end of the first third, or **trimester,** of pregnancy.

Distinct taste buds now cover the inside of the mouth. By birth, taste buds will remain only on the tongue and roof of the mouth.[132]

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[121] Goodlin, 1979, D-128; Humphrey, 1964, 102.
[122] de Vries et al., 1982, 309.
[123] Hepper et al., 1991, 1109.
[124] Grand et al., 1976, 798; Pringle, 1988, 178; Sadler, 2005, 66; Spencer, 1960, 9. [Pringle reports the bowel returns during the ninth or tenth week.]
[125] Cunningham et al., 2001, 133.
[126] O'Rahilly and Müller, 2001, 170-171.
[127] Babler, 1991, 95; Penrose and Ohara, 1973, 201; For an overview of ridge formation in the skin of the hands see Cummins, 1929.
[128] Timor-Tritsch et al., 1990, 291.
[129] Koldovský et al., 1965, 186.
[130] O'Rahilly and Müller, 2001, 336; Wilson, 1926, 29.
[131] Brenner, 1976, 561.
[132] Lecanuet and Schaal, 1996, 3; Miller, 1982, 169; Mistretta and Bradley, 1975, 80.

Bowel movements begin as early as 12 weeks and continue for about 6 weeks.[133] The material first expelled from the fetal and newborn colon is called **meconium** (mē-kō'nē-ŭm).[134] It is composed of digestive enzymes, proteins, and dead cells shed by the digestive tract.[135]

By 12 weeks, upper limb length has nearly reached its final proportion to body size. The lower limbs take longer to attain their ultimate proportions.[136]

With the exception of the back and the top of the head, the body of the entire fetus now responds to light touch.[137]

Sex-dependent developmental differences appear for the first time. For instance, female fetuses exhibit jaw movement more frequently than males.[138]

In contrast to the withdrawal response seen earlier, stimulation near the mouth now evokes a turning *toward* the stimulus and an opening of the mouth.[139] This response is called the "rooting reflex" and it persists after birth, helping the newborn find his or her mother's nipple during breastfeeding.[140]

The face continues to mature as fat deposits begin to fill out the cheeks[141] and tooth development begins.[142]

By 15 weeks, blood-forming stem cells arrive and multiply in the bone marrow. Most blood cell formation will occur here.[143]

Although movement begins in the 6-week embryo, a pregnant woman first senses fetal movement between 14 and 18 weeks.[144] Traditionally, this event has been called **quickening**.[145]

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133 Abramovich and Gray, 1982, 296; Ramón y Cajal and Martinez, 2003, 154-155, report visualizing defecation (bowel movements) with ultrasound in utero in all 240 fetuses studied between 15 and 41 weeks [postmenstrual age].
134 O'Rahilly and Müller, 2001, 257; For a description of meconium by Aristotle see Grand et al., 1976, 791.
135 Grand et al., 1976, 806.
136 Moore and Persaud, 2003, 105.
137 Lecanuet and Schaal, 1996, 2; Reinis and Goldman, 1980, 232.
138 Hepper et al., 1997, 1820.
139 Mancia, 1981, 351.
140 Bates, 1979, 419.
141 Poissonnet et al., 1983, 7; Poissonnet et al., 1984, 3: In a study of 488 fetuses, Poissonnet's group found that adipose tissue (fat) appears in the face from 14 weeks postfertilization. By 15 weeks, fat appears in the abdominal wall, back, kidneys, and shoulders. By 16 weeks, fat is also present throughout the upper and lower limbs.
142 Pringle, 1988, 178. [Thirteenth week postfertilization]
143 Pringle, 1988, 179.
144 Sorokin and Dierker, 1982, 720; Leader, 1995, 595: "Some pregnant women reported fetal flutters as early as 12 weeks (quickening)." Women also tend to accurately recognize fetal movement at earlier fetal ages during second and subsequent pregnancies as compared to first pregnancies.
145 Spraycar, 1995, 1479; Timor-Tritsch et al., 1976, 70.

Chapter 41 – 4 to 5 Months (16 to 20 Weeks): Stress Response, Vernix Caseosa, Circadian Rhythms

By 16 weeks, procedures involving the insertion of a needle into the abdomen of the fetus trigger a **hormonal stress response** releasing **noradrenaline,** or **norepinephrine** (nor-ep'i-nef'rin), into the blood stream.[146]

In the respiratory system, the bronchial tree is now nearly complete.[147]

A protective white substance, called **vernix caseosa** (ver'niks caseo'sa), now covers the fetus. Vernix protects the skin from the irritating effects of amniotic fluid.[148]

From 19 weeks fetal movement, breathing activity, and heart rate begin to follow daily cycles called **circadian** (ser-kā'dē-ăn) **rhythms**.[149]

Chapter 42 – 5 to 6 Months (20 to 24 Weeks): Responds to Sound; Hair and Skin; Age of Viability

By 20 weeks the **cochlea**, which is the organ of hearing, has reached adult size[150] within the fully developed inner ear. From now on, the fetus will respond to a growing range of sounds.[151]

Hair begins to grow on the scalp. All skin layers and structures are present, including hair follicles and glands.[152]

By 21 to 22 weeks after fertilization, the lungs gain some ability to breathe air.[153] This is considered the **age of viability** because survival outside the womb becomes possible for some fetuses.[154]

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[146] Giannakoulopoulos et al., 1999, 494 & 498-499; Glover and Fisk, 1999, 883; Smith et al., 2000, 161. Cortisol levels also rise after invasive procedures following 21 weeks postfertilization - see Giannakoulopoulos et al., 1994, 80.

[147] DiFiore and Wilson, 1994, 221-222; Pringle, 1988, 178. [There is some disagreement among experts regarding when the bronchial tree is complete. Some say completion occurs as early as 16 weeks postfertilization while others say it occurs after birth.]

[148] Campbell, 2004, 48; Moore and Persaud, 2003, 107; O'Rahilly and Müller, 2001, 168.

[149] de Vries et al., 1987, 333; Goodlin and Lowe, 1974, 349; Okai et al., 1992, 391 & 396; Romanini and Rizzo, 1995, 121; For a description of the circadian system see Rosenwasser, 2001, 127; From Vitaterna et al., 2001, 92: Glossary: "Circadian: A term derived from the Latin phrase "circa diem," meaning "about a day;" refers to biological variations or rhythms with a cycle of approximately 24 hours."

[150] Lecanuet and Schaal, 1996, 5-6; Querleu et al., 1989, 410.

[151] Glover and Fisk, 1999, 882; Hepper and Shahidullah, 1994, F81; Querleu et al., 1989, 410; Sorokin and Dierker, 1982, 725 & 730; Valman and Pearson, 1980, 233-234.

[152] Pringle, 1988, 180.

[153] Hansen and Corbet, 1998, 542.

[154] O'Rahilly and Müller, 2001, 92, report the age of viability as 20 weeks postfertilization; Draper et al., 1999, 1094, report a survival rate of 2% at 20 weeks postfertilization, 6% at 21 weeks, and 16% at 22 weeks. Moore and Persaud, 2003, 103, report viability at 22 weeks; Wood et al., 2000, 379, report survival rates of 11% at 21 weeks, 26% at 22 weeks and 44% at 23 weeks (postfertilization weeks) based on premature birth data from the United Kingdom during 1995. Cooper et al. 1998, 976, (Figure 2) report infants with a birth weight over 500 grams experienced survival rates (all approximate) of 28% at 21 weeks postfertilization, 50% at 22 weeks, 67% at 23 weeks, and 77% at 24 weeks. Draper et al., 2003, updated their previously published survival tables for premature infants and now report an overall survival rate of 7% at 20 weeks, 15% at 21 weeks, 29% at 22 weeks, 47% at 23 weeks and 65% at 24 weeks. [All ages corrected to reflect postfertilization age.] These survival tables are available online at

Chapter 43 – 6 to 7 Months (24 to 28 Weeks): Blink-Startle; Pupils Respond to Light; Smell and Taste

By 24 weeks the eyelids reopen[155] and the fetus exhibits a **blink-startle response**.[156] This reaction to sudden, loud noises typically develops earlier in the female fetus.[157]

Several investigators report exposure to loud noise may adversely affect fetal health. Immediate consequences include prolonged increased heart rate, excessive fetal swallowing, and abrupt behavioral changes.[158] Possible long-term consequences include hearing loss.[159]

The fetal respiratory rate can rise as high as 44 inhalation-exhalation cycles per minute.[160]

During the third trimester of pregnancy, rapid brain growth consumes more than 50 percent of the energy used by the fetus. Brain weight increases between 400 and 500 percent.[161]

By 26 weeks the eyes produce tears.[162] The pupils respond to light as early as 27 weeks.[163] This response regulates the amount of light reaching the retina[164] throughout life.

All components required for a functioning sense of smell are operational. Studies of premature babies reveal the ability to detect odors as early as 26 weeks after fertilization.[165]

Placing a sweet substance in the amniotic fluid increases the rate of fetal swallowing. In contrast, decreased fetal swallowing follows the introduction of a bitter substance. Altered facial expressions often follow.[166]

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http://bmj.bmjjournals.com/cgi/content/full/319/7217/1093/DC1. Their methodology is described in their earlier paper (Draper et al., 1999, 1093-1094.) Note: These published survival tables reflect postmenstrual ages. Hoekstra et al., 2004, e3, report a survival rate of 66% at 23 weeks and 81% at 24 weeks “gestational age” [not specifically defined] for premature births from 1996 to 2000 at their center in Minneapolis, Minnesota.

155 Open eyes are visualized by 4D ultrasound following 22 weeks postfertilization per Campbell 2002, 3; De Lia, 2002, personal communication; O’Rahilly and Müller, 2001, 465. For a detailed ultrastructural study of the union between the upper and lower eyelids see Andersen et al., 1967, 293.

156 Birnholz and Benacerraf, 1983, 517 (cited by Drife, 1985, 778); See also Campbell, 2002, 3: Professor Stuart Campbell correctly points out that the eyes of the fetus are closed most of the time and a true blink requires the eyes to be open. Perhaps the “blink-startle” response would be more accurately termed “squint-startle.”

157 Lecanuet and Schaal, 1996, 9.

158 Visser et al., 1989, 285.

159 Gerhardt, 1990, 299; Petrikovsky et al., 1993, 548-549; Pierson, 1996, 21 & 26.

160 Natale et al., 1988, 317.

161 Growth of the human brain, 1975, 6; Mancuso and Palla, 1996, 290.

162 Isenberg et al., 1998, 773-774.

163 Robinson and Tizard, 1966, 52.

164 Noback et al., 1996, 263.

165 Lecanuet and Schaal, 1996, 3.

166 Lecanuet and Schaal, 1996, 3; Liley, 1972, 102; Moore and Persaud, 2003, 219; Reinis and Goldman, 1980, 227.

Through a series of step-like leg motions similar to walking, the fetus performs somersaults.[167]

The fetus appears less wrinkled as additional fat deposits form beneath the skin.[168] Fat plays a vital role in maintaining body temperature and storing energy after birth.

Chapter 44 – 7 to 8 Months (28 to 32 Weeks): Sound Discrimination, Behavioral States

By 28 weeks the fetus can distinguish between high- and low-pitched sounds.[169]

By 30 weeks, breathing movements are more common and occur 30 to 40 percent of the time in an average fetus.[170]

During the last 4 months of pregnancy, the fetus displays periods of coordinated activity punctuated by periods of rest. These **behavioral states** reflect the ever-increasing complexity of the central nervous system.[171]

Chapter 45 – 8 to 9 Months (32 to 36 Weeks): Alveoli Formation, Firm Grasp, Taste Preferences

By approximately 32 weeks, true **alveoli** (al-vē'ō-lī), or air "pocket" cells, begin developing in the lungs. They will continue to form until 8 years *after* birth.[172]

At 35 weeks the fetus has a firm hand grasp.[173]

Fetal exposure to various substances appears to affect flavor preferences after birth. For instance, fetuses whose mothers consumed anise, a substance which gives licorice its taste, showed a preference for anise after birth. Newborns without fetal exposure disliked anise.[174]

Chapter 46 – 9 Months to Birth (36 Weeks through Birth)

The fetus initiates labor[175] by releasing large amounts of a hormone called estrogen (es´trō-jen)[176] and thus begins the transition from fetus to newborn. Labor is marked by powerful contractions of the uterus, resulting in childbirth.[177]

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[167] Liley, 1972, 100.
[168] England, 1983, 29.
[169] Glover and Fisk, 1999, 882; Hepper and Shahidullah, 1994, F81.
[170] Connors et al., 1989, 932; de Vries et al., 1985, 117; Patrick et al., 1980, 26 & 28; Visser et al., 1992, 178.
[171] DiPietro et al., 2002, 2: "One of the hallmarks of development before birth is the coalescence of patterns of fetal and behavioral and cardiac function into behavioral states, which is widely viewed as reflective of the developing integration of the central nervous system."
[172] Lauria et al., 1995, 467.
[173] Moore and Persaud, 2003, 108.
[174] Schaal et al., 2000, 729.
[175] Liley, 1972, 100.
[176] Moore and Persaud, 2003, 131.
[177] Cunningham et al., 2001, 252.

From fertilization to birth and beyond, human development is dynamic, continuous, and complex. New discoveries about this fascinating process increasingly show the vital impact of fetal development on lifelong health. As our understanding of early human development advances, so too will our ability to enhance health – both before and after birth.

Appendix A − Calculations

To the Sun and Back: Determining the Length of DNA in an Adult

Given:

1. The DNA molecule measures 3.4×10^{-9} meters per 10 base pairs.[178]
2. There are 3 billion (3×10^{9}) base pairs per cell.
3. There are an estimated 100 trillion (10^{14}) cells per adult.
4. The distance from the earth to the sun is approximately 93 million miles.
5. There are 2.54 centimeters (cm) per inch.

Step 1 Compute the length of DNA in a single cell:

3.4×10^{-9} meters/10 base pairs × 3×10^{9} base pairs/cell = 1.02 meters of DNA per cell

Step 2 Compute the total length of DNA in an adult's 100 trillion cells:

1.02 meters of DNA/cell × 10^{14} cells = 1.02×10^{14} meters of DNA per adult*

Step 3 Convert 1.02×10^{14} meters to miles:

1.02×10^{14} meters × 100 cm/meter × 1inch/2.54 cm × 1 foot/12 inches × 1 mile/5,280 feet = 6.3379×10^{10} miles of DNA

Step 4 Compute how many round trips from the earth to the sun:

6.3379×10^{10} miles of DNA ÷ (93,000,000 miles/trip × 2 trips/round trip) =

340 round trips between earth and sun

Therefore, the DNA in a single adult, if oriented in linear fashion, would exceed 63 billion miles in length. This is long enough to extend from the earth to the sun and back—340 times.

* Approximately 25 trillion (2.5×10^{13}) red blood cells are present in the adult.[179] It should be noted that red blood cells contain DNA early in their maturation phase but this DNA degenerates and is not present in the mature form. This calculation *includes* the DNA from red blood cells.

[178] Lodish et al., 2000, 104.
[179] Guyton and Hall, 2000, 2.

A Tight Squeeze: Appreciating the Number of Bases in the DNA of a Single Cell

The following page contains a list of 3,808 capital letters each of which represents a single base.

Given:

1. A, G, T, and C each represent a base within the DNA of a single cell.
2. Each line contains 68 letters without spaces representing 68 bases.
3. Each page contains 56 lines. (Page size: 8½ × 11 inches, font: Times New Roman, font size: 10, spaces between letters: none, lines: single spaced, margins: as shown)
4. Each cell contains 3 billion base pairs equaling 6 billion bases.

The calculation of the number of pages required to list all DNA bases in a single cell is as follows:

68 bases/line × 56 lines/page = 3,808 bases/page

6,000,000,000 bases/cell ÷ 3,808 bases/page = *1,575,630 pages/cell*

ATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATCGATCG
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Climate Control: Approximating Normal Embryonic and Fetal Body Temperature

Given:

1. The placenta maintains embryonic and fetal temperature between 0.5 ºC and 1.5 ºC above maternal core temperature.[180]

2. Maternal core temperature is approximately 99.6º Fahrenheit.

3. The formula to convert temperature from Fahrenheit (ºF) to Celsius (ºC) is:

$$ºC = 5/9\ (ºF - 32)$$

The calculation to compute the range of embryonic and fetal body temperature is as follows:

Step 1 Convert maternal core temperature to Celsius:

Maternal core temperature in ºC: ºC = 5/9 (99.6 - 32) = 37.56 ºC

Step 2 Compute lower and upper ranges of fetal body temperature in Celsius:

Lower range (Celsius) = maternal core temperature + 0.5 ºC = 37.56 + 0.5 = 38.2 ºC

Upper range (Celsius) = maternal core temperature + 1.5 ºC = 37.56 + 1.5 = 39.2 ºC

Step 3 Convert results to Fahrenheit:

ºC = 5/9 (ºF - 32) 9/5 ºC = (ºF - 32) ºF = 9/5 ºC + 32

Substituting to find the lower limit of fetal body temperature

ºF = 9/5 ºC + 32 ºF = 9/5 (38.16) + 32 *ºF = 100.7º*

Substituting to find the upper limit of fetal body temperature

ºF = 9/5 ºC + 32 ºF = 9/5 (39.16) + 32 *ºF = 102.5º*

Summary of Normal Embryonic and Fetal Body Temperature Range

	ºF	**ºC**
Lower Limit	100.7	38.2
Upper Limit	102.5	39.2

[180] Liley, 1972, 101.

The Beat Goes On: Estimating the Number of Heartbeats Before Birth and Beyond

The Embryonic Period

Week #	Average Heart Rate (Beats per Minute)	Beats per Week	Running Total
4	113.00	1,139,040	1,139,040
5	132.00	1,330,560	2,469,600
6	151.00	1,522,080	3,991,680
7	170.00	1,713,600	5,705,280
8	169.03	1,703,845	7,409,125
(Approximately 7.4 *million* beats during the embryonic period)			

Various authors agree the heart rate peaks at 7 weeks. Reported heart rates vary however. Van Heeswijk et al. report a peak heart rate of 167 ± 8 beats per minute (bpm)[181] while Leeuwen et al. report a peak rate of 175 bpm.[182] Van Lith et al. report the median fetal heart rate peaks at 177 bpm at 7 weeks.[183] One hundred seventy (170) bpm has been chosen as the peak heart rate for illustration purposes in this calculation. The heart rate for the various weeks from 7 through 38 have been calculated via linear interpolations[184] assuming heart rates of 170 bpm at 7 weeks and 140 bpm at term or 38 weeks.[185]

(Note: Heart rates are estimated. Living conditions and individual experience can and will vary.)

[181] van Heeswijk et al., 1990, 153.
[182] Leeuwen et al., 1999, 265.
[183] van Lith et al., 1992, 741.
[184] See Appendix A.
[185] DiPietro et al., 1996, 2559.

The Fetal Period

Week #	Average Heart Rate (Beats per Minute)	Beats per Week	Running Total
9	168.06	1,694,090	9,103,216
10	167.10	1,684,336	10,787,551
11	166.13	1,674,581	12,462,132
12	165.16	1,664,826	14,126,958
13	164.19	1,655,071	15,782,029
14	163.23	1,645,316	17,427,346
15	162.26	1,635,562	19,062,907
16	161.29	1,625,807	20,688,714
17	160.32	1,616,052	22,304,766
18	159.35	1,606,297	23,911,063
19	158.39	1,596,542	25,507,605
20	157.42	1,586,787	27,094,393
21	156.45	1,577,033	28,671,425
22	155.48	1,567,278	30,238,703
23	154.52	1,557,523	31,796,226
24	153.55	1,547,768	33,343,994
25	152.58	1,538,013	34,882,008
26	151.61	1,528,259	36,410,266
27	150.65	1,518,504	37,928,770
28	149.68	1,508,749	39,437,519
29	148.71	1,498,994	40,936,513
30	147.74	1,489,239	42,425,752
31	146.77	1,479,484	43,905,237
32	145.81	1,469,730	45,374,966
33	144.84	1,459,975	46,834,941
34	143.87	1,450,220	48,285,161
35	142.90	1,440,465	49,725,626
36	141.94	1,430,710	51,156,337
37	140.97	1,420,956	52,577,292
38	140.00	1,411,201	53,988,493
(Approximately 54 *million* beats *before* birth)			

Counting the Beats of a Lifetime: The Postnatal Period from Birth to 80 Years

Year #	Average Heart Rate[186] (Beats per Minute)	Beats per Year	Running Total
1	120	63,115,200	63,115,200
2	110	57,855,600	120,970,800
3	103	54,173,880	175,144,680
4	103	54,173,880	229,318,560
5	103	54,173,880	283,492,440
6	103	54,173,880	337,666,320
7	95	49,966,200	387,632,520
8	95	49,966,200	437,598,720
9	95	49,966,200	487,564,920
10	95	49,966,200	537,531,120
11	85	44,706,600	582,237,720
12	85	44,706,600	626,944,320
13	85	44,706,600	671,650,920
14	85	44,706,600	716,357,520
15	80	42,076,800	758,434,320
16	80	42,076,800	800,511,120
17	75	39,447,000	839,958,120
18	75	39,447,000	879,405,120
19	70	36,817,200	916,222,320
20	70	36,817,200	953,039,520
21-80	70	2,209,032,000	3,162,071,520
(Approximately 3.16 billion heartbeats from birth to age 80 years)			
Estimated Total Heartbeats: From 3 Weeks Postfertilization to Age 80 Years		**3,216,060,000**	
(Approximately 3.2 billion heartbeats from fertilization to age 80 years)			

[186] Age appropriate pediatric heart rates adapted from Bates, 1987, 541.

Appendix B − Relating Embryonic Age and Stage

O'Rahilly and Müller's Age Assignments vs. Carnegie Stages, 1987 to 2001

Carnegie Stage	# Somites	Greatest Length (mm)	1987 Age Convention[187] (in PF Days*)	1999 Age Convention[188] (in PF Days*)	2001 Age Convention[189] (in PF Days*)
1		0.1 - 0.15	1	-	1
2		0.1 - 0.2	1½ - 3	2-3	2-3
3		0.1 - 0.2	4	4-5	4-5
4		0.1 - 0.2	5-6	6	6
5		0.1 - 0.2	7-12	7-12	
5a		0.1	7-8	-	7-8
5b		0.1	9	-	9
5c		0.15 - 0.2	11-12	-	11-12
6		0.2	13	17	17
6a		-	-	-	-
6b		-	-	-	-
7		0.4	16	19	19
8		1.0 – 1.5	18	23	
8a		-	-	-	23
8b		-	-	-	23
9	1-3	1.5 – 2.5	20	26	25
10	4-12	2-3.5	22	29	28
11	13-20	2.5-4.5	24	30	29
12	21-29	3-5	26	31	30
13	30+	4-6	28	32	32
14		5-7	32	33	33
15		7-9	33	35	36
16		8-11	37	37	38
17		11-14	41	40	41
18		13-17	44	42	44
19		16-18	47½	44	46
20		18-22	50½	47	49
21		22-24	52	50	51
22		23-28	54	52	53
23		27-31	56½	56	56

* PF Days = Postfertilization Days

There is international agreement among embryologists that human development during the embryonic period be divided into 23 stages (which were initially proposed by Mall, described by Streeter, and amended by O'Rahilly and Müller in 1987).[190] These have come to be known as Carnegie Stages. Particular internal and external features are

[187] O'Rahilly and Müller, 1987, 3. Greatest length data is essentially uniform throughout the various texts.
[188] O'Rahilly and Müller, 1999a. Various pages.
[189] O'Rahilly and Müller, 2001, 490. Table A-1 – essentially unchanged from the 1996 edition. The 2001 convention differs only slightly from the 1999 convention as shown.
[190] O'Rahilly and Müller, 2001, 3.

required for inclusion in any given embryonic stage. These stages are independent of age and length and the use of the term ‘stage’ should be reserved for reference to this system per O’Rahilly and Müller in multiple publications.

Along with nearly-universal acceptance of the human embryonic staging system, a variety of age assignments have been proposed for each embryonic stage. Streeter believed the embryonic period spanned a 47- to 48-day period instead of the 56-day period accepted today. The Endowment for Human Development adopts the convention set forth by O’Rahilly and Müller in 1987 which has received widespread, but not universal, acceptance. O’Rahilly and Müller have since proposed amending this convention in light of transvaginal ultrasound data through a personal communication with Dr. Josef Wisser[191] in 1992. These alternate proposals are provided for the interested reader.

For instance, the onset of embryonic cardiac contraction (onset of the heartbeat) has long been described as a Carnegie Stage 10 or possibly a late Stage 9 event.[192] We report this event occurring at an age of 3 weeks, 1 day (22 days) postfertilization using the 1987 convention. Others may report this occurrence at 28 or 29 days as shown above. Of interest is a paper by Wisser and Dirschedl who reported using transvaginal ultrasound to visualize the embryonic heartbeat 23 days postfertilization in two embryos fertilized in vitro “with exactly known … age” and “in embryos from 2 mm of greatest length onwards.”[193] This finding most closely coincides with the 1987 age convention. Schats et al. reported the earliest cardiac activity at 25 days after follicle aspiration in embryos conceived in vitro.[194] Tezuka et al. reported the earliest cardiac activity at 23 days postfertilization in embryos conceived naturally.[195]

There is considerable variation in normal human development during the postnatal period. The prenatal period is no different with variations in the size, rate of growth, and order of appearance of some structures or functions. *No one knows the exact age range for each stage with absolute certainty.* These approximations may change in the future as additional knowledge is gained through careful, published research.

[191] O’Rahilly and Müller, 1999a, 13.
[192] See footnote #51.
[193] Wisser and Dirschedl, 1994, 108.
[194] Schats et al., 1990, 989.
[195] Tezuka, 1991, 211.

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Full Names of Journals Cited

Journal Abbreviation	Full Journal Name
Acta Anat	Acta Anatomica
Acta Opthalmol	Acta Ophthalmologica
Adv Contracept	Advances in Contraception
Alcohol Res Health	Alcohol Research & Health
Am J Anat	The American Journal of Anatomy
Am J Cardiol	The American Journal of Cardiology
Am J Kidney Dis	American Journal of Kidney Diseases
Am J Obstet Gynecol	American Journal of Obstetrics and Gynecology
Am J Reprod Immunol	American Journal of Reproductive Immunology and Microbiology
Am J Respir Cell Mol Biol	American Journal of Respiratory Cell and Molecular Biology
Am J Roentgenol	American Journal of Roentgenology
Anat Embryol	Anatomy and Embryology
Ann Otol Rhinol Laryngol	The Annals of Otology, Rhinology, and Laryngology
Ann R Coll Surg Eng	Annals of the Royal College of Surgeons of England
Arch Dis Child	Archives of Disease in Childhood
Arch Ophthalmol	Archives of Ophthalmology
Aust N Z J Psychiatry	The Australian and New Zealand Journal of Psychiatry
Biol Neonate	Biology of the Neonate
Birth Defects Orig Artic Ser	Birth Defects Original Article Series
Br J Obstet Gynaecol	British Journal of Obstetrics and Gynaecology
Br Med Bull	British Medical Bulletin

Journal Abbreviation	Full Journal Name
Br Med J	British Medical Journal
Chem Senses	Chemical Senses
Child Dev	Child Development
Clin Obstet Gynecol	Clinical Obstetrics and Gynecology
Contrib Embryol	Contributions to Embryology
Dev Med Child Neurol	Developmental Medicine and Child Neurology
Dev Pharmacol Ther	Developmental Pharmacology and Therapeutics
Early Hum Dev	Early Human Development
Eur J Obstet Gynecol Reprod Biol	European Journal of Obstetrics, Gynecology, and Reproductive Biology
Eur J Obstet Gynecol Reprod Biol	European Journal of Obstetrics, Gynecology, and Reproductive Biology
Eye	Eye
Facial Plast Surg	Facial Plastic Surgery
Fertil Steril	Fertility and Sterility
Fetal Ther	Fetal Therapy
Gastroenterology	Gastroenterology
Gynecol Invest	Gynecologic Investigation
Gynecol Obstet Invest	Gynecologic and Obstetric Investigation
Int J Psychoanal	The International Journal of Psycho-Analysis
Ir J Med Sci	Irish Journal of Medical Science
J Clin Ultrasound	Journal of Clinical Ultrasound
J Comp Neurol	The Journal of Comparative Neurology

Journal Abbreviation	Full Journal Name
J Med Genet	Journal of Medical Genetics
J Neuroradiol	Journal of Neuroradiology
J Pathol Bacteriol	The Journal of Pathology and Bacteriology
J Pediatr Surg	Journal of Pediatric Surgery
J Perinat Med	Journal of Perinatal Medicine
J Anat	Journal of Anatomy
JAMA	JAMA : The Journal of the American Medical Association
Lancet	Lancet
N Engl J Med	The New England Journal of Medicine
N Z Med J	New Zealand Medical Journal
Nature	Nature
Neurology	Neurology
Neuropsychologia	Neuropsychologia
Nutr Rev	Nutrition Reviews
Obstet Gynecol	Obstetrics & Gynecology
Pediatr Pathol Lab Med	Pediatric Pathology & Laboratory Medicine
Pediatr Res	Pediatric Research
Pediatrics	Pediatrics
Physiol Rev	Physiological Reviews
Science	Science
Semin Pediatr Surg	Seminars in Pediatric Surgery

Journal Abbreviation	**Full Journal Name**
Semin Perinatol	Seminars in Perinatology
Semin Reprod Endocrinol	Seminars in Reproductive Endocrinology
Semin Roentgenol	Seminars in Roentgenology
Teratology	Teratology
Trans Am Neurol Assoc	Transactions of the American Neurological Association
Ultrasound Obstet Gynecol	Ultrasound in Obstetrics & Gynecology
Z Anat Entwicklungsgesch	Zeitschrift fur Anatomie und Entwicklungsgeschichte

Program Index