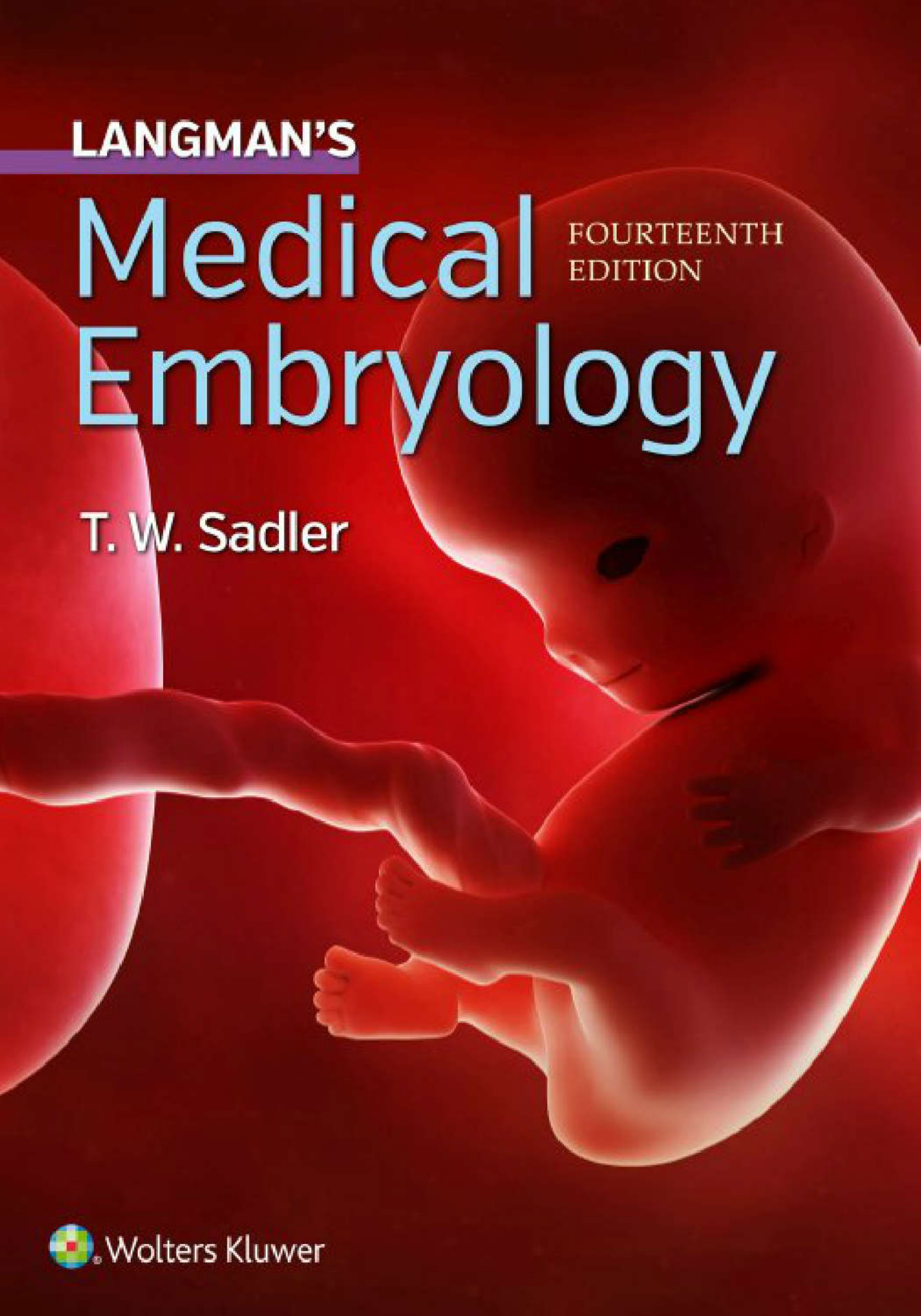
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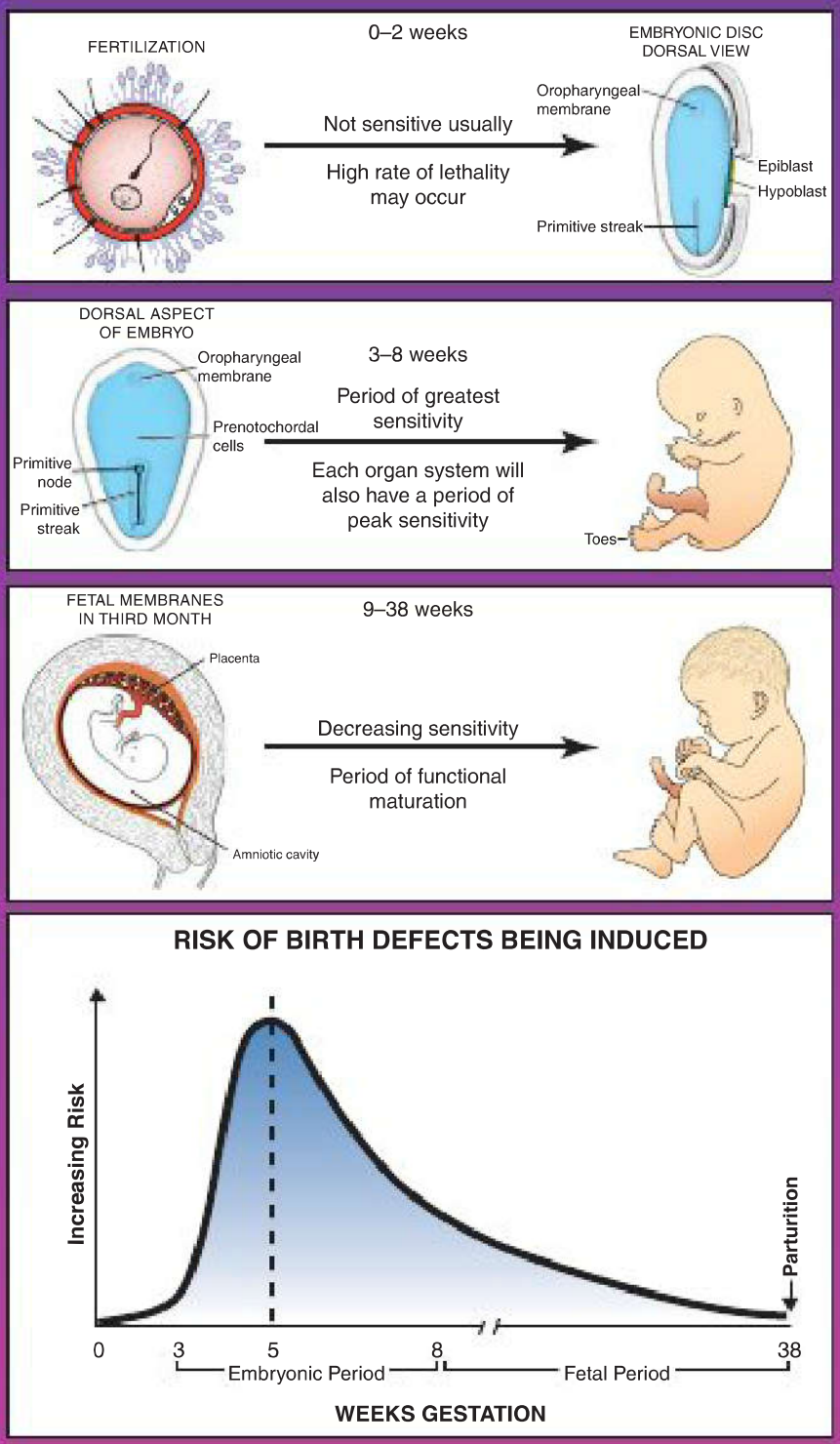
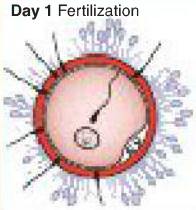
Periods of Susceptibility to Teratogenesis

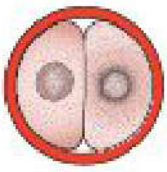


Embryonic Development in Days

Day 1 Fertilization



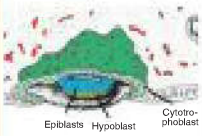
Day 2 Two-cell stage



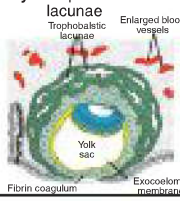
Day 3 Morula

Day 4 Early blastocyst

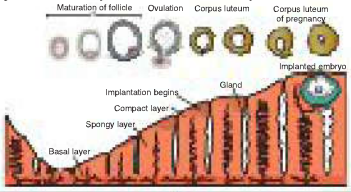
Day 8 Bilaminar disc forms



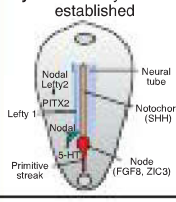
Day 9 Trophoblast with lacunae



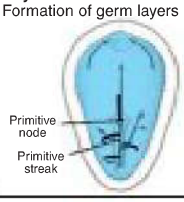
Day 10-11 Embryo in uterus 10-11 days after ovulation



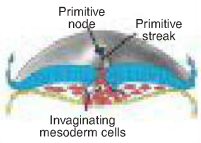
Day 15 Laterality established



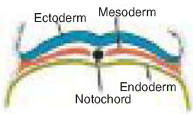
Day 16 Gastrulation: Formation of germ layers



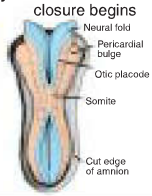
Day 17 Epiblast forms germ layers



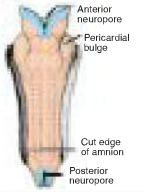
Day 18 Trilaminar embryonic disc



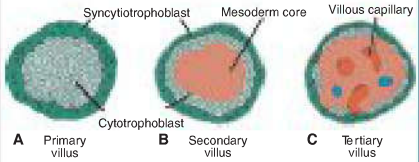
Day 22 Neural tube closure begins



Day 23 Neural tube zippers



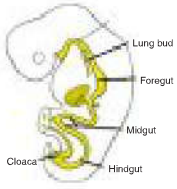
Day 24-25 Villus formation continues in the placenta



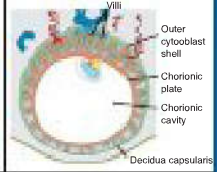
Day 29 Arm and leg buds

Day 30 Developing face

Day 31 Gut development

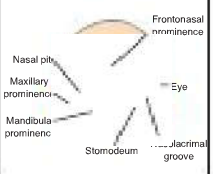


Day 32 Embryo in chorionic cavity

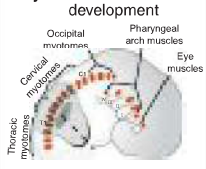


Day 36 Physiological umbilical hernia

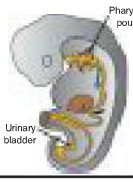
Day 37 Developing face



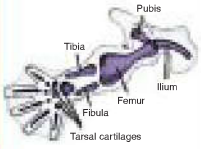
Day 38 Muscle development



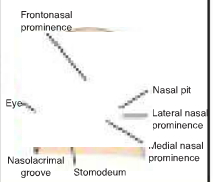
Day 39 Endodermal derivatives



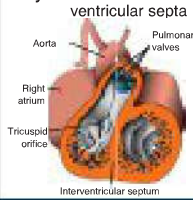
Day 43 Limb cartilages and digital rays



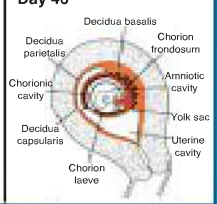
Day 44 Developing face



Day 45 Conotruncal and ventricular septa

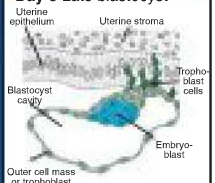


Day 46

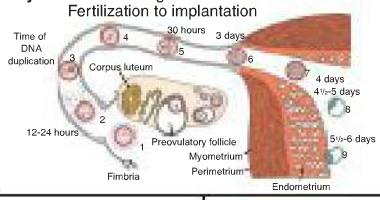


Embryonic Development in Days

Day 5 Late blastocyst

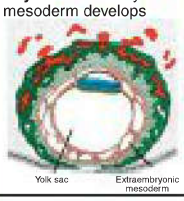


Day 6-7 Events during first week: Fertilization to implantation

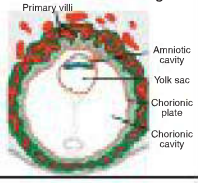


Development Week 1

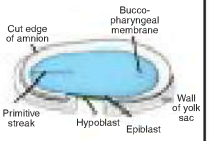
Day 12 Extraembryonic mesoderm develops



Day 13 Uteroplacental circulation begins

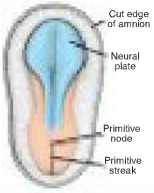


Day 14 Embryonic disc: dorsal view

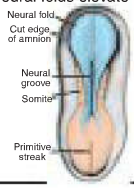


Development Week 2

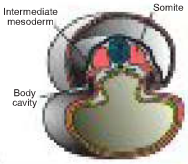
Day 19 CNS induction



Day 20 Neurulation: Neural folds elevate



Day 21 Transverse section through somite region



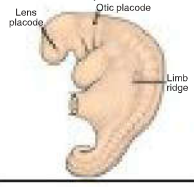
Development Week 3

Day 26 Pharyngeal arches present

Day 27

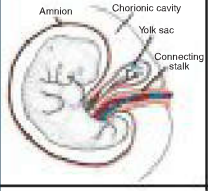
Approx. Age (Days)	No. of Somites
20	1-4
21	4-7
22	7-10
23	10-13
24	13-17
25	17-20
26	20-23
27	23-26
28	26-29
30	34-35

Day 28 Neurulation complete

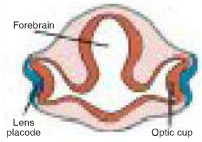


Development Week 4

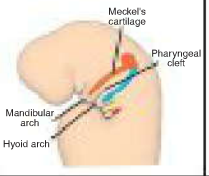
Day 33 Umbilical ring



Day 34 Optic cup and lens placode

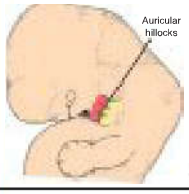


Day 35 Branchial arches and clefts

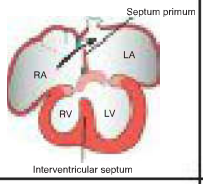


Development Week 5

Day 40 Auricular hillocks



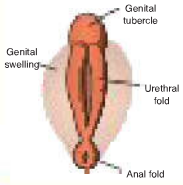
Day 41 Atrial septum formed



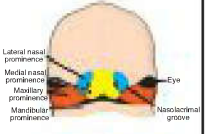
Day 42 Digit formation

Development Week 6

Day 47 External genitalia



Day 48 Facial prominences fused



Day 49 Digits present, eyelids forming

Development Week 7

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Medical Embryology

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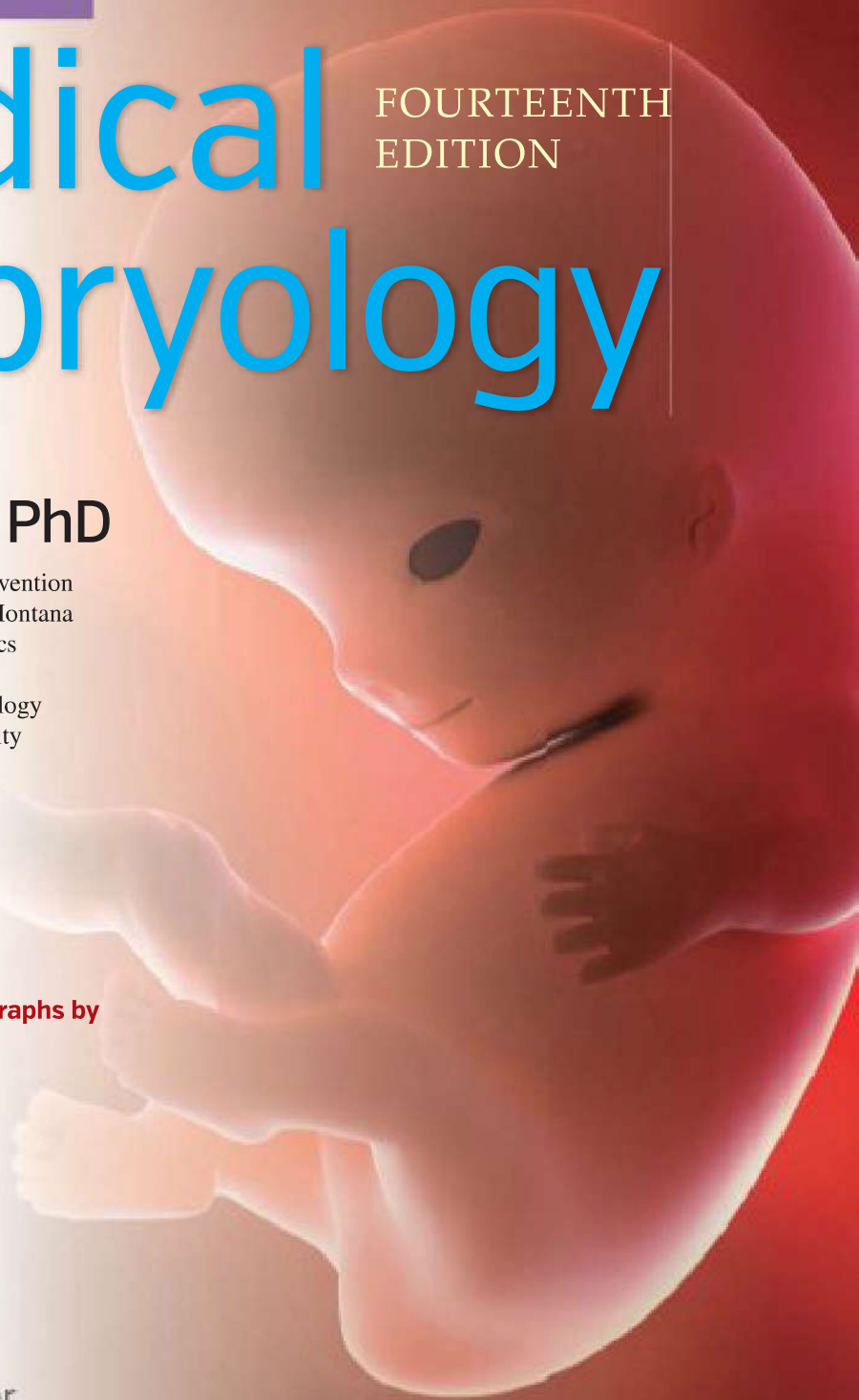

T. W. Sadler, PhD

Consultant, Birth Defects Prevention
Sheridan, Madison County, Montana
Adjunct Professor of Pediatrics
University of Utah
Visiting Professor of Embryology
East Tennessee State University
Quillen School of Medicine
Senior Scholar
Greenwood Genetics Center
Greenwood, South Carolina

Computer Illustrations by
Susan L. Sadler-Redmond

Scanning Electron Micrographs by
Kathy Tosney

Ultrasound Images by
Jan Byrne and
Hytham Imseis

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Dedication

For each and every child

Special thanks to:

Professor J. Calvin Coffey for teaching me the updated anatomy of the mesenteries and their embryological origins. The incorporation of these concepts into this edition represents another example of the clinical relevance and importance of understanding the subjects of Embryology and Anatomy.*

*Professor J. Calvin Coffey
Foundation Chair of Surgery
University of Limerick
Limerick, Ireland

Preface

Every student will be affected by pregnancy, either their mother's, because what happens in the womb does not necessarily stay in the womb, or by someone else's. As health care professionals, you will often encounter women of childbearing age who may be pregnant, or you may have children of your own, or maybe it is a friend who is pregnant. In any case, pregnancy and childbirth are relevant to all of us, and unfortunately, these processes often culminate in negative outcomes. For example, 50% of all embryos are spontaneously aborted. Furthermore, prematurity and birth defects are the leading causes of infant mortality and major contributors to disabilities. Fortunately, new strategies can improve pregnancy outcomes, and health care professionals have a major role to play in implementing these initiatives. However, a basic knowledge of embryology is essential to the success of these strategies, and with this knowledge, every health care professional can play a role in providing healthier babies.

To accomplish its goal of providing a basic understanding of embryology and its clinical relevance, *Langman's Medical Embryology* retains its unique approach of combining an economy of text with excellent diagrams and clinical images. It stresses the clinical importance of the subject by providing numerous clinical examples that result from abnormal embryological events. The following pedagogic features and updates in the 14th edition help facilitate student learning.

Organization of Material: *Langman's Medical Embryology* is organized into two parts. The first provides an overview of early development from gametogenesis through the embryonic period. Also included in this section are chapters on placental and fetal development as well as prenatal diagnosis and birth defects. The second part of the text provides a description of the fundamental processes of embryogenesis for each organ system.

Clinical Correlates: In addition to describing normal events, each chapter contains clinical correlates that appear in highlighted boxes. This material is designed to demonstrate the clinical relevance of embryology and the importance of understanding key developmental events as a first step to improving birth outcomes and having healthier babies. Clinical pictures and case descriptions are used to provide this information, and this material has been increased and updated in this edition.

Genetics: Because of the increasingly important role of genetics and molecular biology in embryology and the study of birth defects, basic genetic and molecular principles are discussed. The first chapter provides an introduction to molecular processes, defines terms commonly used in genetics and molecular biology, and describes key pathways used

in embryonic development. Then, throughout the text, major signaling pathways and genes that regulate embryological development are identified and discussed.

Extensive Art Program: The artwork has always been designed to enhance understanding of the text and includes four-color line drawings, scanning electron micrographs, and clinical pictures. Once again, artwork has been added, especially to Chapter 18, to illustrate new concepts in development of the central nervous system, diaphragm, ear, and other structures.

Summary: At the end of each chapter is a summary that serves as a concise review of the key points described in detail throughout the chapter. Key terms are highlighted and defined in these summaries.

Problems to Solve: Problems related to the key elements of each chapter are provided to assist the students in assessing their understanding of the material. Detailed answers are provided in an appendix at the back of the book.

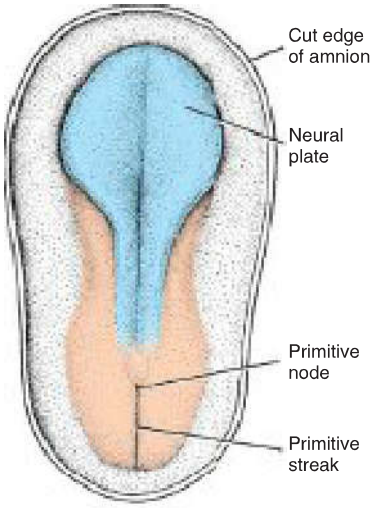
Glossary: A glossary of key terms has been expanded and is located in the back of the book.

thePoint Web site: This site for students and instructors provides an interactive question bank of USMLE board-type questions. Teaching aids for instructors are also provided in the form of an image bank and a series of lectures on the major topics in embryology presented in PowerPoint with accompanying notes.

I hope you find this edition of *Langman's Medical Embryology* to be an excellent resource for learning embryology and its clinical significance. Together, the textbook and online site, thePoint, are designed to provide a user-friendly and innovative approach to understanding the subject.

T.W. Sadler
Sheridan, MT

Placode: **A local thickening in the embryonic ectoderm layer that develops into a sensory organ or ganglion.**



19 days

ODE TO A PLACODE

There once was a flat sheet of cells
That were stumpy and ugly as hell;
But one day they arose, stood tall on their toes,
and declared they were the best cells of all.

Presumptuously they cried that their lineage was high
and right proudly they bragged of their codes;
But soon it was clear, they weren't like the ear
and they were nixed in their dreams as placodes.

Semantics, they screamed, please maintain our dreams,
but their pleas were unheeded and late;
And now to this day in repast they must lay
as a misconstrued, flat neural plate!

T.W. Sadler
Sheridan, MT

Introduction

Embryology: Clinical Relevance and Historical Perspective

CLINICAL RELEVANCE

From a single cell to a baby in 9 months—a developmental process that represents an amazing integration of increasingly complex phenomena. The study of these phenomena is called **embryology**, and the field includes investigations of the molecular, cellular, and structural factors contributing to the formation of an organism. These studies are important because they provide knowledge essential for creating health care strategies for better reproductive outcomes. Thus, our increasingly greater understanding of embryology has resulted in new techniques for prenatal diagnoses and treatments; therapeutic procedures to circumvent problems with infertility; and mechanisms to prevent birth defects, the leading cause of infant mortality. These improvements in prenatal and reproductive health care are significant not only for their contributions to improved birth outcomes but also for their long-term effects postnatally. For example, both our cognitive capacity and our behavioral characteristics are affected by our prenatal experiences, and factors such as maternal smoking, nutrition, stress, diabetes, etc., play a role in our postnatal health. Furthermore, prenatal experiences, in combination with molecular and cellular factors, determine our potential to develop certain adult diseases, such as cancer and cardiovascular disease. Thus, our prenatal development produces many ramifications affecting our health for both the short and long term, making the study of embryology and fetal development an important topic for all health care professionals. Also, with the exception of a few specialties, most physicians and health care workers will have an opportunity to interact with women of childbearing age, creating the potential for these providers to have a major impact on the outcome of developmental processes and their sequelae.

A BRIEF HISTORY OF EMBRYOLOGY

The process of progressing from a single cell through the period of establishing organ primordia (the first 8 weeks of human development) is called the period of **embryogenesis** (sometimes called the period of **organogenesis**); the period from that point on until birth is called the **fetal period**, a time when differentiation continues while the fetus grows and gains weight. Scientific approaches to study embryology have progressed over hundreds of years. Not surprisingly, anatomical approaches dominated early investigations. Observations were made, and these became more sophisticated with advances in optical equipment and dissection techniques. Comparative and evolutionary studies were part of this equation as scientists made comparisons among species and so began to understand the

progression of developmental phenomena. Also investigated were offspring with birth defects, and these examples were compared to organisms with normal developmental patterns. The study of the embryological origins and causes for these birth defects was called **teratology**.

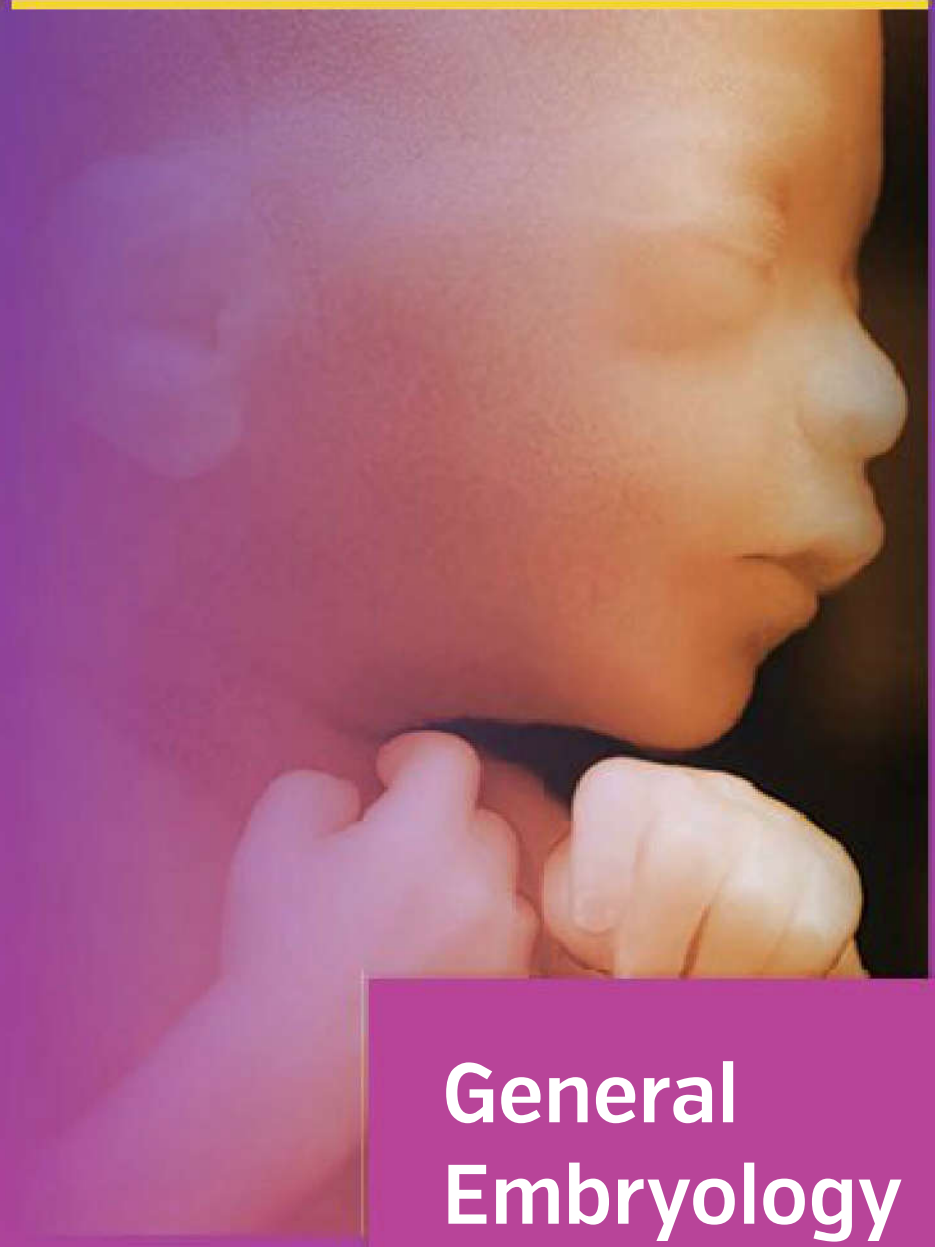
In the 20th century, the field of experimental embryology blossomed. Numerous experiments were devised to trace cells during development to determine their cell lineages. These approaches included observations of transparent embryos from tunicates that contained pigmented cells which could be visualized through a microscope. Later, vital dyes were used to stain living cells to follow their fates. Still later in the 1960s, radioactive labels and autoradiographic techniques were employed. One of the first genetic markers also arose about this time with the creation of chick-quail chimeras. In this approach, quail cells, which have a unique pattern to their heterochromatin distribution around the nucleolus, were grafted into chick embryos at early stages of development. Later, host embryos were examined histologically, and the fates of the quail cells were determined. Permutations of this approach included development of antibodies specific to quail cell antigens that greatly assisted in the identification of these cells. Monitoring cell fates with these and other techniques provides valuable information about the origins of different organs and tissues.

Grafting experiments also provided the first insights into signaling between tissues. Examples of such experiments included grafting the primitive node from its normal position on the body axis to another and showing that this structure could induce a second germ disc. In another example, employing developing limb buds, it was shown that if a piece of tissue from the posterior axial border of one limb was grafted to the anterior border of a second limb, then digits on the host limb would be duplicated as the mirror image of each other. This posterior signaling region was called the **zone of polarizing activity (ZPA)**, and it is now known that the signaling molecule is **SONIC HEDGEHOG (SHH)**.

In 1961, the science of teratology became prominent because of the drug **thalidomide** that was given as an antinauseant and sedative to pregnant women. Unfortunately, the drug caused birth defects, including unique abnormalities of the limbs in which one or more limbs was absent (amelia) or was lacking the long bones such that only a hand or foot was attached to the torso (phocomelia). The association between the drug and birth defects was recognized independently by two clinicians, W. Lenz and W. McBride, and showed that the conceptus was vulnerable to maternal factors that crossed the placenta. Soon, numerous animal models demonstrating an association between environmental factors, drugs, and genes provided further insights between developmental events and the origin of birth defects.

Today, molecular approaches have been added to the list of experimental paradigms used to study normal and abnormal development. Numerous means of identifying cells using reporter genes, fluorescent probes, and other marking techniques have improved our ability to map cell fates. Using other techniques to alter gene expression, such as knockout, knock-in, and antisense technologies, has created new ways to produce abnormal development and allowed the study of a single gene's function in specific tissues. Thus, the advent of molecular biology has advanced the field of embryology to the next level, and as we decipher the roles of individual genes and their interplay with environmental factors, our understanding of normal and abnormal developmental processes progresses.

Part 1



General Embryology

Introduction to Molecular Regulation and Signaling

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Molecular biology has opened the doors to new ways to study embryology and to enhance our understanding of normal and abnormal development. Sequencing the human genome, together with creating techniques to investigate gene regulation at many levels of complexity, has taken embryology to the next level. Thus, from the anatomical to the biochemical to the molecular level, the story of embryology has progressed, and each chapter has enhanced our knowledge.

Embryonic development is directed by **genomes** that contain all of the information required to make an individual. The information is encoded in **DNA** in sequences called **genes** that code for proteins. In turn, proteins regulate expression of other genes and act as signal molecules to orchestrate development.

There are approximately 23,000 genes in the human genome, which represents only one-fifth of the number (100,000) predicted prior to completion of the Human Genome Project. Because of various levels of regulation, however, the number of proteins derived from these genes is closer to the original predicted number of genes. What has been disproved is the one gene–one protein hypothesis. Thus, through a variety of mechanisms, a single gene may give rise to many proteins.

Gene expression can be regulated at several levels: (1) Different genes may be transcribed, (2) DNA transcribed from a gene may be selectively processed to regulate which RNAs reach the cytoplasm to become messenger RNAs (mRNAs), (3) mRNAs may be selectively translated, and (4) proteins made from the mRNAs may be differentially modified.

GENE TRANSCRIPTION

Genes are contained in a complex of DNA and proteins (mostly histones) called **chromatin**, and its basic unit of structure is the **nucleosome** (Fig. 1.1). Each nucleosome is composed of an octamer of **histone proteins** and approximately 140 base pairs of DNA. Nucleosomes themselves are joined into clusters by binding of DNA existing between nucleosomes (**linker DNA**) with other histone proteins (H1 histones; Fig. 1.1). Nucleosomes keep the DNA tightly coiled, such that it cannot be transcribed. In this inactive state, chromatin appears as beads of nucleosomes on a string of DNA and is referred to as **heterochromatin**. For transcription to occur, this DNA must be uncoiled from the beads. In this uncoiled state, chromatin is referred to as **euchromatin**.

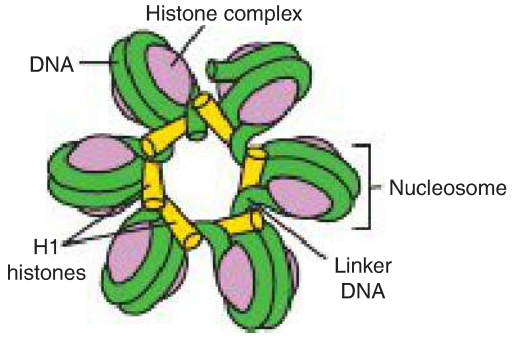

FIGURE 1.1 Drawing showing nucleosomes that form the basic unit of chromatin. Each nucleosome consists of an octamer of histone proteins and approximately 140 base pairs of DNA. Nucleosomes are joined into clusters by linker DNA and other histone proteins.

Genes reside within the DNA strand and contain regions called **exons**, which can be translated into proteins, and **introns**, which are interspersed between exons and which are not transcribed into proteins (Fig. 1.2). In addition to exons and introns, a typical gene includes the following: a **promoter region** that binds **RNA**

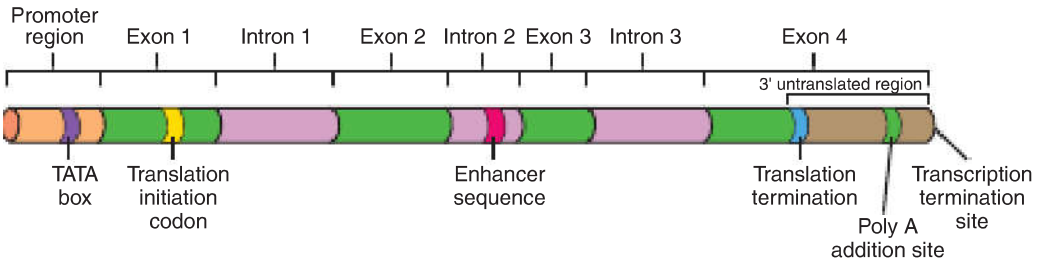

FIGURE 1.2 Drawing of a "typical" gene showing the promoter region containing the TATA box; exons that contain DNA sequences that are translated into proteins; introns; the transcription initiation site; the translation initiation site that designates the code for the first amino acid in a protein; and the 3′ untranslated region that includes the poly A addition site that participates in stabilizing the mRNA, allows it to exit the nucleus, and permits its translation into a protein.

polymerase for the initiation of **transcription**; a **transcription initiation site**; a **translation initiation site** to designate the first amino acid in the protein; a **translation termination codon**; and a **3′** untranslated region that includes a sequence (the poly A addition site) that assists with stabilizing the mRNA, allows it to exit the nucleus, and permits it to be translated into protein (Fig. 1.2). By convention, the 5′ and the 3′ regions of a gene are specified in relation to the RNA transcribed from the gene. Thus, DNA is transcribed from the 5′ to the 3′ end, and the promoter region is upstream from the transcription initiation site (Fig. 1.2). The promoter region, where the RNA polymerase binds, usually contains the sequence TATA, and this site is called the **TATA box** (Fig. 1.2). In order to bind to this site, however, the polymerase requires additional proteins called **transcription factors** (Fig. 1.3). Transcription factors also have a specific **DNA-binding domain** plus a **transactivating domain** that activates or inhibits transcription of the gene whose promoter or enhancer it has bound. In combination with other proteins, transcription factors activate gene expression by causing the DNA nucleosome complex to unwind, by releasing the polymerase so that it can transcribe the DNA template, and by preventing new nucleosomes from forming.

Enhancers are regulatory elements of DNA that activate utilization of promoters to control their efficiency and the rate of transcription from the promoter. Enhancers can reside anywhere along the DNA strand and do not have to reside close to a promoter. Like promoters, enhancers bind transcription factors (through the transcription factor's transactivating domain) and are used to regulate the timing of a gene's expression and its cell-specific location. For example, separate enhancers in a gene can be used to direct the same gene to be expressed in different tissues. The *PAX6* transcription factor, which participates in pancreas, eye, and neural tube development, contains three separate enhancers, each of which regulates the gene's expression in the appropriate tissue. Enhancers act by altering chromatin to expose the promoter or by facilitating binding of the RNA polymerase. Sometimes,

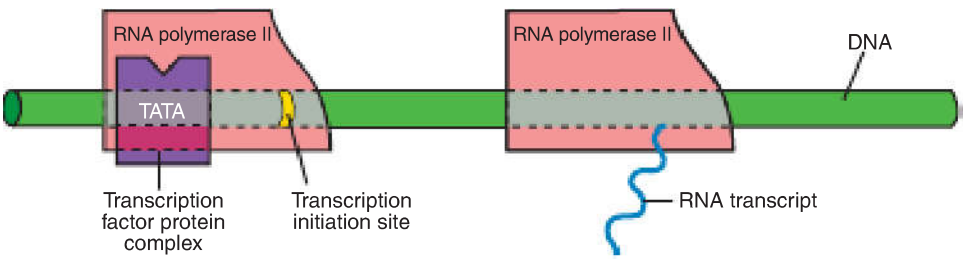

FIGURE 1.3 Drawing showing binding of RNA polymerase II to the TATA box site of the promoter region of a gene. This binding requires a complex of proteins plus an additional protein called a *transcription factor*. Transcription factors have their own specific DNA-binding domain and function to regulate gene expression.

enhancers can inhibit transcription and are called **silencers**. This phenomenon allows a transcription factor to activate one gene while silencing another by binding to different enhancers. Thus, transcription factors themselves have a DNA-binding domain specific to a region of DNA plus a transactivating domain that binds to a promoter or an enhancer and activates or inhibits the gene regulated by these elements.

DNA Methylation Represses Transcription

Methylation of cytosine bases in the promoter regions of genes represses transcription of those genes. Thus, some genes are silenced by this mechanism. For example, one of the X chromosomes in each cell of a female is inactivated (**X chromosome inactivation**) by this methylation mechanism. Similarly, genes in different types of cells are repressed by methylation, such that muscle cells make muscle proteins (their promoter DNA is mostly unmethylated) but not blood proteins (their DNA is highly methylated). In this manner, each cell can maintain its characteristic differentiated state. DNA methylation is also responsible for genomic **imprinting** in which only a gene inherited from the father or the mother is expressed, whereas the other gene is silenced. Approximately 40 to 60 human genes are imprinted, and their methylation patterns are established during spermatogenesis and oogenesis. Methylation silences DNA by inhibiting binding of transcription factors or by altering histone binding resulting in stabilization of nucleosomes and tightly coiled DNA that cannot be transcribed.

OTHER REGULATORS OF GENE EXPRESSION

The initial transcript of a gene is called **nuclear RNA (nRNA)** or sometimes **premessenger RNA**. nRNA is longer than mRNA because it contains introns that are removed (**spliced out**) as the nRNA moves from the nucleus to the cytoplasm. In fact, this splicing process provides a means for cells to produce different proteins from a single gene. For example, by removing different introns, exons are "spliced" in different patterns, a process called **alternative splicing** (Fig. 1.4). The process is carried out by **spliceosomes**, which are complexes of **small nuclear RNAs (snRNAs)** and proteins that recognize specific splice sites at the 5′ or the 3′ ends of the nRNA. Proteins derived from the same gene are called **splicing isoforms** (also called **splice variants** or **alternative splice forms**), and these afford the opportunity for different cells to use the same gene to make proteins specific for that cell type. For example, isoforms of the *WT1* gene have different functions in gonadal versus kidney development.

Even after a protein is made (translated), there may be **posttranslational modifications** that affect its function. For example, some proteins have to be cleaved to become active, or they might have to be phosphorylated. Others need to combine with other proteins or be released

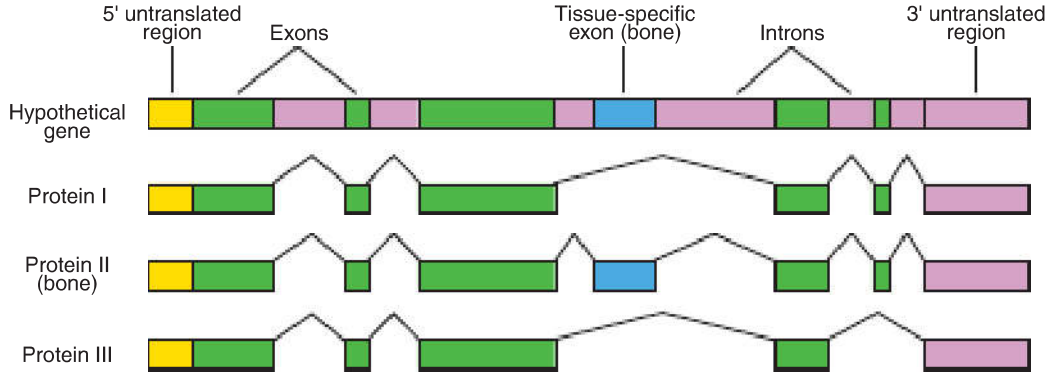

FIGURE 1.4 Drawing of a hypothetical gene illustrating the process of alternative splicing to form different proteins from the same gene. Spliceosomes recognize specific sites on the initial transcript of nRNA from a gene. Based on these sites, different introns are "spliced out" to create more than one protein from a single gene. Proteins derived from the same gene are called *splicing isoforms*.

from sequestered sites or be targeted to specific cell regions. Thus, there are many regulatory levels for synthesizing and activating proteins, such that although only 23,000 genes exist, the potential number of proteins that can be synthesized is probably closer to five times the number of genes.

INDUCTION AND ORGAN FORMATION

Organs are formed by interactions between cells and tissues. Most often, one group of cells or tissues causes another set of cells or tissues to change their fate, a process called **induction**. In each such interaction, one cell type or tissue is the **inducer** that produces a signal, and one is the **responder** to that signal. The capacity to respond to such a signal is called **competence**, and competence requires activation of the responding tissue by a **competence factor**. Many inductive interactions occur between epithelial and mesenchymal cells and are called **epithelial–mesenchymal interactions** (Fig. 1.5). Epithelial cells are joined together in tubes or sheets, whereas mesenchymal cells are fibroblastic in appearance and dispersed in extracellular matrices (Fig. 1.5). Examples of epithelial–mesenchymal interactions include the following: gut endoderm and surrounding mesenchyme to produce gut-derived organs, including the liver and pancreas; limb mesenchyme with overlying ectoderm (epithelium) to produce limb outgrowth and differentiation; and endoderm of the ureteric bud and mesenchyme from the metanephric blastema to produce nephrons in the kidney. Inductive interactions can also occur between two epithelial tissues, such as induction of the lens by epithelium of the optic cup. Although an initial signal by the inducer to the responder initiates the inductive event, **crosstalk** between the two tissues or cell types is essential for differentiation to continue (Fig. 1.5, *arrows*).

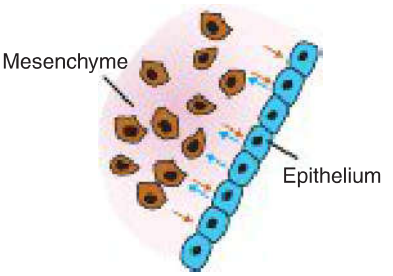

FIGURE 1.5 Drawing illustrating an epithelial–mesenchymal interaction. Following an initial signal from one tissue, a second tissue is induced to differentiate into a specific structure. The first tissue constitutes the inducer, and the second is the responder. Once the induction process is initiated, signals (*arrows*) are transmitted in both directions to complete the differentiation process.

CELL SIGNALING

Cell-to-cell signaling is essential for induction, for conference of competency to respond, and for crosstalk between inducing and responding cells. These lines of communication are established by **paracrine interactions**, whereby proteins synthesized by one cell diffuse over short distances to interact with other cells, or by **juxtacrine interactions**, which do not involve diffusable proteins. The diffusable proteins responsible for paracrine signaling are called **paracrine factors** or **growth and differentiation factors (GDFs)**.

Signal Transduction Pathways

Paracrine Signaling

Paracrine factors act by **signal transduction pathways** either by activating a pathway directly or by blocking the activity of an inhibitor of a pathway (inhibiting an inhibitor, as is the case with hedgehog signaling). Signal transduction pathways include a **signaling molecule** (the **ligand**) and a **receptor** (Fig. 1.6). The receptor spans the cell membrane and has an **extracellular domain** (the **ligand-binding region**), a **transmembrane domain**, and a **cytoplasmic domain**. When a ligand binds its receptor, it induces a conformational change in the receptor that activates its cytoplasmic domain. Usually, the result of this activation is to confer enzymatic activity to the receptor, and most often, this activity is a **kinase** that can **phosphorylate** other proteins using ATP as a substrate. In turn, phosphorylation activates these proteins to phosphorylate additional proteins, and thus, a cascade of protein interactions is established that ultimately activates a **transcription factor**. This transcription factor then activates or inhibits gene expression. The pathways are numerous and complex and in some cases are characterized by one protein inhibiting another that in turn activates another protein (much like the situation with hedgehog signaling).