

William J. Larsen

Human Embryology



T H I R D E D I T I O N

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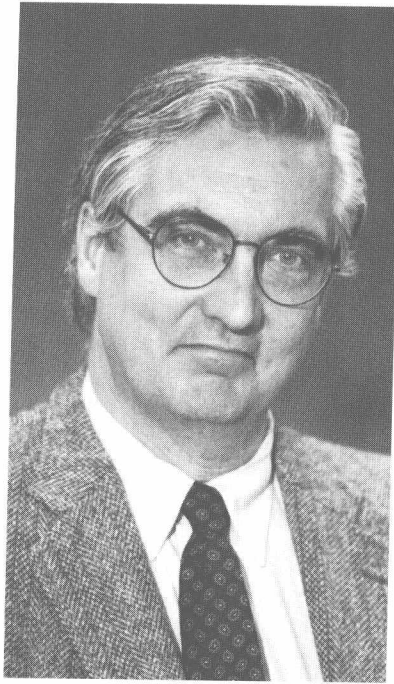
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William J. Larsen, Ph.D.

1942–2000

Developmental biology research scientist and teacher par excellence,
author of *Human Embryology* and *Human Anatomy* (in press),
furniture builder, lover of the Southwest, superlative storyteller and
humorist, gourmet cook, thoughtful advisor,
exciting and generous personality—a truly unique and exceptional
human being.

Preface to the Third Edition

The completion of the human genome project was indeed an amazing milestone for research in human genetics. This work is generating—and will undoubtedly continue to generate—an incredible new surge of experimental studies, with exciting prospects for applying the knowledge of human genetics to human embryology and medical clinical practice. The National Board of Medical Examiners has, in fact, recognized the growing importance of this area of medical education and has created both an Embryology and a Developmental Biology and Human Genetics Task Force. Dr. Larsen was invited to participate in both. (After he served on these task forces, he joined the Anatomy Test Committee.)

A short time ago, I received a concrete example of the relevance of human embryology to the practice of medicine: A physician wrote to Dr. Larsen requesting his collaboration on a chapter of a book for pediatric physicians. The goal of the chapter would be to present the ways in which knowledge of the embryology of congenital heart defects informs clinical practice for pediatric anesthesiology. It is with great sorrow, however, that I must announce that William Larsen died suddenly in January of 2000 and therefore was not able to participate personally in this project. He would have been delighted by this evidence of a real and direct use of embryologic knowledge for diagnosing and treating patients—a trend that will undoubtedly grow exponentially in the coming years.

Dr. Larsen had the work for this edition well under way before he died. He had completed several of the experimental and clinical section updates, selected current research, and outlined areas to be revised for all other chapters. Three colleagues in the area of developmental research, who had contributed to and reviewed previous editions, graciously agreed to take on the task of completing this revision. They are Doctors Lawrence S. Sherman, S. Steven Potter, and William J. Scott. These three individuals reviewed vast amounts of current published research articles and conferred

with, or elicited the help of, other clinical and research colleagues to update both the experimental and clinical sections of each chapter—exactly as Bill had done in previous editions. Descriptive embryology sections of the book were also updated where necessary, and over 40 figures were enhanced. I am incredibly grateful to them for taking on this task. Their commitment, time, and expertise, as well as their good humor and positive interactions, have made a difficult job much more enjoyable. Together, they have produced a book current in every respect.

The Human Embryology website has also been updated with the addition of a number of new animations and will be kept current by Bill's son, Eric Larsen, who originally created the website and the animations.

I have lost the love of my life, my inspiration and supporter, the marvelous father of our children, and my closest friend. The world has lost a person with a great zest for life, a superlative storyteller, and a caring, generous person. His gift to embryology and medical education was his ability to see the whole picture and synthesize it for others—a gift that makes this book unique among embryology textbooks. His vision is reflected in the structure of this book in which classical embryology has been combined with a brief overview of exciting new research. This provides beginning medical students with the tools to understand research discoveries that will forever change the future of their medical careers. I am happy that this book, which reflects Bill's greatest professional passions—his excitement about embryology and his devotion to the art of teaching—so excellently carries on his spirit.

Human Embryology Third Edition Editors

Lawrence S. Sherman, Ph.D., Assistant Professor—Graduate Programs in Neuroscience, Molecular and Developmental Biology, Cell and Molecular Biology, and Physician Scientist Training Program. His research area is development of the

peripheral nervous system, with a focus on how processes that occur during development are recapitulated after nerve injury and in nervous system cancers.

S. Steven Potter, Ph.D., Professor of Pediatrics in the Division of Developmental Biology. He is studying the roles of homeobox genes in limb, urogenital, and central nervous system development, with a special focus on left-right axis determination.

William J. Scott, Ph.D., Professor of Pediatrics, codirected (with William Larsen) a graduate level course for students of Developmental Biology research and genetic counseling. His research interests are in teratology, especially drug-induced congenital malformations of the limbs.

The following people reviewed and offered suggestions on various sections of the text for this edition: Jeffrey Whitsett, Larry Patterson, Richard Miller, Robert Gendron, and Robert Arceci. I am grateful to all of them.

I am also indebted to Marianne Bronner-Fraser, George Daston, David Repaske, Sheila Bell, Cliff Tabin, Andrew McMahon, Dorothy Supp, Jay Hoying, Peter Stambrook, Gail Benson, Tom Doetschman, Stephen D. Smith, Richard Maas, R. A. Conlon, Mario Cappechi, Susan Wert, Kathryn Yutzey, Melissa Colbert, Margaret Kirby, Bjorn Olsen, Thomas Reid, George Nikas, Tariq Siddiqui, K. Lawson, Jonathan Cooke, J. E. Cook, Lee Niswander, Raymond Gasser, C. R. Ball, Donald R. Cahill, Lewis Williams, Y. Fukui, Stephan Carmichael, Ann Hirschfield, David Chan, Martin J. Coh, R. Hunt, C. Ward Kirscher, Stefan Mundlos, Herbert Steinbeisser, Richard Brand, Robb Krumlauf, Claire Shreiner, Igor Dawid, Michael Gershon, Bruce Carlson, Colin Wendell-Smith, Jean Marx, M. Bruecker, John Saunders, Cynthia Loomis, John Fallon, and E. L. Cardell. Without their insights and suggestions, this book would not have been possible.

JUDITH I. LARSEN

Preface to the Second Edition

The revolution in mammalian and human embryology described in the preface to the first edition of *Human Embryology* has continued and accelerated. It has been just ten years since *Hox* genes were discovered in mammals; by the time the first edition of this book was written, only a few other regulatory genes inherited from our evolutionary ancestors had been described. Nevertheless, it seemed likely that these initial discoveries held fundamental significance for our understanding of human development. Research carried out in the last few years has clearly demonstrated the authenticity of this hope. The number and functions of developmental regulatory genes in mammals, including humans, have expanded exponentially. Indeed, it appears that many ancestral gene cascades have been co-opted for the regulation of unique vertebrate or mammalian developmental processes that do not even occur in lower organisms.

These new findings are exciting in their own right, but the significance of the new molecular discoveries to congenital disease and clinical practice attests to their practical value as well. This is illustrated by the movement of several discussions in the Experimental Principles sections of the first edition to Clinical Applications sections of the second. In most cases, this has occurred as a consequence of mapping and/or cloning of the human homolog of specific regulatory genes or discovery that their disruption results in human congenital disease. A few of the many examples include *PAX3* (Hirschsprung's disease), surfactant B (surfactant B deficiency), *HOXD13* (syndactyly), and *SHH* (limb and craniofacial malformations). Identification of genes that underlie many other human congenital malformations are also on the horizon, including genes that underlie situs defects and Down syndrome. In addition, it is now known that several human regulatory genes or related genes also function as tumor suppressor genes. Indeed, disruptions of some of these genes are among the most common causes of significant

human cancers. While this information is particularly relevant to diagnosis, it is likely that effective therapies will also evolve more rapidly once the genetic and mechanistic bases of specific congenital disease are understood. Finally, advances in techniques such as spectral karyotyping, Southern blotting, and RT-PCR have also improved the efficiency and accuracy of clinical screening and diagnoses. This second edition, therefore, has attempted to update many of these new advances, although the rapidity and volume of change and limitations of space have forced the need to be selective.

The study of human embryology continues to provide a useful basis for the understanding of definitive human anatomy; to this end, several revisions to figures and new scanning electron micrographs have also been included in this second edition. Perhaps the most important didactic improvements of this edition to the teaching of descriptive embryology and anatomy, however, are numerous animations and interactive testing exercises that can be found on the new World Wide Web site for *Human Embryology* (<http://www.med.uc.edu/embryology>). The web site will also be useful to those who wish to keep abreast of new information as it unfolds between the second and third editions and for those who wish to comment or provide suggestions for improvements.

I owe a debt of sincere gratitude to the many colleagues who graciously contributed figures or who read, critiqued, or made suggestions for the second edition. They include George Daston, David Repaske, William J. Scott, Sheila Bell, Cliff Tabin, Andrew McMahon, Larry Sherman, Steve Potter, Dorothy Supp, Jay Hoying, Robert Gendron, Peter Stambrook, Gail Benson, Tom Doetschman, Stephen D. Smith, Richard Maas, R. A. Conlon, Mario Cappechi, Susan Wert, Kathryn Yutzey, Melissa Colbert, Margaret Kirby, Bjorn Olsen, Thomas Reid, George Nikas, Tariq Siddiqui, K. Lawson, Jonathan Cooke, J. E. Cook, Lee Niswander, Raymond Gasser, C. R. Ball, Donald R.

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Bruce Carlson, Colin Wendell-Smith, Jean Marx, M. Brueckner, John Saunders, Cynthia Loomis, John Fallon, and E. L. Cardell.

WILLIAM J. LARSEN, PH.D.

Preface to the First Edition

A torrent of new findings and techniques has revolutionized embryology. As a result, this discipline is relevant not only to understanding adult structure but also, increasingly, to a physician's direct practice. I have written *Human Embryology* to meet the needs of first-year medical students in gross anatomy and neuroanatomy courses and to offer them a glimpse of some of the exciting applications that are currently in use or on the horizon. This text is used at the University of Cincinnati in conjunction with the twelve embryology lectures given in the gross anatomy course. It will also interest other readers, including premedical undergraduates, graduate students in developmental biology programs, nursing students, and allied health students in disciplines such as the burgeoning field of genetic counseling.

I researched this book intensively in an attempt to make it wholly up-to-date. In the course of that process, I learned a great deal that has renewed my own fascination with embryology, including the truth behind a number of venerable chestnuts that have been passed down in generations of embryology texts. It is my hope that the students who read this text will be as enthralled by modern embryology as I am.

This text uses a modular design that allows students to review the material in several ways and that will let instructors tailor the book to their specific needs. The first six chapters describe gametogenesis, fertilization, and the initial weeks of development; Chapters 7 to 14 deal with the individual organ systems; and the last chapter covers aspects of fetal development. Each chapter opens with a summary that gives a condensed version of the material in the chapter. In accordance with a frequent demand of my students, these summaries are supplemented by full-page timeline illustrations that graphically display the timing of the events described. The main portion of each chapter is devoted to a concise descriptive embryology of its subject. Other topics, such as theoretical discussions and description of congenital anomalies, are

segregated in special Clinical Applications and Experimental Principles sections, where they will not clutter the essential story. I have worked hard to make the descriptions of morphogenetic processes complete as well as concise, because I know from experience that gaps in the explanation make these processes difficult to visualize and, hence, to remember. The text headings are written in sentence style so as to encapsulate the main points of the chapter.

Good three-dimensional illustrations are obviously central to an embryology text. Once a chapter has been mastered, the reader ought to be able to review it by thumbing through the pictures and skimming the captions. Within the limits of space and expense, I have tried to illustrate enough critical stages of each process to obviate "leaps of faith." In the interests of clarity, I have converted all length, somite number, and stage designations to approximate gestation time in days and weeks. However, a complete table relating Carnegie stages, embryo length in millimeters, and numbers of somites is provided on pages xv and xvi. Structures are usually shown in their real context in the embryo, rather than left to float on the page, and color is used abundantly to indicate the derivation of structures and tissues. Where possible, I have included scanning electron micrographs to show how the structures in question actually look.

Although the Clinical Applications and Experimental principles sections relate to the descriptive text, they are free-standing and can be assigned or omitted at will. Topics such as multifactorial inheritance, sensitive periods, teratogenicity, and prenatal diagnosis, as well as a selection of congenital abnormalities, are covered in the Clinical Applications sections. These sections will sharpen the interest of first-year students by showing the relation of embryology to clinical practice. Some of them will also prove useful in later training. A student studying Hirschsprung's disease in a second-year pathology course, for example, can refer to the section on the pathogenesis of the underlying

parasympathetic anomaly, and a student on a third-year clinical rotation can review the common cardiac anomalies.

Even a cursory reading of the short Experimental Principles sections will show how the information in the description embryology sections was obtained and will give a glimpse of the frontiers of diagnosis, therapy, and research. Some of these sections are essential to a first-year student, but others are of fundamental utility, such as the discussion of induction in Chapter 4 and the section on the pathogenetic bases of cardiac anomalies in Chapter 7. These sections may also be used to support the multidisciplinary approaches currently employed in some schools.

The past decade has witnessed a revolution in the diagnosis and treatment of congenital diseases. Many diseases can be identified in utero, and fetal operations may soon be routine. However, the revolution is only beginning: The studies now being carried out on novel molecular techniques, such as gene therapy, are thrusting us abruptly into a new age of prenatal medicine. Techniques to cure such diseases as congenital immunodeficiency syndromes and cystic fibrosis are being tested in animal models, for example. Because of this prospect of therapeutic payoff, the molecular basis of development has become a highly funded topic in medical research. Here in the United States, the number of grant applications submitted to the Molecular Genetics section of the National Institute of Child Health and Human Development is increasing at an unprecedented rate. It will not be possible to develop appropriate applications for these new molecular techniques, however, without

input from classical experimental and descriptive embryologic research. That task of integration and application—as well as the daunting social and ethical challenges that the new prenatal and genetic techniques will bring in their train—will fall largely to the students who are now studying medicine, nursing, developmental and molecular biology, and genetic counseling.

WILLIAM J. LARSEN, PH.D.

*Now the Mother Earth
and the Father Sky
Meeting, joining one another,
Helpmates ever, they*

*All is beautiful
All is beautiful
All is beautiful, indeed*

*And the white corn
And the yellow corn
Meeting, joining one another
Helpmates ever, they*

*All is beautiful
All is beautiful
All is beautiful, indeed*

(From Song of the Earth [Navajo], George W. Cronin [ed]: Songs of the Southwest. In: American Indian Poetry: Anthology of Songs and Chants. Liveright, New York, 1934, with permission.)

Correlation of Timing Systems Used For Human Embryos (Weeks 1 Through 8)

Week	Day	Length (mm) ^a	Number of Somites	Carnegie Stage	Features (<i>chapters in which features are discussed</i>) ^b
1	1	0.1–0.15	—	1	Fertilization (1)
	1.5–3	0.1–0.2	—	2	First cleavage divisions occur (2–16 cells) (1)
	4	0.1–0.2	—	3	Blastocyst is free in uterus (1)
	5–6	0.1–0.2	—	4	Blastocyst hatches and begins implanting (1, 2)
2	7–12	0.1–0.2	—	5	Blastocyst fully implanted (1, 2)
	13	0.2	—	6	Primary stem villi appear (2); primitive streak develops (3)
3	16	0.4	—	7	Gastrulation commences; notochordal process forms (3)
	18	1–1.5	—	8	Primitive pit forms (3); neural plate and neural groove appear (3, 4)
	20	1.5–2.5	1–3	9	Caudal eminence and first somites form (3); neuromeres appear in presumptive brain vesicles (4, 13); primitive heart tube is forming (7); vasculature begins to develop in embryonic disc (8)
4	22	2–3.5	4–12	10	Neural folds begin to fuse; cranial end of embryo undergoes rapid flexion (4, 13); pulmonary primordium appears (6); myocardium forms and heart begins to pump (7); hepatic plate appears (9); first two pharyngeal arches and optic sulci begin to form (12)
	24	2.5–4.5	13–20	11	Primordial germ cells begin to migrate from wall of yolk sac (1); cranial neuropore closes (4); buccopharyngeal membrane ruptures (12); optic vesicles develop (12); optic pit begins to form
	26	3–5	21–29	12	Caudal neuropore closes (4); cystic diverticulum and dorsal pancreatic bud appear (9); urorectal septum begins to form (9, 10); upper limb buds appear (11); pharyngeal arches 3 and 4 form (12)
	28	4–6	30+	13	Dorsal and ventral columns begin to differentiate in mantle layer of spinal cord and brain stem (4, 13); septum primum begins to form in heart (7); spleen appears (9); ureteric buds appear (10); lower limb buds appear (11); otic vesicle and lens placode appear (12); motor nuclei of cranial nerves appear (13)
5	32	5–7	—	14	Spinal nerves begin to sprout (5); semilunar valves begin to form in heart (7); lymphatics and coronary vessels appear (8); greater and lesser stomach curvatures and primary intestinal loop form (9); metanephros begins to develop (10); lens pit invaginates into optic cup; endolymphatic appendage appears (12); secondary brain vesicles begin to form; cerebral hemispheres become visible (13)
	33	7–9	—	15	Atrioventricular valves and definitive pericardial cavity begin to form (7); cloacal folds and genital tubercle appear (10); hand plate develops (11); lens vesicle forms and invagination of nasal pit creates medial and lateral nasal processes (12); sensory and parasympathetic cranial nerve ganglia begin to form; primary olfactory neurons send axons into telencephalon (13)

Correlation of Timing Systems Used For Human Embryos (Weeks 1 Through 8)

Week	Day	Length (mm) ^a	Number of Somites	Carnegie Stage	Features (<i>chapters in which features are discussed</i>) ^b
6	37	8–11	—	16	Muscular ventricular septum begins to form (7); gut tube lumen becomes occluded (9); major calyces of kidney begin to form and kidneys begin to ascend; genital ridges appear (10); foot plate forms on lower limb bud (11); pigment appears in retina; auricular hill-ocks develop (12)
	41	11–14	—	17	Bronchopulmonary segment primordia appear (6); septum intermedium of heart is complete (7); subcardinal vein system forms (8); minor calyces of kidney are forming (10); finger rays are distinct (11); nasolacrimal groove forms (12); cerebellum begins to form (13); melanocytes enter epidermis; dental laminae form (14)
7	44	13–17	—	18	Skeletal ossification begins (4, 11); Sertoli cells begin to differentiate in the male gonad (10); elbows and toe rays appear (11); intermaxillary process and eyelids form in face (12); thalami of diencephalon expand (13); nipples and first hair follicles appear (14)
	47	16–18	—	19	Septum primum fuses with septum intermedium in heart (7); urogenital membrane ruptures (10); trunk elongates and straightens (15)
8	50	18–22	—	20	Primary intestinal loop completes initial counterclockwise rotation (9); in males, paramesonephric ducts begin to regress and vasa deferentia begin to form (10); upper limbs bend at elbows (11)
	52	22–24	—	21	Pericardioperitoneal canals close (6); hands and feet approach each other at the midline (11)
	54	23–28	—	22	Eyelids and auricles are more developed (12)
	56	27–31	—	23	Chorionic cavity is obliterated by the growth of the amniotic sac (6); definitive superior vena cava and major branches of the aortic arch are established (8); lumen of gut tube is almost completely recanalized (9); primary teeth are at cap stage (14)

^aLength is the greatest length of embryo.

^bTiming of some events will differ slightly in some embryos.

(Columns 1 through 5 from O'Rabilly R, Müller F. 1987. *Developmental Stages in Human Embryos*. Carnegie Institute, Washington, D.C., Publ. No. 637, with permission.)

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