

Contents

Preface	v		
Learning from this book	vii		
About the authors	x		
List of boxes	xxiii		
Reviewer acknowledgments	xxv		
Chapter 1 History and basic concepts	1		
The origins of developmental biology	3		
1.1 Aristotle first defined the problem of epigenesis versus preformation	3		
■ Box 1A Basic stages of <i>Xenopus laevis</i> development	4		
1.2 Cell theory changed how people thought about embryonic development and heredity	4		
1.3 Two main types of development were originally proposed	6		
■ Cell Biology Box 1B The mitotic cell cycle	7		
1.4 The discovery of induction showed that one group of cells could determine the development of neighboring cells	8		
1.5 Developmental biology emerged from the coming together of genetics and embryology	8		
1.6 Development is studied mainly through selected model organisms	9		
1.7 The first developmental genes were identified as spontaneous mutations	11		
Summary	13		
A conceptual tool kit	13		
1.8 Development involves the emergence of pattern, change in form, cell differentiation, and growth	14		
■ Cell Biology Box 1C Germ layers	15		
1.9 Cell behavior provides the link between gene action and developmental processes	17		
1.10 Genes control cell behavior by specifying which proteins are made	17		
1.11 The expression of developmental genes is under tight control	19		
■ Experimental Box 1D Visualizing gene expression in embryos	20		
1.12 Development is progressive and the fates of cells become determined at different times	22		
1.13 Inductive interactions make cells different from each other	24		
■ Cell Biology Box 1E Signal transduction and intracellular signaling pathways	26		
1.14 The response to inductive signals depends on the state of the cell	26		
1.15 Patterning can involve the interpretation of positional information	27		
■ Medical Box 1F When development goes awry	28		
1.16 Lateral inhibition can generate spacing patterns	30		
1.17 Localization of cytoplasmic determinants and asymmetric cell division can make daughter cells different from each other	30		
1.18 The embryo contains a generative rather than a descriptive program	32		
1.19 The reliability of development is achieved by various means	32		
1.20 The complexity of embryonic development is due to the complexity of cells themselves	33		
1.21 Development is a central element in evolution	33		
Summary	34		
Summary to Chapter 1	35		
Chapter 2 Development of the <i>Drosophila</i> body plan	37		
<i>Drosophila</i> life cycle and overall development	38		
2.1 The early <i>Drosophila</i> embryo is a multinucleate syncytium	38		
2.2 Cellularization is followed by gastrulation and segmentation	40		
2.3 After hatching, the <i>Drosophila</i> larva develops through several larval stages, pupates, and then undergoes metamorphosis to become an adult	41		
2.4 Many developmental genes were identified in <i>Drosophila</i> through large-scale genetic screening for induced mutations	42		
■ Experimental Box 2A Mutagenesis and genetic screening strategy for identifying developmental mutants in <i>Drosophila</i>	43		
Summary	44		
Setting up the body axes	44		
2.5 The body axes are set up while the <i>Drosophila</i> embryo is still a syncytium	45		

2.6 Maternal factors set up the body axes and direct the early stage of *Drosophila* development

2.7 Three classes of maternal genes specify the antero-posterior axis

2.8 Bicoid protein provides an antero-posterior gradient of a morphogen

2.9 The posterior pattern is controlled by the gradients of Nanos and Caudal proteins

2.10 The anterior and posterior extremities of the embryo are specified by activation of a cell-surface receptor

2.11 The dorso-ventral polarity of the embryo is specified by localization of maternal proteins in the egg vitelline envelope

2.12 Positional information along the dorso-ventral axis is provided by the Dorsal protein

■ **Cell Biology Box 2B** The Toll signaling pathway: a multifunctional pathway

Summary

Localization of maternal determinants during oogenesis

2.13 The antero-posterior axis of the *Drosophila* egg is specified by signals from the preceding egg chamber and by interactions of the oocyte with follicle cells

■ **Cell Biology Box 2C** The JAK-STAT signaling pathway

2.14 Localization of maternal mRNAs to either end of the egg depends on the reorganization of the oocyte cytoskeleton

2.15 The dorso-ventral axis of the egg is specified by movement of the oocyte nucleus followed by signaling between oocyte and follicle cells

Summary

Patterning the early embryo

2.16 The expression of zygotic genes along the dorso-ventral axis is controlled by Dorsal protein

2.17 The Decapentaplegic protein acts as a morphogen to pattern the dorsal region

2.18 The antero-posterior axis is divided up into broad regions by gap gene expression

2.19 Bicoid protein provides a positional signal for the anterior expression of zygotic *hunchback*

2.20 The gradient in Hunchback protein activates and represses other gap genes

■ **Experimental Box 2D** Targeted gene expression and misexpression screening

Summary

Activation of the pair-rule genes and the establishment of parasegments

2.21 Parasegments are delimited by expression of pair-rule genes in a periodic pattern

2.22 Gap gene activity positions stripes of pair-rule gene expression

Summary

46 Segmentation genes and segment patterning

47 2.23 Expression of the *engrailed* gene defines the boundary of a parasegment, which is also a boundary of cell lineage restriction

48 2.24 Segmentation genes stabilize parasegment boundaries

50 2.25 Signals generated at the parasegment boundary delimit and pattern the future segments

■ **Cell Biology Box 2E** The Hedgehog signaling pathway

■ **Experimental Box 2F** Mutants in denticle pattern provided clues to the logic of segment patterning

52 Summary

53 Specification of segment identity

54 2.26 Segment identity in *Drosophila* is specified by Hox genes

54 2.27 Homeotic selector genes of the bithorax complex are responsible for diversification of the posterior segments

55 2.28 The Antennapedia complex controls specification of anterior regions

56 2.29 The order of Hox gene expression corresponds to the order of genes along the chromosome

58 2.30 The *Drosophila* head region is specified by genes other than the Hox genes

58 Summary

Summary to Chapter 2

60 Chapter 3 Vertebrate development I: life cycles and experimental techniques

61 Vertebrate life cycles and outlines of development

62 3.1 The frog *Xenopus laevis* is the model amphibian for studying development of the body plan

62 3.2 The zebrafish embryo develops around a large mass of yolk

64 3.3 Birds and mammals resemble each other and differ from *Xenopus* in some important features of early development

66 3.4 The early chicken embryo develops as a flat disc of cells overlying a massive yolk

67 3.5 The mouse egg has no yolk and early development involves the allocation of cells to form the placenta and extra-embryonic membranes

68 Experimental approaches to studying vertebrate development

69 3.6 Gene expression in embryos can be mapped by *in situ* nucleic acid hybridization

70 ■ **Experimental Box 3A** Gene-expression profiling by DNA microarrays and RNA seq

71 3.7 Fate mapping and lineage tracing reveal which cells in which parts of the early embryo give rise to particular adult structures

73

75	3.8 Not all techniques are equally applicable to all vertebrates	120	4.7 Mesoderm induction occurs during a limited period in the blastula stage	155
75	3.9 Developmental genes can be identified by spontaneous mutation and by large-scale mutagenesis screens	121	4.8 Zygotic gene expression is turned on at the mid-blastula transition	156
76	■ Experimental Box 3B Large-scale mutagenesis screens for recessive mutations in zebrafish	123	4.9 Mesoderm-inducing and patterning signals are produced by the vegetal region, the organizer, and the ventral mesoderm	157
77	3.10 Transgenic techniques enable animals to be produced with mutations in specific genes	124	4.10 Members of the TGF- β family have been identified as mesoderm inducers	158
78	■ Experimental Box 3C The Cre/ <i>loxP</i> system: a strategy for making gene knock-outs in mice	127	■ Experimental Box 4D Investigating receptor function using dominant-negative proteins	159
80	■ Experimental Box 3D The CRISPR-Cas9 genome-editing system	128	4.11 The zygotic expression of mesoderm-inducing and patterning signals is activated by the combined actions of maternal VegT and Wnt signaling	159
81	3.11 Gene function can also be tested by transient transgenesis and gene silencing	130	4.12 Threshold responses to gradients of signaling proteins are likely to pattern the mesoderm	161
83	Human embryonic development	131	Summary	162
84	3.12 The early development of a human embryo is similar to that of the mouse	131	The Spemann organizer and neural induction	163
85	■ Medical Box 3E Preimplantation genetic diagnosis	134	■ Cell Biology Box 4E The fibroblast growth factor signaling pathway	163
86	3.13 The timing of formation and the anatomy of the human placenta differs from that in the mouse	135	4.13 Signals from the organizer pattern the mesoderm dorso-ventrally by antagonizing the effects of ventral signals	164
87	3.14 Some studies of human development are possible but are subject to strict laws	136	4.14 The antero-posterior axis of the embryo emerges during gastrulation	165
87	■ Box 3F Identical twins	137	4.15 The neural plate is induced in the ectoderm	168
88	Summary to Chapter 3	138	4.16 The nervous system is patterned along the antero-posterior axis by signals from the mesoderm	170
89	Chapter 4 Vertebrate development II: <i>Xenopus</i> and zebrafish	142	4.17 The final body plan emerges by the end of gastrulation and neurulation	171
94	Setting up the body axes	143	Summary	172
95	4.1 The animal-vegetal axis is maternally determined in <i>Xenopus</i>	143	Development of the body plan in zebrafish	172
98	■ Cell Biology Box 4A Intercellular protein signals in vertebrate development	145	4.18 The body axes in zebrafish are established by maternal determinants	173
102	■ Cell Biology Box 4B The Wnt/ β -catenin signaling pathway	146	4.19 The germ layers are specified in the zebrafish blastoderm by similar signals to those in <i>Xenopus</i>	173
105	4.2 Local activation of Wnt/ β -catenin signaling specifies the future dorsal side of the embryo	147	4.20 The shield in zebrafish is the embryonic organizer	176
106	4.3 Signaling centers develop on the dorsal side of the blastula	149	■ Box 4F A zebrafish gene regulatory network	176
110	Summary	150	Summary to Chapter 4	178
110	The origin and specification of the germ layers	150	Chapter 5 Vertebrate development III: chick and mouse—completing the body plan	183
115	4.4 The fate map of the <i>Xenopus</i> blastula makes clear the function of gastrulation	151	Development of the body plan in chick and mouse and generation of the spinal cord	184
116	4.5 Cells of the early <i>Xenopus</i> embryo do not yet have their fates determined and regulation is possible	152	5.1 The antero-posterior polarity of the chick blastoderm is related to the primitive streak	184
117	4.6 Endoderm and ectoderm are specified by maternal factors, whereas mesoderm is induced from ectoderm by signals from the vegetal region	152	5.2 Early stages in mouse development establish separate cell lineages for the embryo and the extra-embryonic structures	186
118	■ Cell Biology Box 4C Signaling by members of the TGF- β family of growth factors	155		

5.3 Movement of the anterior visceral endoderm indicates the definitive antero-posterior axis in the mouse embryo	190	Chapter 6 Development of nematodes and sea urchins	235
5.4 The fate maps of vertebrate embryos are variations on a basic plan	192	Nematodes	236
■ Cell Biology Box 5A Fine-tuning Nodal signaling	193	■ Cell Biology Box 6A Apoptotic pathways in nematodes, <i>Drosophila</i> , and mammals	238
5.5 Mesoderm induction and patterning in the chick and mouse occurs during primitive streak formation	195	6.1 The cell lineage of <i>Caenorhabditis elegans</i> is largely invariant	239
5.6 The node that develops at the anterior end of the streak in chick and mouse embryos is equivalent to the Spemann organizer in <i>Xenopus</i>	196	6.2 The antero-posterior axis in <i>Caenorhabditis elegans</i> is determined by asymmetric cell division	239
5.7 Neural induction in chick and mouse is initiated by FGF signaling with inhibition of BMP signaling being required in a later step	198	■ Experimental Box 6B Gene silencing by antisense RNA and RNA interference	241
■ Cell Biology Box 5B Chromatin-remodeling complexes	201	6.3 The dorso-ventral axis in <i>Caenorhabditis elegans</i> is determined by cell-cell interactions	242
5.8 Axial structures in chick and mouse are generated from self-renewing cell populations	202	6.4 Both asymmetric divisions and cell-cell interactions specify cell fate in the early nematode embryo	245
Summary	204	6.5 Cell differentiation in the nematode is closely linked to the pattern of cell division	246
Somite formation and antero-posterior patterning	205	6.6 Hox genes specify positional identity along the antero-posterior axis in <i>Caenorhabditis elegans</i>	247
■ Cell Biology Box 5C Retinoic acid: a small-molecule intercellular signal	206	6.7 The timing of events in nematode development is under genetic control that involves microRNAs	248
5.9 Somites are formed in a well-defined order along the antero-posterior axis	206	■ Box 6C Gene silencing by microRNAs	250
■ Cell Biology Box 5D The Notch signaling pathway	211	6.8 Vulval development is initiated through the induction of a small number of cells by short-range signals from a single inducing cell	251
5.10 Identity of somites along the antero-posterior axis is specified by Hox gene expression	213	Summary	253
■ Box 5E The Hox genes	214	Echinoderms	254
5.11 Deletion or overexpression of Hox genes causes changes in axial patterning	217	6.9 The sea urchin embryo develops into a free-swimming larva	255
5.12 Hox gene expression is activated in an anterior to posterior pattern	219	6.10 The sea urchin egg is polarized along the animal-vegetal axis	256
5.13 The fate of somite cells is determined by signals from the adjacent tissues	221	6.11 The sea urchin fate map is finely specified, yet considerable regulation is possible	257
Summary	223	6.12 The vegetal region of the sea urchin embryo acts as an organizer	258
The origin and patterning of neural crest	223	6.13 The sea urchin vegetal region is demarcated by the nuclear accumulation of β -catenin	260
5.14 Neural crest cells arise from the borders of the neural plate and migrate to give rise to a wide range of different cell types	223	6.14 The animal-vegetal axis and the oral-aboral axis can be considered to correspond to the antero-posterior and dorso-ventral axes of other deuterostomes	261
5.15 Neural crest cells migrate from the hindbrain to populate the branchial arches	225	6.15 The pluteus skeleton develops from the primary mesenchyme	262
Summary	226	6.16 The oral-aboral axis in sea urchins is related to the plane of the first cleavage	263
Determination of left-right asymmetry	227	6.17 The oral ectoderm acts as an organizing region for the oral-aboral axis	264
5.16 The bilateral symmetry of the early embryo is broken to produce left-right asymmetry of internal organs	227		
5.17 Left-right symmetry breaking may be initiated within cells of the early embryo	229		
Summary	230		
Summary to Chapter 5	230		

235	■ Experimental Box 6D The gene regulatory network for sea urchin endomesoderm specification		
236	Summary	265	
238	Summary to Chapter 6	266	
239	Chapter 7 Morphogenesis: change in form in the early embryo	267	
239	Cell adhesion	271	
241	■ Cell Biology Box 7A Cell-adhesion molecules and cell junctions	273	
242	7.1 Sorting out of dissociated cells demonstrates differences in cell adhesiveness in different tissues	274	
245	7.2 Cadherins can provide adhesive specificity	275	
246	7.3 The activity of the cytoskeleton regulates the mechanical properties of cells and their interactions with each other	276	
247	■ Cell Biology Box 7B The cytoskeleton, cell-shape change, and cell movement	277	
248	7.4 Transitions of tissues from an epithelial to a mesenchymal state, and vice versa, involve changes in adhesive junctions	278	
250	Summary	279	
251	Cleavage and formation of the blastula	280	
253	7.5 The orientation of the mitotic spindle determines the plane of cleavage at cell division	280	
254	7.6 The positioning of the spindle within the cell also determines whether daughter cells will be the same or different sizes	281	
255	7.7 Cells become polarized in the sea urchin blastula and the mouse morula	283	
256	7.8 Fluid accumulation as a result of tight-junction formation and ion transport forms the blastocoel of the mammalian blastocyst	285	
257	Summary	287	
258	Gastrulation movements	288	
260	7.9 Gastrulation in the sea urchin involves an epithelial-to-mesenchymal transition, cell migration, and invagination of the blastula wall	289	
261	7.10 Mesoderm invagination in <i>Drosophila</i> is due to changes in cell shape controlled by genes that pattern the dorso-ventral axis	289	
262	7.11 Germ-band extension in <i>Drosophila</i> involves myosin-dependent remodeling of cell junctions and cell intercalation	293	
263	7.12 Planar cell polarity confers directionality on a tissue	295	
264	7.13 Gastrulation in amphibians and fish involves involution, epiboly, and convergent extension	296	
	■ Box 7C Convergent extension	299	
	7.14 <i>Xenopus</i> notochord development illustrates the dependence of medio-lateral cell elongation and cell intercalation on a pre-existing antero-posterior polarity	302	
		305	
	7.15 Gastrulation in chick and mouse embryos involves the separation of individual cells from the epiblast and their ingression through the primitive streak		306
	Summary		309
	Neural tube formation		311
	7.16 Neural tube formation is driven by changes in cell shape and convergent extension		311
	■ Cell Biology Box 7D Eph receptors and their ephrin ligands		313
	■ Medical Box 7E Neural tube defects		314
	Summary		315
	Formation of tubes and branching morphogenesis		316
	7.17 The <i>Drosophila</i> tracheal system is a prime example of branching morphogenesis		316
	7.18 The vertebrate vascular system develops by vasculogenesis followed by sprouting angiogenesis		318
	7.19 New blood vessels are formed from pre-existing vessels in angiogenesis		319
	Summary		320
	Cell migration		320
	7.20 Embryonic neural crest gives rise to a wide range of different cell types		321
	7.21 Neural crest migration is controlled by environmental cues		321
	7.22 The formation of the lateral-line primordium in fishes is an example of collective cell migration		323
	7.23 Body wall closure occurs in <i>Drosophila</i> , <i>Caenorhabditis</i> , mammals, and chick		324
	Summary		325
	Summary to Chapter 7		326
	Chapter 8 Cell differentiation and stem cells		333
	■ Box 8A Conrad Waddington's 'epigenetic landscape' provides a framework for thinking about how cells differentiate		335
	The control of gene expression		337
	8.1 Control of transcription involves both general and tissue-specific transcriptional regulators		338
	8.2 Gene expression is also controlled by epigenetic chemical modifications to DNA and histone proteins that alter chromatin structure		341
	■ Cell Biology Box 8B Epigenetic control of gene expression by chromatin modification		344
	8.3 Patterns of gene activity can be inherited by persistence of gene-regulatory proteins or by maintenance of chromatin modifications		347
	8.4 Changes in patterns of gene activity during differentiation can be triggered by extracellular signals		348
	Summary		349

Cell differentiation and stem cells 350

8.5 Muscle differentiation is determined by the MyoD family of transcription factors 350

8.6 The differentiation of muscle cells involves withdrawal from the cell cycle, but is reversible 352

8.7 All blood cells are derived from multipotent stem cells 354

8.8 Intrinsic and extrinsic changes control differentiation of the hematopoietic lineages 357

■ **Experimental Box 8C** Single-cell analysis of cell-fate decisions 358

8.9 Developmentally regulated globin gene expression is controlled by control regions far distant from the coding regions 361

8.10 The epidermis of adult mammalian skin is continually being replaced by derivatives of stem cells 363

■ **Medical Box 8D** Treatment of junctional epidermolysis bullosa with skin grown from genetically corrected stem cells 366

8.11 Stem cells use different modes of division to maintain tissues 367

8.12 The lining of the gut is another epithelial tissue that requires continuous renewal 368

8.13 Skeletal muscle and neural cells can be renewed from stem cells in adults 370

8.14 Embryonic stem cells can proliferate and differentiate into many cell types in culture and contribute to normal development *in vivo* 372

■ **Experimental Box 8E** The derivation and culture of mouse embryonic stem cells 374

Summary 375

The plasticity of the differentiated state 376

8.15 Nuclei of differentiated cells can support development 376

8.16 Patterns of gene activity in differentiated cells can be changed by cell fusion 378

8.17 The differentiated state of a cell can change by transdifferentiation 379

8.18 Adult differentiated cells can be reprogrammed to form pluripotent stem cells 381

■ **Experimental Box 8F** Induced pluripotent stem cells 382

8.19 Stem cells could be a key to regenerative medicine 382

■ **Experimental Box 8G** Stem cells can be cultured *in vitro* to produce 'organoids'—structures that mimic tissues and organs 386

8.20 Various approaches can be used to generate differentiated cells for cell-replacement therapies 388

Summary 391

Summary to Chapter 8 391

Chapter 9 Germ cells, fertilization, and sex determination 397

The development of germ cells 398

9.1 Germ cell fate is specified in some embryos by a distinct germplasm in the egg 398

9.2 In mammals germ cells are induced by cell-cell interactions during development 401

9.3 Germ cells migrate from their site of origin to the gonad 402

9.4 Germ cells are guided to their destination by chemical signals 403

9.5 Germ cell differentiation involves a halving of chromosome number by meiosis 404

■ **Box 9A** Polar bodies 405

9.6 Oocyte development can involve gene amplification and contributions from other cells 408

9.7 Factors in the cytoplasm maintain the totipotency of the egg 408

9.8 In mammals some genes controlling embryonic growth are 'imprinted' 409

Summary 411

Fertilization 411

9.9 Fertilization involves cell-surface interactions between egg and sperm 413

9.10 Changes in the egg plasma membrane and enveloping layers at fertilization block polyspermy 415

9.11 Sperm-egg fusion causes a calcium wave that results in egg activation 416

Summary 418

Determination of the sexual phenotype 419

9.12 The primary sex-determining gene in mammals is on the Y chromosome 419

9.13 Mammalian sexual phenotype is regulated by gonadal hormones 420

9.14 The primary sex-determining factor in *Drosophila* is the number of X chromosomes and is cell autonomous 422

9.15 Somatic sexual development in *Caenorhabditis* is determined by the number of X chromosomes 424

9.16 Determination of germ cell sex depends on both genetic constitution and intercellular signals 425

9.17 Various strategies are used for dosage compensation of X-linked genes 427

Summary 429

Summary to Chapter 9 431

Chapter 10 Organogenesis 435

The insect wing and leg 436

10.1 Imaginal discs arise from the ectoderm in the early *Drosophila* embryo 437

397	10.2 Imaginal discs arise across parasegment boundaries and are patterned by signaling at compartment boundaries	438	10.20 Self-organization may be involved in the development of the limb	475
398	10.3 The adult wing emerges at metamorphosis after folding and evagination of the wing imaginal disc	439	■ Box 10E Reaction-diffusion mechanisms	476
399	10.4 A signaling center at the boundary between anterior and posterior compartments patterns the <i>Drosophila</i> wing disc along the antero-posterior axis	440	10.21 Limb muscle is patterned by the connective tissue	477
401	■ Box 10A Positional information and morphogen gradients	443	10.22 The initial development of cartilage, muscles, and tendons is autonomous	478
402	10.5 A signaling center at the boundary between dorsal and ventral compartments patterns the <i>Drosophila</i> wing along the dorso-ventral axis	445	10.23 Joint formation involves secreted signals and mechanical stimuli	478
403	10.6 Vestigial is a key regulator of wing development that acts to specify wing identity and control wing growth	445	10.24 Separation of the digits is the result of programmed cell death	479
404	10.7 The <i>Drosophila</i> wing disc is also patterned along the proximo-distal axis	447	Summary	480
405	10.8 The leg disc is patterned in a similar manner to the wing disc, except for the proximo-distal axis	448	Teeth	481
409	10.9 Different imaginal discs can have the same positional values	450	10.25 Tooth development involves epithelial-mesenchymal interactions and a homeobox gene code specifies tooth identity	482
412	Summary	450	Summary	484
412	The vertebrate limb	452	Vertebrate lungs	484
413	10.10 The vertebrate limb develops from a limb bud and its development illustrates general principles	452	10.26 The vertebrate lung develops from a bud of endoderm	484
415	10.11 Genes expressed in the lateral plate mesoderm are involved in specifying limb position, polarity, and identity	452	■ Medical Box 10F What developmental biology can teach us about breast cancer	486
416	10.12 The apical ectodermal ridge is required for limb-bud outgrowth and the formation of structures along the proximo-distal axis of the limb	454	10.27 Morphogenesis of the lung involves three modes of branching	488
418	10.13 Formation and outgrowth of the limb bud involves oriented cell behavior	457	Summary	489
419	10.14 Positional value along the proximo-distal axis of the limb bud is specified by a combination of graded signaling and a timing mechanism	458	The vertebrate heart	489
420	10.15 The polarizing region specifies position along the limb's antero-posterior axis	460	10.28 The development of the vertebrate heart involves morphogenesis and patterning of a mesodermal tube	489
422	10.16 Sonic hedgehog is the polarizing region morphogen	462	The vertebrate eye	492
424	■ Medical Box 10B Too many fingers: mutations that affect antero-posterior patterning can cause polydactyly	464	10.29 Development of the vertebrate eye involves interactions between an extension of the forebrain and the ectoderm of the head	493
425	■ Cell Biology Box 10C Sonic hedgehog signaling and the primary cilium	465	Summary	497
427	10.17 The dorso-ventral axis of the limb is controlled by the ectoderm	466	Summary to Chapter 10	497
429	■ Medical Box 10D Teratogens and the consequences of damage to the developing embryo	468	Chapter 11 Development of the nervous system	505
431	10.18 Development of the limb is integrated by interactions between signaling centers	470	Specification of cell identity in the nervous system	507
435	10.19 Hox genes have multiple inputs into the patterning of the limbs	470	11.1 Initial regionalization of the vertebrate brain involves signals from local organizers	507
436		472	11.2 Local signaling centers pattern the brain along the antero-posterior axis	508
437			11.3 The cerebral cortex is patterned by signals from the anterior neural ridge	509
			11.4 The hindbrain is segmented into rhombomeres by boundaries of cell-lineage restriction	509
			11.5 Hox genes provide positional information in the developing hindbrain	512
			11.6 The pattern of differentiation of cells along the dorso-ventral axis of the spinal cord depends on ventral and dorsal signals	513

11.7 Neuronal subtypes in the ventral spinal cord are specified by the ventral to dorsal gradient of Shh	515	Chapter 12 Growth, post-embryonic development, and regeneration	553
11.8 Spinal cord motor neurons at different dorso-ventral positions project to different trunk and limb muscles	516	Growth	554
11.9 Antero-posterior pattern in the spinal cord is determined in response to secreted signals from the node and adjacent mesoderm	517	12.1 Tissues can grow by cell proliferation, cell enlargement, or accretion	555
Summary	518	12.2 Cell proliferation is controlled by regulating entry into the cell cycle	556
The formation and migration of neurons	518	12.3 Cell division in early development can be controlled by an intrinsic developmental program	557
11.10 Neurons in <i>Drosophila</i> arise from proneural clusters	519	12.4 Extrinsic signals coordinate cell division, cell growth, and cell death in the developing <i>Drosophila</i> wing	558
11.11 The development of neurons in <i>Drosophila</i> involves asymmetric cell divisions and timed changes in gene expression	521	■ Cell Biology Box 12A The core Hippo signaling pathways in <i>Drosophila</i> and mammals	559
11.12 The production of vertebrate neurons involves lateral inhibition, as in <i>Drosophila</i>	522	12.5 Cancer can result from mutations in genes that control cell proliferation	560
■ Box 11A Specification of the sensory organs of adult <i>Drosophila</i>	523	12.6 The relative contributions of intrinsic and extrinsic factors in controlling size differ in different mammalian organs	562
11.13 Neurons are formed in the proliferative zone of the vertebrate neural tube and migrate outwards	524	12.7 Overall body size depends on the extent and the duration of growth	564
■ Experimental Box 11B Timing the birth of cortical neurons	526	12.8 Hormones and growth factors coordinate the growth of different tissues and organs and contribute to determining overall body size	565
11.14 Many cortical interneurons migrate tangentially	528	12.9 Elongation of the long bones illustrates how growth can be determined by a combination of an intrinsic growth program and extracellular factors	566
Summary	528	■ Box 12B Digit length ratio is determined in the embryo	568
Axon navigation	529	12.10 The amount of nourishment an embryo receives can have profound effects in later life	570
11.15 The growth cone controls the path taken by a growing axon	530	Summary	571
■ Box 11C The development of the neural circuit for the knee-jerk reflex	532	Molting and metamorphosis	572
11.16 Motor neuron axons in the chick limb are guided by ephrin-Eph interactions	533	12.11 Arthropods have to molt in order to grow	572
11.17 Axons crossing the midline are both attracted and repelled	534	12.12 Insect body size is determined by the rate and duration of larval growth	573
11.18 Neurons from the retina make ordered connections with visual centers in the brain	535	12.13 Metamorphosis in amphibians is under hormonal control	575
Summary	538	Summary	576
Synapse formation and refinement	539	Regeneration	577
11.19 Synapse formation involves reciprocal interactions	539	12.14 Regeneration involves repatterning of existing tissues and/or growth of new tissues	578
11.20 Many motor neurons die during normal development	542	12.15 Amphibian limb regeneration involves cell dedifferentiation and new growth	578
■ Medical Box 11D Autism: a developmental disorder that involves synapse dysfunction	543	■ Box 12C Regeneration in <i>Hydra</i>	580
11.21 Neuronal cell death and survival involve both intrinsic and extrinsic factors	544	■ Box 12D Planarian regeneration	582
11.22 The map from eye to brain is refined by neural activity	545	12.16 Limb regeneration in amphibians depends on the presence of nerves	586
Summary	546	12.17 The limb blastema gives rise to structures with positional values distal to the site of amputation	587
Summary to Chapter 11	547		

553	12.18 Retinoic acid can change proximo-distal positional values in regenerating limbs	589	13.12 The regular arrangement of leaves on a stem is generated by regulated auxin transport	629
554	12.19 Mammals can regenerate the tips of the digits	590	13.13 The outgrowth of secondary shoots is under hormonal control	630
555	12.20 Insect limbs intercalate positional values by both proximo-distal and circumferential growth	591	13.14 Root tissues are produced from <i>Arabidopsis</i> root apical meristems by a highly stereotyped pattern of cell divisions	633
556	■ Box 12E Why can't we regenerate our limbs?	592	13.15 Root hairs are specified by a combination of positional information and lateral inhibition	635
557	12.21 Heart regeneration in zebrafish involves the resumption of cell division by cardiomyocytes	594	Summary	636
558	Summary	596	Flower development and control of flowering	636
558	Aging and senescence	597	13.16 Homeotic genes control organ identity in the flower	637
559	12.22 Genes can alter the timing of senescence	598	■ Box 13C The basic model for the patterning of the <i>Arabidopsis</i> flower	639
559	12.23 Cell senescence blocks cell proliferation	600	13.17 The <i>Antirrhinum</i> flower is patterned dorso-ventrally, as well as radially	640
560	12.24 Elimination of senescent cells in adult salamanders explains why regenerative ability does not diminish with age	601	13.18 The internal meristem layer can specify floral meristem patterning	641
560	Summary	602	13.19 The transition of a shoot meristem to a floral meristem is under environmental and genetic control	642
562	Summary to Chapter 12	602	■ Box 13D The circadian clock coordinates plant growth and development	643
564	Chapter 13 Plant development	609	13.20 Vernalization reflects the epigenetic memory of winter	643
564	13.1 The model plant <i>Arabidopsis thaliana</i> has a short life cycle and a small diploid genome	611	13.21 Most flowering plants are hermaphrodites, but some produce unisexual flowers	645
565	Embryonic development	612	Summary	646
565	13.2 Plant embryos develop through several distinct stages	612	Summary to Chapter 13	647
566	■ Box 13A Angiosperm embryogenesis	614	Chapter 14 Evolution and development	651
568	13.3 Gradients of the signal molecule auxin establish the embryonic apical-basal axis	616	■ Box 14A Darwin's finches	654
570	13.4 Plant somatic cells can give rise to embryos and seedlings	617	The evolution of development	655
571	13.5 Cell enlargement is a major process in plant growth and morphogenesis	619	14.1 Multicellular organisms evolved from single-celled ancestors	655
572	■ Experimental Box 13B Plant transformation and genome editing	620	14.2 Genomic evidence is throwing light on the evolution of animals	657
572	Summary	621	■ Box 14B The metazoan family tree	658
573	Meristems	622	14.3 How gastrulation evolved is not known	659
575	13.6 A meristem contains a small, central zone of self-renewing stem cells	623	14.4 More general characteristics of the body plan develop earlier than specializations	660
576	13.7 The size of the stem cell area in the meristem is kept constant by a feedback loop to the organizing center	623	14.5 Embryonic structures have acquired new functions during evolution	661
577	13.8 The fate of cells from different meristem layers can be changed by changing their position	624	14.6 Evolution of different types of eyes in different animal groups is an example of parallel evolution	663
578	13.9 A fate map for the embryonic shoot meristem can be deduced using clonal analysis	626	Summary	664
580	13.10 Meristem development is dependent on signals from other parts of the plant	627	The diversification of body plans	665
582	13.11 Gene activity patterns the proximo-distal and adaxial-abaxial axes of leaves developing from the shoot meristem	628	14.7 Hox gene complexes have evolved through gene duplication	665
586				
587				

14.8 Differences in Hox gene expression determine the variation in position and type of paired appendages in arthropods	667	14.15 Adaptive evolution within the same species provides a way of studying the developmental basis for evolutionary change	68
14.9 Changes in Hox gene expression and their target genes contributed to the evolution of the vertebrate axial skeleton	671	■ Experimental Box 14D Pelvic reduction in sticklebacks is based on mutations in a gene control region	68
14.10 The basic body plan of arthropods and vertebrates is similar, but the dorso-ventral axis is inverted	672	Summary	68
Summary	673	Changes in the timing of developmental processes	68
The evolutionary modification of specialized characters	674	14.16 Changes in growth can modify the basic body plan	68
14.11 Limbs evolved from fins	674	■ Box 14E Origins of morphological diversity in dogs	68
14.12 Limbs have evolved to fulfill different specialized functions	678	14.17 Evolution can be due to changes in the timing of developmental events	69
14.13 The evolution of limblessness in snakes is associated with changes in axial gene expression and mutations in a limb-specific enhancer	679	14.18 The evolution of life histories has implications for development	69
14.14 Butterfly wing markings have evolved by redeployment of genes previously used for other functions	680	■ Box 14F Long- and short-germ development in insects	69
■ Experimental Box 14C Using CRISPR-Cas9 genome-editing techniques to test the functioning of the snake ZRS	681	Summary	69
		Summary to Chapter 14	69
		Glossary	70
		Index	72