

# Contents

## List of boxes

## Reviewer acknowledgments

## Chapter 1 History and basic concepts

### The origins of developmental biology

1.1 Aristotle first defined the problem of epigenesis versus preformation

■ **Box 1A** Basic stages of *Xenopus laevis* development

1.2 Cell theory changed how people thought about embryonic development and heredity

1.3 Two main types of development were originally proposed

■ **Box 1B** The mitotic cell cycle

1.4 The discovery of induction showed that one group of cells could determine the development of neighboring cells

1.5 Developmental biology emerged from the coming together of genetics and embryology

1.6 Development is studied mainly through selected model organisms

1.7 The first developmental genes were identified as spontaneous mutations

### Summary

### A conceptual tool kit

1.8 Development involves the emergence of pattern, change in form, cell differentiation, and growth

■ **Box 1C** Germ layers

1.9 Cell behavior provides the link between gene action and developmental processes

1.10 Genes control cell behavior by specifying which proteins are made

1.11 The expression of developmental genes is under tight control

■ **Box 1D** Visualizing gene expression in embryos

1.12 Development is progressive and the fates of cells become determined at different times

1.13 Inductive interactions make cells different from each other

■ **Box 1E** Signal transduction and intracellular signaling pathways

1.14 The response to inductive signals depends on the state of the cell

xxii

xxiv

1

3

3

4

4

6

7

8

8

9

11

13

13

14

15

17

17

19

20

22

24

26

26

1.15 Patterning can involve the interpretation of positional information

■ **Box 1F** When development goes awry

1.16 Lateral inhibition can generate spacing patterns

1.17 Localization of cytoplasmic determinants and asymmetric cell division can make daughter cells different from each other

1.18 The embryo contains a generative rather than a descriptive program

1.19 The reliability of development is achieved by various means

1.20 The complexity of embryonic development is due to the complexity of cells themselves

1.21 Development is a central element in evolution

### Summary

### Summary to Chapter 1

## Chapter 2 Development of the *Drosophila* body plan

### *Drosophila* life cycle and overall development

2.1 The early *Drosophila* embryo is a multinucleate syncytium

2.2 Cellularization is followed by gastrulation and segmentation

2.3 After hatching, the *Drosophila* larva develops through several larval stages, pupates, and then undergoes metamorphosis to become an adult

2.4 Many developmental genes were identified in *Drosophila* through induced large-scale genetic screening

■ **Box 2A** Mutagenesis and genetic screening strategy for identifying developmental mutants in *Drosophila*

### Summary

### Setting up the body axes

2.5 The body axes are set up while the *Drosophila* embryo is still a syncytium

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

27

28

30

30

31

32

32

33

34

34

37

38

38

40

41

41

43

44

44

44

46

46

46

49



2.10	The anterior and posterior extremities of the embryo are specified by activation of a cell-surface receptor	50	2.26	Signals generated at the parasegment boundary delimit and pattern the future segments	79
2.11	The dorso-ventral polarity of the embryo is specified by localization of maternal proteins in the egg vitelline envelope	51	■ Box 2F	The Hedgehog signaling pathway	82
2.12	Positional information along the dorso-ventral axis is provided by the Dorsal protein	52	2.27	Compartment boundaries persist into the adult fly	83
<b>Summary</b>		53	■ Box 2G	Mutants in denticle pattern provided clues to the logic of segment patterning	84
■ Box 2B	The Toll signaling pathway: a multifunctional pathway	54	■ Box 2H	Genetic mosaics and mitotic recombination	86
<b>Localization of maternal determinants during oogenesis</b>		54	2.28	Insect epidermal cells become individually polarized in an antero-posterior direction in the plane of the epithelium	87
2.13	The antero-posterior axis of the <i>Drosophila</i> egg is specified by signals from the preceding egg chamber and by interactions of the oocyte with follicle cells	55	■ Box 2I	Planar cell polarity in <i>Drosophila</i>	88
■ Box 2C	The JAK-STAT signaling pathway	57	<b>Summary</b>		89
2.14	Localization of maternal mRNAs to either end of the egg depends on the reorganization of the oocyte cytoskeleton	58	<b>Specification of segment identity</b>		90
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	60	2.29	Segment identity in <i>Drosophila</i> is specified by Hox genes	91
<b>Summary</b>		60	2.30	Homeotic selector genes of the bithorax complex are responsible for diversification of the posterior segments	92
<b>Patterning the early embryo</b>		61	2.31	The Antennapedia complex controls specification of anterior regions	93
2.16	The expression of zygotic genes along the dorso-ventral axis is controlled by Dorsal protein	61	2.32	The order of Hox gene expression corresponds to the order of genes along the chromosome	93
2.17	The Decapentaplegic protein acts as a morphogen to pattern the dorsal region	64	2.33	The <i>Drosophila</i> head region is specified by genes other than the Hox genes	94
2.18	The antero-posterior axis is divided up into broad regions by gap-gene expression	66	<b>Summary</b>		94
2.19	The bicoid protein provides a positional signal for the anterior expression of zygotic <i>hunchback</i>	66	<b>Summary to Chapter 2</b>		95
2.20	The gradient in Hunchback protein activates and represses other gap genes	68	<b>Chapter 3 Vertebrate development I: life cycles and experimental techniques</b>		103
■ Box 2D	P-element-mediated transformation	69	<b>Vertebrate life cycles and outlines of development</b>		104
■ Box 2E	Targeted gene expression and misexpression screening	70	3.1	The frog <i>Xenopus laevis</i> is the model amphibian for studying development of the body plan	107
<b>Summary</b>		71	3.2	The zebrafish embryo develops around a large mass of yolk	111
<b>Activation of the pair-rule genes and the establishment of parasegments</b>		71	3.3	Birds and mammals resemble each other and differ from <i>Xenopus</i> in some important features of early development	113
2.21	Parasegments are delimited by expression of pair-rule genes in a periodic pattern	72	3.4	The early chicken embryo develops as a flat disc of cells overlying a massive yolk	114
2.22	Gap-gene activity positions stripes of pair-rule gene expression	72	3.5	The mouse egg has no yolk and early development involves the allocation of cells to form the placenta and extra-embryonic membranes	119
2.23	Some insects use different mechanisms for patterning the body plan	75	3.6	The early development of a human embryo is similar to that of the mouse	123
<b>Summary</b>		77	<b>Experimental approaches to studying vertebrate development</b>		125
<b>Segmentation genes and segment patterning</b>		77	■ Box 3A	Preimplantation genetic diagnosis	126
2.24	Expression of the <i>engrailed</i> gene defines the boundary of a parasegment which is also a boundary of cell-lineage restriction	77	■ Box 3B	Gene-expression profiling by DNA microarrays and RNA seq	128
2.25	Segmentation genes stabilize parasegment boundaries	79	3.7	Fate mapping and lineage tracing reveal what parts of the body cells in the early embryo give rise to which adult structures	129



3.8 Not all techniques are equally applicable to all vertebrates	131	■ <b>Box 4D</b> Investigating receptor function using dominant-negative mutations	161
3.9 Developmental genes can be identified by spontaneous mutation and by large-scale mutagenesis screens	132	4.11 The zygotic expression of mesoderm-inducing and patterning signals is activated by the combined actions of maternal VegT and Wnt signaling	161
■ <b>Box 3C</b> Large-scale mutagenesis screens for recessive mutations in zebrafish	134	4.12 Threshold responses to gradients of signaling proteins are likely to pattern the mesoderm	162
3.10 Transgenic techniques enable animals to be produced with mutations in specific genes	135	<b>Summary</b>	164
■ <b>Box 3D</b> The Cre/loxP system: a strategy for making gene knock-outs in mice	138	<b>The Spemann organizer and neural induction</b>	164
3.11 Gene function can also be tested by transient transgenesis and gene silencing	139	■ <b>Box 4E</b> The FGF signaling pathway	165
3.12 Gene regulatory networks in embryonic development can be revealed by chromatin immunoprecipitation techniques	139	4.13 Signals from the organizer pattern the mesoderm dorso-ventrally by antagonizing the effects of ventral signals	166
<b>Summary to Chapter 3</b>	140	4.14 The antero-posterior axis of the embryo emerges during gastrulation	167
<b>Chapter 4 Vertebrate development II: <i>Xenopus</i> and zebrafish</b>	144	4.15 The neural plate is induced in the ectoderm	169
<b>Setting up the body axes</b>	145	4.16 The nervous system is patterned along the antero-posterior axis by signals from the mesoderm	172
4.1 The animal-vegetal axis is maternally determined in <i>Xenopus</i>	145	4.17 The final body plan emerges by the end of gastrulation and neurulation	173
■ <b>Box 4A</b> Intercellular protein signals in vertebrate development	147	<b>Summary</b>	174
■ <b>Box 4B</b> The Wnt/ $\beta$ -catenin signaling pathway	148	<b>Development of the body plan in zebrafish</b>	174
4.2 Local activation of Wnt/ $\beta$ -catenin signaling specifies the future dorsal side of the embryo	149	4.18 The body axes in zebrafish are established by maternal determinants	175
4.3 Signaling centers develop on the dorsal side of the blastula	151	4.19 The germ layers are specified in the zebrafish blastoderm by similar signals to those in <i>Xenopus</i>	175
<b>Summary</b>	152	4.20 The shield in zebrafish is the embryonic organizer like the Spemann organizer in <i>Xenopus</i>	177
<b>The origin and specification of the germ layers</b>	152	<b>Summary to Chapter 4</b>	178
4.4 The fate map of the <i>Xenopus</i> blastula makes clear the function of gastrulation	153	<b>Chapter 5 Vertebrate development III: Chick and mouse—completing the body plan</b>	185
4.5 Cells of the early <i>Xenopus</i> embryo do not yet have their fates determined and regulation is possible	154	<b>Development of the body plan in chick and mouse</b>	186
4.6 Endoderm and ectoderm are specified by maternal factors, whereas mesoderm is induced from ectoderm by signals from the vegetal region	154	5.1 The antero-posterior polarity of the chick blastoderm is related to the primitive streak	186
■ <b>Box 4C</b> Signaling by members of the TGF- $\beta$ family of growth factors	157	5.2 Early stages in mouse development establish separate cell lineages for the embryo and the extra-embryonic structures	188
4.7 Mesoderm induction occurs during a limited period in the blastula stage	157	5.3 Movement of the anterior visceral endoderm indicates the definitive antero-posterior axis in the mouse embryo	192
4.8 Zygotic gene expression is turned on at the mid-blastula transition	158	5.4 The fate maps of vertebrate embryos are variations on a basic plan	193
4.9 Mesoderm-inducing and patterning signals are produced by the vegetal region, the organizer, and the ventral mesoderm	159	■ <b>Box 5A</b> Fine-tuning Nodal signaling	194
4.10 Members of the TGF- $\beta$ family have been identified as mesoderm inducers	160	5.5 Mesoderm induction and patterning in the chick and mouse occurs during primitive-streak formation	196
		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>	198



5.7 Neural induction in chick and mouse is initiated by FGF signaling with inhibition of BMP signaling being required in a later step	200	6.3 The dorso-ventral axis in <i>Caenorhabditis elegans</i> is determined by cell-cell interactions	242
■ <b>Box 5B</b> Chromatin-remodeling complexes	202	6.4 Both asymmetric divisions and cell-cell interactions specify cell fate in the early nematode embryo	244
5.8 Axial structures in chick and mouse are generated from self-renewing cell populations	203	6.5 Cell differentiation in the nematode is closely linked to the pattern of cell division	246
<b>Summary</b>	205	6.6 Hox genes specify positional identity along the antero-posterior axis in <i>Caenorhabditis elegans</i>	247
■ <b>Box 5C</b> 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
<b>Somite formation and antero-posterior patterning</b>	207	■ <b>Box 6C</b> Gene silencing by microRNAs	250
5.9 Somites are formed in a well-defined order along the antero-posterior axis	208	6.8 Vulval development is initiated by the induction of a small number of cells by short-range signals from a single inducing cell	250
■ <b>Box 5D</b> The Notch signaling pathway	212	<b>Summary</b>	253
5.10 Identity of somites along the antero-posterior axis is specified by Hox gene expression	213	<b>Echinoderms</b>	254
■ <b>Box 5E</b> The Hox genes	215	6.9 The sea-urchin embryo develops into a free-swimming larva	254
5.11 Deletion or overexpression of Hox genes causes changes in axial patterning	218	6.10 The sea-urchin egg is polarized along the animal-vegetal axis	255
5.12 Hox gene expression is activated in an anterior to posterior pattern	219	6.11 The sea-urchin fate map is finely specified, yet considerable regulation is possible	257
5.13 The fate of somite cells is determined by signals from the adjacent tissues	220	6.12 The vegetal region of the sea-urchin embryo acts as an organizer	258
<b>Summary</b>	222	6.13 The sea-urchin vegetal region is demarcated by the nuclear accumulation of $\beta$ -catenin	259
<b>The origin and patterning of neural crest</b>	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	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	6.15 The pluteus skeleton develops from the primary mesenchyme	261
5.15 Neural crest cells migrate from the hindbrain to populate the branchial arches	224	6.16 The oral-aboral axis in sea urchins is related to the plane of the first cleavage	263
<b>Summary</b>	225	6.17 The oral ectoderm acts as an organizing region for the oral-aboral axis	264
<b>Determination of left-right asymmetry</b>	226	■ <b>Box 6D</b> The gene regulatory network for sea-urchin endomesoderm specification	265
5.16 The bilateral symmetry of the early embryo is broken to produce left-right asymmetry of internal organs	226	<b>Summary</b>	266
5.17 Left-right symmetry breaking may be initiated within cells of the early embryo	228	<b>Summary to Chapter 6</b>	266
<b>Summary</b>	229		
<b>Summary to Chapter 5</b>	229	<b>Chapter 7 Plant development</b>	272
<b>Chapter 6 Development of nematodes and sea urchins</b>	235	7.1 The model plant <i>Arabidopsis thaliana</i> has a short life cycle and a small diploid genome	274
<b>Nematodes</b>	236	<b>Embryonic development</b>	275
■ <b>Box 6A</b> Apoptotic pathways in nematodes, <i>Drosophila</i> and mammals	238	7.2 Plant embryos develop through several distinct stages	275
6.1 The cell lineage of <i>Caenorhabditis elegans</i> is largely invariant	239	■ <b>Box 7A</b> Angiosperm embryogenesis	276
6.2 The antero-posterior axis in <i>Caenorhabditis elegans</i> is determined by asymmetric cell division	239	7.3 Gradients of the signal molecule auxin establish the embryonic apical-basal axis	278
■ <b>Box 6B</b> Gene silencing by antisense RNA and RNA interference	241		



7.4 Plant somatic cells can give rise to embryos and seedlings	280	8.2 Gene expression is also controlled by chemical and structural modifications to DNA and histone proteins that alter chromatin structure	316
■ <b>Box 7B</b> Transgenic plants	281	■ <b>Box 8A</b> Epigenetic control of gene expression by chromatin modification	317
7.5 Cell enlargement is a major process in plant growth and morphogenesis	281	8.3 Patterns of gene activity can be inherited by persistence of gene-regulatory proteins or by maintenance of chromatin modifications	318
<b>Summary</b>	282	8.4 Changes in patterns of gene activity during differentiation can be triggered by extracellular signals	319
<b>Meristems</b>	283	<b>Summary</b>	321
7.6 A meristem contains a small, central zone of self-renewing stem cells	284	<b>Models of cell differentiation and stem cells</b>	322
7.7 The size of the stem-cell area in the meristem is kept constant by a feedback loop to the organizing center	284	8.5 Muscle differentiation is determined by the MyoD family of transcription factors	322
7.8 The fate of cells from different meristem layers can be changed by changing their position	285	8.6 The differentiation of muscle cells involves withdrawal from the cell cycle, but is reversible	324
7.9 A fate map for the embryonic shoot meristem can be deduced using clonal analysis	287	8.7 All blood cells are derived from multipotent stem cells	325
7.10 Meristem development is dependent on signals from other parts of the plant	288	8.8 Intrinsic and extrinsic changes control differentiation of the hematopoietic lineages	328
7.11 Gene activity patterns the proximo-distal and adaxial-abaxial axes of leaves developing from the shoot meristem	289	8.9 Developmentally regulated globin gene expression is controlled by regulatory sequences far distant from the coding regions	330
7.12 The regular arrangement of leaves on a stem is generated by regulated auxin transport	290	8.10 The epidermis of adult mammalian skin is continually being replaced by derivatives of stem cells	332
7.13 Root tissues are produced from <i>Arabidopsis</i> root apical meristems by a highly stereotyped pattern of cell divisions	292	8.11 Stem cells use different modes of division to maintain tissues	334
7.14 Root hairs are specified by a combination of positional information and lateral inhibition	294	8.12 The lining of the gut is another epithelial tissue that requires continuous renewal	336
<b>Summary</b>	294	8.13 Skeletal muscle and neural cells can be renewed from stem cells in adults	338
<b>Flower development and control of flowering</b>	295	8.14 Embryonic stem cells can proliferate and differentiate into many cell types in culture and contribute to normal development <i>in vivo</i>	339
7.15 Homeotic genes control organ identity in the flower	296	■ <b>Box 8B</b> The derivation and culture of mouse embryonic stem cells (ES cells)	341
■ <b>Box 7C</b> The basic model for the patterning of the <i>Arabidopsis</i> flower	298	<b>Summary</b>	342
7.16 The <i>Antirrhinum</i> flower is patterned dorso-ventrally as well as radially	299	<b>The plasticity of the differentiated state</b>	343
7.17 The internal meristem layer can specify floral meristem patterning	300	8.15 Nuclei of differentiated cells can support development	344
7.18 The transition of a shoot meristem to a floral meristem is under environmental and genetic control	300	8.16 Patterns of gene activity in differentiated cells can be changed by cell fusion	346
7.19 Most flowering plants are hermaphrodites, but some produce unisexual flowers	302	8.17 The differentiated state of a cell can change by transdifferentiation	346
<b>Summary</b>	303	8.18 Stem cells could be a key to regenerative medicine	348
<b>Summary to Chapter 7</b>	304	■ <b>Box 8C</b> Tissue engineering using stem cells	349
<b>Chapter 8 Cell differentiation and stem cells</b>	309	■ <b>Box 8D</b> Induced pluripotent stem cells (iPS cells)	350
<b>The control of gene expression</b>	312	8.19 Various approaches can be used to generate differentiated cells for cell-replacement therapies	352
8.1 Control of transcription involves both general and tissue-specific transcriptional regulators	313		



Summary	355	Summary	391
Summary to Chapter 8	355	<b>Neural tube formation</b>	392
<b>Chapter 9 Morphogenesis: change in form in the early embryo</b>	361	9.14 Neural tube formation is driven by changes in cell shape and convergent extension	393
<b>Cell adhesion</b>	363	■ <b>Box 9D</b> Eph receptors and their ephrin ligands	395
9.1 Sorting out of dissociated cells demonstrates differences in cell adhesiveness in different tissues	363	■ <b>Box 9E</b> Neural tube defects	396
■ <b>Box 9A</b> Cell-adhesion molecules and cell junctions	365	Summary	396
9.2 Cadherins can provide adhesive specificity	366	<b>Cell migration</b>	397
9.3 Transitions of tissues from an epithelial to a mesenchymal state, and vice versa, involve changes in adhesive junctions	367	9.15 Embryonic neural crest gives rise to a wide range of different cell types	397
■ <b>Box 9B</b> The cytoskeleton, cell-shape change and cell movement	368	9.16 Neural crest migration is controlled by environmental cues	397
Summary	369	9.17 The formation of the lateral-line primordium in fishes is an example of collective cell migration	399
<b>Cleavage and formation of the blastula</b>	369	9.18 Dorsal closure in <i>Drosophila</i> and ventral closure in <i>Caenorhabditis elegans</i> are brought about by the action of filopodia	400
9.4 The orientation of the mitotic spindle determines the plane of cleavage at cell division	370	Summary	401
9.5 The positioning of the spindle within the cell also determines whether daughter cells will be the same or different sizes	372	<b>Directed dilation</b>	402
9.6 Cells become polarized in the sea-urchin blastula and the mouse morula	373	9.19 Later extension and stiffening of the notochord occurs by directed dilation	402
9.7 Fluid accumulation as a result of tight-junction formation and ion transport forms the blastocoel of the mammalian blastocyst	375	9.20 Circumferential contraction of hypodermal cells elongates the nematode embryo	403
Summary	376	Summary	403
<b>Gastrulation movements</b>	377	<b>Summary to Chapter 9</b>	404
9.8 Gastrulation in the sea urchin involves an epithelial-to-mesenchymal transition, cell migration, and invagination of the blastula wall	377	<b>Chapter 10 Germ cells, fertilization, and sex</b>	409
9.9 Mesoderm invagination in <i>Drosophila</i> is due to changes in cell shape controlled by genes that pattern the dorso-ventral axis	380	<b>The development of germ cells</b>	410
9.10 Germ-band extension in <i>Drosophila</i> involves myosin-dependent remodeling of cell junctions and cell intercalation	382	10.1 Germ-cell fate is specified in some embryos by a distinct germplasm in the egg	411
9.11 Gastrulation in amphibians and fish involves involution, epiboly, and convergent extension	383	10.2 In mammals germ cells are induced by cell-cell interactions during development	413
■ <b>Box 9C</b> Convergent extension	385	10.3 Germ cells migrate from their site of origin to the gonad	414
9.12 <i>Xenopus</i> notochord development illustrates the dependence of medio-lateral cell polarity on a pre-existing antero-posterior polarity	387	10.4 Germ cells are guided to their final destination by chemical signals	415
9.13 Gastrulation in chick and mouse embryos involves the delamination of cells from the epiblast and their ingression through the primitive streak	389	10.5 Germ-cell differentiation involves a halving of chromosome number by meiosis	416
		■ <b>Box 10A</b> Polar bodies	417
		10.6 Oocyte development can involve gene amplification and contributions from other cells	419
		10.7 Factors in the cytoplasm maintain the totipotency of the egg	420
		10.8 In mammals some genes controlling embryonic growth are 'imprinted'	420
		Summary	423
		<b>Fertilization</b>	424



10.9 Fertilization involves cell-surface interactions between egg and sperm	424	11.11 Development of the limb is integrated by interactions between signaling centers	465
10.10 Changes in the egg plasma membrane and enveloping layers at fertilization block polyspermy	426	■ <b>Box 11D</b> Sonic hedgehog signaling and the primary cilium	466
10.11 Sperm-egg fusion causes a calcium wave that results in egg activation	427	11.12 Different interpretations of the same positional signals give different limbs	467
<b>Summary</b>	429	11.13 Hox genes have multiple inputs into the patterning of the limb	468
<b>Determination of the sexual phenotype</b>	430	11.14 Self-organization may be involved in the development of the limb bud	471
10.12 The primary sex-determining gene in mammals is on the Y chromosome	430	■ <b>Box 11E</b> Reaction-diffusion mechanisms	472
10.13 Mammalian sexual phenotype is regulated by gonadal hormones	431	11.15 Limb muscle is patterned by the connective tissue	473
10.14 The primary sex-determining signal in <i>Drosophila</i> is the number of X chromosomes and is cell autonomous	433	11.16 The initial development of cartilage, muscles, and tendons is autonomous	473
10.15 Somatic sexual development in <i>Caenorhabditis</i> is determined by the number of X chromosomes	435	11.17 Joint formation involves secreted signals and mechanical stimuli	474
10.16 Determination of germ-cell sex depends on both genetic constitution and intercellular signals	436	11.18 Separation of the digits is the result of programmed cell death	475
10.17 Various strategies are used for dosage compensation of X-linked genes	438	<b>Summary</b>	476
<b>Summary</b>	440	<b>Insect wings and legs</b>	476
<b>Summary to Chapter 10</b>	441	11.19 The adult wing emerges at metamorphosis after folding and evagination of the wing imaginal disc	477
<b>Chapter 11 Organogenesis</b>	446	11.20 A signaling center at the boundary between anterior and posterior compartments patterns the <i>Drosophila</i> wing along the antero-posterior axis	478
<b>The vertebrate limb</b>	447	11.21 A signaling center at the boundary between dorsal and ventral compartments patterns the <i>Drosophila</i> wing along the dorso-ventral axis	481
11.1 The vertebrate limb develops from a limb bud	447	11.22 Vestigial is a key regulator of wing development that acts to specify wing identity and control wing growth	481
11.2 Genes expressed in the lateral plate mesoderm are involved in specifying the position and type of limb	449	11.23 How the proximo-distal axis of the <i>Drosophila</i> wing is patterned is not yet clear	483
11.3 The apical ectodermal ridge is required for limb outgrowth and the formation of structures along the proximo-distal axis of the limb	451	11.24 The leg disc is patterned in a similar manner to the wing disc, except for the proximo-distal axis	483
11.4 Outgrowth of the limb bud involves oriented cell behavior	452	11.25 Butterfly wing markings are organized by additional positional fields	485
11.5 Patterning of the limb bud involves positional information	454	11.26 Different imaginal discs can have the same positional values	486
11.6 How position along the proximo-distal axis of the limb bud is specified is still a matter of debate	454	<b>Summary</b>	488
11.7 The polarizing region specifies position along the limb's antero-posterior axis	456	<b>Vertebrate and insect eyes</b>	489
■ <b>Box 11A</b> Teratogens and the consequences of damage to the developing embryo	458	11.27 The vertebrate eye develops mainly from the neural tube and the ectoderm of the head	490
■ <b>Box 11B</b> Positional information and morphogen gradients	460	11.28 Patterning of the <i>Drosophila</i> eye involves cell-cell interactions	494
11.8 Sonic hedgehog is the polarizing region morphogen	461	<b>Summary</b>	497
11.9 How digit identity is encoded is not yet known	462	<b>Vertebrate lungs and insect tracheal system</b>	498
■ <b>Box 11C</b> Too many fingers: mutations that affect antero-posterior patterning can cause polydactyly	463	11.29 The vertebrate lung develops by branching of epithelial tubes	499
11.10 The dorso-ventral axis of the limb is controlled by the ectoderm	464		



11.30 The <i>Drosophila</i> tracheal system is a prime example of branching morphogenesis	500	12.13 Neurons are formed in the proliferative zone of the vertebrate neural tube and migrate outwards	539
<b>Summary</b>	502	■ <b>Box 12B</b> Timing the birth of cortical neurons	541
<b>Vertebrate blood vessels and heart</b>	502	12.14 Many cortical interneurons migrate tangentially	543
11.31 The vascular system develops by vasculogenesis followed by sprouting angiogenesis	502	<b>Summary</b>	543
11.32 The development of the vertebrate heart involves morphogenesis and patterning of a mesodermal tube	504	<b>Axon navigation</b>	544
<b>Teeth</b>	507	12.15 The growth cone controls the path taken by a growing axon	545
11.33 Tooth development involves epithelial-mesenchymal interactions and a homeobox gene code specifies tooth identity	507	■ <b>Box 12C</b> The development of the neural circuit for the knee-jerk reflex	547
<b>Summary</b>	510	12.16 Motor neuron axons in the chick limb are guided by ephrin-Eph interactions	548
<b>Summary to Chapter 11</b>	510	12.17 Axons crossing the midline are both attracted and repelled	549
 		12.18 Neurons from the retina make ordered connections with visual centers in the brain	550
<b>Chapter 12 Development of the nervous system</b>	520	<b>Summary</b>	553
<b>Specification of cell identity in the nervous system</b>	522	<b>Synapse formation and refinement</b>	554
12.1 Initial regionalization of the vertebrate brain involves signals from local organizers	522	12.19 Synapse formation involves reciprocal interactions	556
12.2 Local signaling centers pattern the brain along the antero-posterior axis	523	■ <b>Box 12D</b> Autism: a developmental disorder that involves synapse dysfunction	558
12.3 The cerebral cortex is patterned by signals from the anterior neural ridge	524	12.20 Many motor neurons die during normal development	559
12.4 The hindbrain is segmented into rhombomeres by boundaries of cell-lineage restriction	525	12.21 Neuronal cell death and survival involve both intrinsic and extrinsic factors	559
12.5 Hox genes provide positional information in the developing hindbrain	527	12.22 The map from eye to brain is refined by neural activity	560
12.6 The pattern of differentiation of cells along the dorso-ventral axis of the spinal cord depends on ventral and dorsal signals	528	<b>Summary</b>	561
12.7 Neuronal subtypes in the ventral spinal cord are specified by the ventral to dorsal gradient of Shh	530	<b>Summary to Chapter 12</b>	562
12.8 Spinal cord motor neurons at different dorso-ventral positions project to different trunk and limb muscles	531	 	
12.9 Antero-posterior pattern in the spinal cord is determined in response to secreted signals from the node and adjacent mesoderm	532	<b>Chapter 13 Growth, post-embryonic development and regeneration</b>	569
<b>Summary</b>	533	<b>Growth</b>	570
<b>The formation and migration of neurons</b>	533	13.1 Tissues can grow by cell proliferation, cell enlargement, or accretion	571
12.10 Neurons in <i>Drosophila</i> arise from proneural clusters	533	13.2 Cell proliferation is controlled by regulating entry into the cell cycle	572
12.11 The development of neurons in <i>Drosophila</i> involves asymmetric cell divisions and timed changes in gene expression	536	13.3 Cell division in early development can be controlled by an intrinsic developmental program	573
■ <b>Box 12A</b> Specification of the sensory organs of adult <i>Drosophila</i>	537	13.4 Extrinsic signals coordinate cell division, cell growth, and cell death in the developing <i>Drosophila</i> wing	574
12.12 The production of vertebrate neurons involves lateral inhibition, as in <i>Drosophila</i>	538	■ <b>Box 13A</b> The core Hippo signaling pathways in <i>Drosophila</i> and mammals	575
		13.5 Cancer can result from mutations in genes that control cell proliferation	576
		13.6 Size-control mechanisms differ in different organs	578
		13.7 Overall body size depends on the extent and the duration of growth	580



13.8 Hormones and growth factors coordinate the growth of different tissues and organs and contribute to determining overall body size	581	<b>Chapter 14 Evolution and development</b>	623
■ <b>Box 13B</b> The major determinant of body size in dogs is the growth hormone-IGF-1 axis	582	■ <b>Box 14A</b> Darwin's finches	625
13.9 Elongation of the long bones illustrates how growth can be determined by a combination of an intrinsic growth program and extracellular factors	583	<b>The evolution of development</b>	626
■ <b>Box 13C</b> Digit length ratio is determined in the embryo	586	14.1 Genomic evidence is throwing light on the origin of metazoans	626
13.10 The amount of nourishment an embryo receives can have profound effects in later life	587	14.2 Multicellular organisms evolved from single-celled ancestors	628
<b>Summary</b>	588	<b>Summary</b>	629
<b>Molting and metamorphosis</b>	588	<b>The evolutionary modification of embryonic development</b>	629
13.11 Arthropods have to molt in order to grow	589	14.3 Hox gene complexes have evolved through gene duplication	630
13.12 Insect body size is determined by the rate and duration of larval growth	589	14.4 Changes in both Hox genes and their target genes generated the elaboration and diversification of bilaterian body plans	632
13.13 Metamorphosis in amphibians is under hormonal control	592	14.5 Differences in Hox gene expression determine the variation in position and type of paired appendages in arthropods	634
<b>Summary</b>	593	14.6 The basic body plan of arthropods and vertebrates is similar, but the dorso-ventral axis is inverted	638
<b>Regeneration</b>	594	14.7 Limbs evolved from fins	639
13.14 There are two types of regeneration—morphallaxis and epimorphosis	595	14.8 Limbs have evolved to fulfill different specialized functions	641
13.15 Regeneration of amphibian and insect limbs involves epimorphosis	595	■ <b>Box 14B</b> How the bird wing evolved	642
■ <b>Box 13D</b> Regeneration in <i>Hydra</i>	596	■ <b>Box 14C</b> Pelvic reduction in sticklebacks is based on mutations in a gene control region	644
13.16 Amphibian limb regeneration involves cell dedifferentiation and new growth	597	14.9 Adaptive evolution within the same species provides a way of studying the developmental basis for evolutionary change	645
■ <b>Box 13E</b> Planarian regeneration	598	14.10 Evolution of different types of eyes in different animal groups is an example of parallel evolution using an ancient genetic circuitry	646
13.17 Limb regeneration in amphibians is dependent on the presence of nerves	602	14.11 Embryonic structures have acquired new functions during evolution	647
13.18 The limb blastema gives rise to structures with positional values distal to the site of amputation	603	<b>Summary</b>	649
13.19 Retinoic acid can change proximo-distal positional values in regenerating limbs	605	<b>Changes in the timing of developmental processes</b>	649
13.20 Mammals can regenerate the tips of the digits	607	14.12 Changes in growth can modify the basic body plan	649
13.21 Insect limbs intercalate positional values by both proximo-distal and circumferential growth	607	14.13 Evolution can be due to changes in the timing of developmental events	651
13.22 Heart regeneration in zebrafish involves the resumption of cell division by cardiomyocytes	609	14.14 The evolution of life histories has implications for development	653
■ <b>Box 13F</b> Why can't we regenerate our limbs?	611	<b>Summary</b>	653
<b>Summary</b>	612	<b>Summary to Chapter 14</b>	654
<b>Aging and senescence</b>	613	<i>Glossary</i>	659
13.23 Genes can alter the timing of senescence	613	<i>Index</i>	681
13.24 Cell senescence blocks cell multiplication	615		
<b>Summary</b>	616		
<b>Summary to Chapter 13</b>	616		