

Bruce M. Carlson



UPDATED EDITION

# HUMAN EMBRYOLOGY AND DEVELOPMENTAL BIOLOGY



Third Edition

# Human Embryology and Developmental Biology

Bruce M. Carlson, MD, PhD

Professor, Department of Cell and Developmental Biology

Director, Institute of Gerontology

University of Michigan

Ann Arbor, Michigan

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## Developmentally Important Molecules Mentioned in Text

Abbreviation	Name	Type of Molecule
—	Activin	Signaling molecule
—	Angiopoietin-1	Signaling molecule
BF-2	—	Transcription factor
BMP-1 to -9	Bone morphogenetic protein 1-9	Signaling molecule
—	Cadherins	Cell attachment proteins
Cbfa1	Core-binding factor a1	Transcription factor
—	Cerberus	Signaling molecule
—	Chordin	Signaling molecule
c-Met	—	Receptor molecule
—	Cripto	Signaling molecule
c-Ret	—	Receptor molecule
—	Cyclops	Signaling molecule
Dax1	—	Transcription factor
dpp	Decapentaplegic	Signaling molecule
Dlx	Distalless	Transcription factor
E12	—	Transcriptional activator
EGF	Epidermal growth factor	Signaling molecule
Egr-1	Early growth response-1	Transcription factor
Emx-2	—	Transcription factor
En-1 and -2	Engrailed-1 and -2	Transcription factor
ET-1	Endothelin-1	Signaling molecule
—	Epimorphin	Cell surface protein
Eya-1,-2	Eyes absent-1, -2	Nuclear protein, unknown function
FGF-1 to -10	Fibroblast growth factor-1 to -10	Signaling molecule
—	Follistatin	Signaling molecule
GATA	—	Transcription factor
Gbx2	Gastrulation brain homeobox 2	Transcription factor
Gdf-5	Growth/differentiation factor-5	Signaling molecule
Gli-1, -3	—	Transcription factor
GDNF	Glial cell-derived neurotrophic factor	Signaling molecule
Gsc	Goosecoid	Signaling molecule
—	Hand-1, -2	Transcription factor
HGF	Hepatic growth factor (also scatter factor)	Signaling molecule
HNF-3 $\beta$	Hepatic nuclear factor 3 $\beta$	Transcription factor
Hoxa-d	Homeobox-containing a-d	Transcription factor
Id	Inhibitor of differentiation	Transcriptional inhibitor
IGF	Insulin-like growth factor	Signaling molecule
Ihh	Indian hedgehog	Signaling molecule
—	Inhibin	Signaling molecule
—	Integrins	Cell attachment proteins
Isl-1	Isl-1	Transcription factor
Krox-20	—	Transcription factor
Lbx-1	—	Transcription factor
Lef-1	Lymphoid enhancer factor-1	Transcription factor
—	Lefty	Signaling molecule
Lhx-3, -4	—	Transcription factor
LIF	Leukemia inhibitory factor	Growth factor
Lim-1	—	Transcription factor
Lmx-1	—	Transcription factor
Maf	—	Protooncogene
—	Mastocyte growth factor	Signaling molecule
MEF-2	Myocyte enhancer factor-2	Transcription factor
MFH-1	Mesenchyme forkhead-1	Transcription factor
MIS	Müllerian inhibitory substance	Signaling molecule
MRF-4	—	Myogenic regulatory factor
Msx-1, -2	—	Transcription factor
myf-5	—	Myogenic regulatory factor
MyoD	—	Myogenic regulatory factor
NCAM	Neural cell adhesion molecule	Cellular adhesion molecule
—	Netrins	Chemoattractant molecules
NGF	Nerve growth factor	Signaling molecule
Nkx2	—	Transcription factor
N-myc	—	Protooncogene
—	Nodal	Signaling molecule

A yellow decorative shape, possibly a stylized letter 'C' or a partial circle, is located in the top-left corner of the page.

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*To Mom, Jean, Marty and Jim*

# Preface to the Third Edition

As was the case in the first two editions of this book, one of the main themes of the preface is the enormous amount of new knowledge that has accumulated in the previous four years and the difficulty of integrating it into a package that is digestible for students. If anything, the pace of new discovery in embryology and development has accelerated. Sometimes the new information has allowed the presentation of certain aspects of embryology to be simplified, whereas in others, connecting the links within new collections of individual data are less apparent. All this aside, these are exciting times in which to be writing an embryology text because it is increasingly possible to provide mechanistic explanations at a certain level for developmental phenomena that in former times could only be described.

Many parts of the text have been extensively rewritten for the third edition. A major change is the addition of a separate chapter intended to introduce the student to fundamental aspects of molecular mechanisms in development. Although many students have already had courses in molecular biology or biochemistry, it has been my experience as a teacher that they have often lost sight of the forest as they have worked at learning the molecular trees. This chapter is by no means comprehensive, but it does introduce the student to major families of important developmental molecules, such as the homeobox-containing genes, members of the transforming growth factor family, the fibroblast growth factor family, and *Pax* genes. Two developmentally important molecules, sonic hedgehog and retinoic acid, have been treated in some depth in order to give the student some appreciation of the kinds of molecular pathways that stimulate developmental processes.

Space does not permit a complete enumeration of all parts of the text that were extensively updated for the third edition, but some of the major ones include the basis for left-right asymmetry, major signaling centers in the early embryo, the cross-sectional organization of the central nervous system, the molecular organization of the gut, and the basis for early establishment of the vascular system.

As usual, I invite comments on the revised text, and I am especially appreciative when readers point out errors in the text or the figures. I can be readily reached by e-mail at [brcarl@umich.edu](mailto:brcarl@umich.edu). One mechanism that has proven to be exceptionally successful in getting students both to read the text and to realize that textbooks are not infallible is to offer one extra credit point for every new mistake found in the book. For this I credit my organic chemistry professor in college, Dr. Arne Langsjoen, who used to collect such mistakes in our text and then relay them to the appreciative author.

The production of any book involves far more people than just the author. I thank my editors, William Schmidt and Jason Malley, for their overall guidance of the project, the reviewers of early drafts of the text and the production staff, especially Joanie Milnes and Keith Roberts, for shepherding the transformation of the final



manuscript into a real book. I am very grateful to Dr. Bradley R. Smith, Director of the Program in Medical and Biological Illustration at the University of Michigan, for providing one of his wonderful embryo images for use in the cover design. A book on embryology is especially dependent upon the quality of its artwork, and I want to extend my special thanks to Alexandra Baker of DNA Illustrations, Inc. for her superb translations of my chicken scratches into intelligible figures. Finally, my special thanks are due to my wife, Jean, for her usual forbearance of the general disruption that is involved in the birthing of yet another book.

Bruce M. Carlson

## DEVELOPMENTAL TABLES

**Carnegie Stages of Early Human Embryonic Development (Weeks 1-8)**

Age (days)	External features	Carnegie stage	Crown-rump length (mm)	Pairs of somites
1	Fertilized oocyte	1	0.1	
2-3	Morula (4-16 cells)	2	0.1	
4	Free blastocyst	3	0.1	
5-6	Attachment of blastocyst to endometrium	4	0.1	
7-12	Implantation, bilaminar embryo with primary yolk sac	5	0.1-0.2	
13-15	Trilaminar embryo with primitive streak, chorionic villi	6	0.2-0.3	
16	Gastrulation, formation of notochordal process	7	0.4	
18	Hensen's node and primitive pit, notochord and neurenteric canal, appearance of neural plate, neural folds, and blood islands	8	1.0-1.5	
20	Appearance of first somites, deep neural groove, elevation of cranial neural folds, early heart tubes	9	1.5-2.5	1-3
22	Beginning of fusion of neural folds, formation of optic sulci, presence of first two pharyngeal arches, beginning heart beat, curving of embryo	10	2.0-3.5	4-12
24	Closure of cranial neuropore, formation of optic vesicles, rupture of oropharyngeal membrane	11	2.5-4.5	13-20
26	Closure of caudal neuropore, formation of pharyngeal arches 3 and 4, appearance of upper limb buds and tail bud, formation of otic vesicle	12	3-5	21-29
28	Appearance of lower limb buds, lens placode, separation of otic vesicle from surface ectoderm	13	4-6	301
32	Formation of lens vesicle, optic cup, and nasal pits	14	5-7	
33	Development of hand plates, primary urogenital sinus, prominent nasal pits, evidence of cerebral hemispheres	15	7-9	
37	Development of foot plates, visible retinal pigment, development of auricular hillocks, formation of upper lip	16	8-11	
41	Appearance of finger rays, rapid head enlargement, six auricular hillocks, formation of nasolacrimal groove	17	11-14	
44	Appearance of toe rays and elbow regions, beginning of formation of eyelids, tip of nose distinct, presence of nipples	18	13-17	
48	Elongation and straightening of trunk, beginning of herniation of midgut into umbilical cord	19	16-18	
51	Bending of arms at elbows, distinct but webbed fingers, appearance of scalp vascular plexus, degeneration of anal and urogenital membranes	20	18-22	
52	Longer and free fingers, distinct but webbed toes, indifferent external genitalia	21	22-24	
54	Longer and free toes, better development of eyelids and external ear	22	23-28	
57	More rounded head, fusion of eyelids	23	27-31	

Data taken largely from O'Rahilly R, Müller F: Developmental stages in human embryos, Pub 637, Washington, DC, 1987, Carnegie Institution of Washington.

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**Major Developmental Events During the Fetal Period**


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**External features****Internal features****8 WEEKS**

Head is almost half the total length of fetus.  
 Cervical flexure is about 30 degrees.  
 Indifferent external genitalia are present.  
 Eyes are converging.  
 Eyelids are unfused.  
 Tail disappears.  
 Nostrils are closed by epithelial plugs.

Midgut herniation into umbilical cord occurs.  
 Extraembryonic portion of allantois has degenerated.  
 Ducts and alveoli of lacrimal glands form.  
 Paramesonephric ducts begin to regress in males.  
 Recanalization of lumen of gut tube occurs.  
 Lungs are becoming glandlike.  
 Diaphragm is completed.  
 First ossification begins in skeleton.  
 Definitive aortic arch system takes shape.

**9 WEEKS**

Neck develops and chin rises from thorax.  
 Cranial flexure is about 22 degrees.  
 Chorion is divided into chorion laeve and chorion frondosum.  
 Eyelids meet and fuse.  
 External genitalia begin to become gender specific.

Intestines are herniated into umbilical cord.  
 Early muscular movements occur.  
 ACTH and gonadotropins are produced by pituitary.  
 Corticosteroids are produced by adrenal cortex.  
 Semilunar valves in heart are completed.  
 Fused paramesonephric ducts join vaginal plate.  
 Urethral folds begin to fuse in males.

**10 WEEKS**

Cervical flexure is about 15 degrees.  
 Gender differences are apparent in external genitalia.  
 Fingernails appear.  
 Eyelids are fused.

Intestines return into body cavity from umbilical cord.  
 Bile is secreted.  
 Blood islands are established in spleen.  
 Thymus is infiltrated by lymphoid stem cells.  
 Prolactin production by pituitary occurs.  
 First permanent tooth buds form.  
 Deciduous teeth are in early bell stage.  
 Epidermis has three layers.

**11 WEEKS**

Cervical flexure is about 8 degrees.  
 Nose begins to develop bridge.

Urine is excreted into amniotic fluid.  
 Stomach musculature can contract.  
 T lymphocytes emigrate into bloodstream.  
 Colloid appears in thyroid follicles.

**12 WEEKS**

Head is erect.  
 Neck is almost straight and well defined.  
 External ear is taking form and has moved close to its definitive position in the head.  
 Yolk sac has shrunk.  
 Fetus swallows amniotic fluid.  
 Fetus can respond to skin stimulation.

Ovaries descend below pelvic rim.  
 Parathyroid hormone is produced.  
 Blood can coagulate.

**4 MONTHS**

Skin is thin; blood vessels can easily be seen through it.  
 Nostrils are almost formed.  
 Fetus may begin to suck its thumb.  
 Eyes have moved to front of face.  
 Legs are longer than arms.  
 Fine lanugo hairs appear on head.  
 Fingernails are well formed; toenails are forming.  
 Epidermal ridges appear on fingers and palms of hand.  
 Enough amniotic fluid is present to permit amniocentesis.  
 Mother can feel fetal movements.

Seminal vesicle forms.  
 Transverse grooves appear on dorsal surface of cerebellum.  
 Bile is produced by liver and stains meconium green.  
 Gastric glands bud off from gastric pits.  
 Brown fat begins to form.  
 Pyramidal tracts begin to form in brain.  
 Hematopoiesis begins in bone marrow.  
 Ovaries contain primordial follicles.

---

**Major Developmental Events During the Fetal Period—cont'd**


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**External features****Internal features****5 MONTHS**

Epidermal ridges form on toes and soles of feet.  
 Vernix caseosa begins to be deposited on skin.  
 Abdomen begins to fill out.  
 Eyelids and eyebrows develop.  
 Lanugo hairs cover most of body.

Myelination of spinal cord begins.  
 Sebaceous glands begin to function.  
 Thyroid-stimulating hormone is released by pituitary.  
 Testes begin to descend.

**6 MONTHS**

Skin is wrinkled and red.  
 Decidua capsularis degenerates because of reduced blood supply.  
 Lanugo hairs darken.

Surfactant begins to be secreted.  
 Tip of spinal cord is at S1 level.

**7 MONTHS**

Eyelids begin to open.  
 Eyelashes are well developed.  
 Scalp hairs are lengthening (longer than lanugo).  
 Skin is slightly wrinkled.

Sulci and gyri begin to appear on brain.  
 Subcutaneous fat storage begins.  
 Testes are descending into scrotum.

Termination of splenic erythropoiesis occurs.

**8 MONTHS**

Skin is pink and smooth.  
 Eyes are capable of pupillary light reflex.  
 Fingernails have reached tip of fingers.

Regression of hyaloid vessels from lens occurs.  
 Testes enter scrotum.

**9 MONTHS**

Toenails have reached tip of toes.  
 Most lanugo hairs are shed.  
 Skin is covered with vernix caseosa.  
 Attachment of umbilical cord becomes central in abdomen.  
 About 1 L of amniotic fluid is present.  
 Placenta weighs about 500 g.  
 Fingernails extend beyond fingertips.  
 Breasts protrude and secrete "witches' milk."

Larger amounts of pulmonary surfactant are secreted.  
 Ovaries are still above brim of pelvis.  
 Testes have descended into scrotum.  
 Tip of spinal cord is at L3.  
 Myelination of brain begins.

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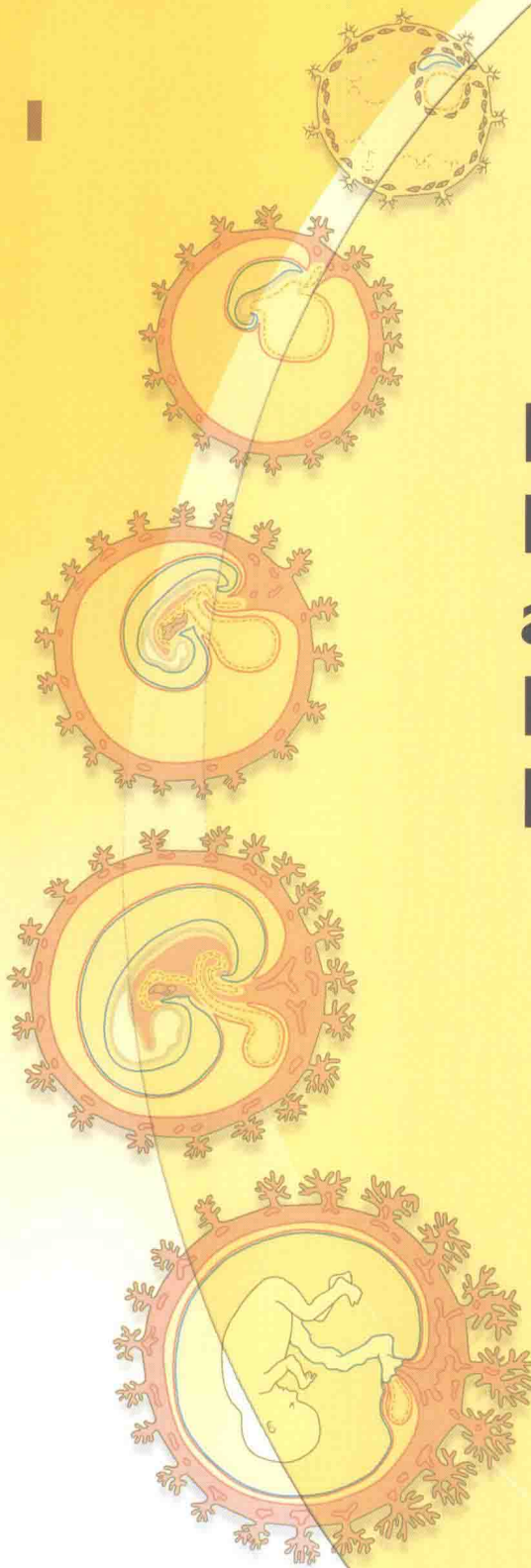
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**PART I**



# **Early Development and the Fetal-Maternal Relationship**



