

instant access to key research in this field. The unique user-interface allows you to view the site in three different formats, highlighting text, images or a combination of both, to best support your teaching style.

**Instructor's Resource Manual** (0-13-144944-3)

**Test Item File** (0-13-144945-1)

**Transparency Package** (0-13-144946-X)

***For the Student:***

**Student Study Companion:** This study tool provides students with the resources to review fundamental concepts from the text through practice questions and exercises. Additional study aids help students to study more effectively.

**Website with E-Book** ([www.prenhall.com/lewin](http://www.prenhall.com/lewin)) This powerful website contains an online version of the text, supported by weekly updates to maintain currency on key topics. Links connect the student directly to the original source material for immediate access to key articles wherever possible. The unique user-interface allows students to view the site in three different formats, highlighting text, images or a combination of both, to best support their learning style.

## Outline

### Part 1 Genes

---

1 Genes are DNA	1
2 The interrupted gene	33
3 The content of the genome	51
4 Clusters and repeats	85

### Part 2 Proteins

---

5 Messenger RNA	113
6 Protein synthesis	135
7 Using the genetic code	167
8 Protein localization	195

### Part 3 Gene expression

---

9 Transcription	241
10 The operon	279
11 Regulatory circuits	301
12 Phage strategies	329

### Part 4 DNA

---

13 The replicon	353
14 DNA replication	387
15 Recombination and repair	419
16 Transposons	467
17 Retroviruses and retroposons	493
18 Rearrangement of DNA	513

### Part 5 The Nucleus

---

19 Chromosomes	545
20 Nucleosomes	571
21 Promoters and enhancers	597
22 Activating transcription	631
23 Controlling chromatin structure	657
24 RNA splicing and processing	697
25 Catalytic RNA	731
26 Immune diversity	751

### Part 6 Cells

---

27 Protein trafficking	787
28 Signal transduction	811
29 Cell cycle and growth regulation	843
30 Oncogenes and cancer	889
31 Gradients, cascades, and signaling pathways	939

<b>Glossary</b>	981
-----------------	-----

---

<b>Index</b>	1003
--------------	------

---

# Contents

## Part 1 Genes

---

### 1 Genes are DNA

1.1 Introduction	1
1.2 DNA is the genetic material of bacteria	3
1.3 DNA is the genetic material of viruses	3
1.4 DNA is the genetic material of animal cells	4
1.5 Polynucleotide chains have nitrogenous bases linked to a sugar-phosphate backbone	5
1.6 DNA is a double helix	6
1.7 DNA replication is semiconservative	7
1.8 DNA strands separate at the replication fork	8
1.9 Nucleic acids hybridize by base pairing	9
1.10 Mutations change the sequence of DNA	10
1.11 Mutations may affect single base pairs or longer sequences	11
1.12 The effects of mutations can be reversed	13
1.13 Mutations are concentrated at hotspots	13
1.14 Many hotspots result from modified bases	14
1.15 A gene codes for a single polypeptide	15
1.16 Mutations in the same gene cannot complement	16
1.17 Mutations may cause loss-of-function or gain-of-function	18
1.18 A locus may have many different mutant alleles	18
1.19 A locus may have more than one wild-type allele	19
1.20 Recombination occurs by physical exchange of DNA	20
1.21 The genetic code is triplet	21
1.22 Every sequence has three possible reading frames	23
1.23 Prokaryotic genes are colinear with their proteins	24
1.24 Several processes are required to express the protein product of a gene	25
1.25 Proteins are <i>trans</i> -acting but sites on DNA are <i>cis</i> -acting	26
1.26 Genetic information can be provided by DNA or RNA	27
1.27 Some hereditary agents are extremely small	29
1.28 Summary	30

---

### 2 The interrupted gene

2.1 Introduction	33
2.2 An interrupted gene consists of exons and introns	34
2.3 Restriction endonucleases are a key tool in mapping DNA	35
2.4 Organization of interrupted genes may be conserved	36
2.5 Exon sequences are conserved but introns vary	37
2.6 Genes can be isolated by the conservation of exons	38
2.7 Genes show a wide distribution of sizes	40
2.8 Some DNA sequences code for more than one protein	41
2.9 How did interrupted genes evolve?	43
2.10 Some exons can be equated with protein functions	45
2.11 The members of a gene family have a common organization	46
2.12 Is all genetic information contained in DNA?	48
2.13 Summary	49

---

### 3 The content of the genome

3.1 Introduction	51
3.2 Genomes can be mapped by linkage, restriction cleavage, or DNA sequence	52
3.3 Individual genomes show extensive variation	53
3.4 RFLPs and SNPs can be used for genetic mapping	54

3.5	Why are genomes so large?	56
3.6	Eukaryotic genomes contain both nonrepetitive and repetitive DNA sequences	57
3.7	Bacterial gene numbers range over an order of magnitude	58
3.8	Total gene number is known for several eukaryotes	60
3.9	How many different types of genes are there?	61
3.10	The conservation of genome organization helps to identify genes	63
3.11	The human genome has fewer genes than expected	65
3.12	How are genes and other sequences distributed in the genome?	67
3.13	More complex species evolve by adding new gene functions	68
3.14	How many genes are essential?	69
3.15	Genes are expressed at widely differing levels	72
3.16	How many genes are expressed?	73
3.17	Expressed gene number can be measured <i>en masse</i>	74
3.18	Organelles have DNA	75
3.19	Organelle genomes are circular DNAs that code for organelle proteins	76
3.20	Mitochondrial DNA organization is variable	77
3.21	Mitochondria evolved by endosymbiosis	78
3.22	The chloroplast genome codes for many proteins and RNAs	79
3.23	Summary	80

#### 4 Clusters and repeats

4.1	Introduction	85
4.2	Gene duplication is a major force in evolution	86
4.3	Globin clusters are formed by duplication and divergence	87
4.4	Sequence divergence is the basis for the evolutionary clock	89
4.5	The rate of neutral substitution can be measured from divergence of repeated sequences	92
4.6	Pseudogenes are dead ends of evolution	93
4.7	Unequal crossing-over rearranges gene clusters	95
4.8	Genes for rRNA form tandem repeats	98
4.9	The repeated genes for rRNA maintain constant sequence	99
4.10	Crossover fixation could maintain identical repeats	100
4.11	Satellite DNAs often lie in heterochromatin	103
4.12	Arthropod satellites have very short identical repeats	105
4.13	Mammalian satellites consist of hierarchical repeats	106
4.14	Minisatellites are useful for genetic mapping	109
4.15	Summary	111

### Part 2 Proteins

#### 5 Messenger RNA

5.1	Introduction	113
5.2	mRNA is produced by transcription and is translated	114
5.3	Transfer RNA forms a cloverleaf	114
5.4	The acceptor stem and anticodon are at ends of the tertiary structure	116
5.5	Messenger RNA is translated by ribosomes	117
5.6	Many ribosomes bind to one mRNA	118
5.7	The life cycle of bacterial messenger RNA	119
5.8	Eukaryotic mRNA is modified during or after its transcription	121
5.9	The 5' end of eukaryotic mRNA is capped	122
5.10	The 3' terminus is polyadenylated	123
5.11	Bacterial mRNA degradation involves multiple enzymes	124
5.12	mRNA stability depends on its structure and sequence	125
5.13	mRNA degradation involves multiple activities	126
5.14	Nonsense mutations trigger a surveillance system	127
5.15	Eukaryotic RNAs are transported	128
5.16	mRNA can be specifically localized	130
5.17	Summary	131

#### 6 Protein synthesis

6.1	Introduction	135
6.2	Protein synthesis occurs by initiation, elongation, and termination	136
6.3	Special mechanisms control the accuracy of protein synthesis	138
6.4	Initiation in bacteria needs 30S subunits and accessory factors	139
6.5	A special initiator tRNA starts the polypeptide chain	140
6.6	Use of fMet-tRNA <sub>f</sub> is controlled by IF-2 and the ribosome	141
6.7	Initiation involves base pairing between mRNA and rRNA	142
6.8	Small subunits scan for initiation sites on eukaryotic mRNA	144
6.9	Eukaryotes use a complex of many initiation factors	146
6.10	Elongation factor Tu loads aminoacyl-tRNA into the A site	148
6.11	The polypeptide chain is transferred to aminoacyl-tRNA	149
6.12	Translocation moves the ribosome	150
6.13	Elongation factors bind alternately to the ribosome	151
6.14	Three codons terminate protein synthesis	152
6.15	Termination codons are recognized by protein factors	153
6.16	Ribosomal RNA pervades both ribosomal subunits	155
6.17	Ribosomes have several active centers	157
6.18	16S rRNA plays an active role in protein synthesis	159
6.19	23S rRNA has peptidyl transferase activity	161
6.20	Summary	162

#### 7 Using the genetic code

7.1	Introduction	167
7.2	Codon-anticodon recognition involves wobbling	169
7.3	tRNAs are processed from longer precursors	170
7.4	tRNA contains modified bases	171
7.5	Modified bases affect anticodon-codon pairing	173
7.6	There are sporadic alterations of the universal code	174
7.7	Novel amino acids can be inserted at certain stop codons	176
7.8	tRNAs are charged with amino acids by synthetases	177
7.9	Aminoacyl-tRNA synthetases fall into two groups	178
7.10	Synthetases use proofreading to improve accuracy	180
7.11	Suppressor tRNAs have mutated anticodons that read new codons	182
7.12	There are nonsense suppressors for each termination codon	183
7.13	Suppressors may compete with wild-type reading of the code	184
7.14	The ribosome influences the accuracy of translation	185
7.15	Recoding changes codon meanings	188
7.16	Frameshifting occurs at slippery sequences	189
7.17	Bypassing involves ribosome movement	190
7.18	Summary	191

#### 8 Protein localization

8.1	Introduction	195
8.2	Passage across a membrane requires a special apparatus	196
8.3	Protein translocation may be post-translational or co-translational	197
8.4	Chaperones may be required for protein folding	198
8.5	Chaperones are needed by newly synthesized and by denatured proteins	199
8.6	The Hsp70 family is ubiquitous	201
8.7	Hsp60/GroEL forms an oligomeric ring structure	202
8.8	Signal sequences initiate translocation	203
8.9	The signal sequence interacts with the SRP	205
8.10	The SRP interacts with the SRP receptor	206
8.11	The translocon forms a pore	207
8.12	Translocation requires insertion into the translocon and (sometimes) a ratchet in the ER	209
8.13	Reverse translocation sends proteins to the cytosol for degradation	210
8.14	Proteins reside in membranes by means of hydrophobic regions	211
8.15	Anchor sequences determine protein orientation	212
8.16	How do proteins insert into membranes?	213

8.17	Post-translational membrane insertion depends on leader sequences	214
8.18	A hierarchy of sequences determines location within organelles	215
8.19	Inner and outer mitochondrial membranes have different translocons	217
8.20	Peroxisomes employ another type of translocation system	219
8.21	Bacteria use both co-translational and post-translational translocation	220
8.22	The <i>Sec</i> system transports proteins into and through the inner membrane	221
8.23	<i>Sec</i> -independent translation systems in <i>E. coli</i>	222
8.24	Pores are used for nuclear import and export	223
8.25	Nuclear pores are large symmetrical structures	224
8.26	The nuclear pore is a size-dependent sieve for smaller material	225
8.27	Proteins require signals to be transported through the pore	226
8.28	Transport receptors carry cargo proteins through the pore	227
8.29	Ran controls the direction of transport	228
8.30	RNA is exported by several systems	230
8.31	Ubiquitination targets proteins for degradation	231
8.32	The proteasome is a large machine that degrades ubiquitinated proteins	232
8.33	Summary	234

### Part 3 Gene expression

#### 9 Transcription

9.1	Introduction	241
9.2	Transcription occurs by base pairing in a "bubble" of unpaired DNA	242
9.3	The transcription reaction has three stages	243
9.4	Phage T7 RNA polymerase is a useful model system	244
9.5	A model for enzyme movement is suggested by the crystal structure	245
9.6	Bacterial RNA polymerase consists of multiple subunits	246
9.7	RNA polymerase consists of the core enzyme and sigma factor	248
9.8	The association with sigma factor changes at initiation	249
9.9	A stalled RNA polymerase can restart	250
9.10	How does RNA polymerase find promoter sequences?	251
9.11	Sigma factor controls binding to DNA	252
9.12	Promoter recognition depends on consensus sequences	253
9.13	Promoter efficiencies can be increased or decreased by mutation	255
9.14	RNA polymerase binds to one face of DNA	256
9.15	Supercoiling is an important feature of transcription	258
9.16	Substitution of sigma factors may control initiation	259
9.17	Sigma factors directly contact DNA	261
9.18	Sigma factors may be organized into cascades	263
9.19	Sporulation is controlled by sigma factors	264
9.20	Bacterial RNA polymerase terminates at discrete sites	266
9.21	There are two types of terminators in <i>E. coli</i>	267
9.22	How does rho factor work?	268
9.23	Antitermination is a regulatory event	270
9.24	Antitermination requires sites that are independent of the terminators	271
9.25	Termination and anti-termination factors interact with RNA polymerase	272
9.26	Summary	274

#### 10 The operon

10.1	Introduction	279
10.2	Regulation can be negative or positive	280
10.3	Structural gene clusters are coordinately controlled	281
10.4	The <i>lac</i> genes are controlled by a repressor	282
10.5	The <i>lac</i> operon can be induced	283
10.6	Repressor is controlled by a small molecule inducer	284
10.7	<i>cis</i> -acting constitutive mutations identify the operator	286
10.8	<i>trans</i> -acting mutations identify the regulator gene	287
10.9	Multimeric proteins have special genetic properties	288
10.10	Repressor protein binds to the operator	288
10.11	Binding of inducer releases repressor from the operator	289

10.12	The repressor monomer has several domains	290
10.13	Repressor is a tetramer made of two dimers	291
10.14	DNA-binding is regulated by an allosteric change in conformation	291
10.15	Mutant phenotypes correlate with the domain structure	292
10.16	Repressor binds to three operators and interacts with RNA polymerase	293
10.17	Repressor is always bound to DNA	294
10.18	The operator competes with low-affinity sites to bind repressor	295
10.19	Repression can occur at multiple loci	297
10.20	Summary	298

#### 11 Regulatory circuits

11.1	Introduction	301
11.2	Distinguishing positive and negative control	302
11.3	Glucose repression controls use of carbon sources	304
11.4	Cyclic AMP is an inducer that activates CRP to act at many operons	305
11.5	CRP functions in different ways in different target operons	305
11.6	CRP bends DNA	307
11.7	The stringent response produces (p)ppGpp	308
11.8	(p)ppGpp is produced by the ribosome	309
11.9	ppGpp has many effects	310
11.10	Translation can be regulated	311
11.11	r-protein synthesis is controlled by autogenous regulation	312
11.12	Phage T4 p32 is controlled by an autogenous circuit	313
11.13	Autogenous regulation is often used to control synthesis of macromolecular assemblies	314
11.14	Alternative secondary structures control attenuation	315
11.15	Termination of <i>B. subtilis trp</i> genes is controlled by tryptophan and by tRNA <sup>Trp</sup>	316
11.16	The <i>E. coli tryptophan</i> operon is controlled by attenuation	316
11.17	Attenuation can be controlled by translation	318
11.18	Antisense RNA can be used to inactivate gene expression	319
11.19	Small RNA molecules can regulate translation	320
11.20	Bacteria contain regulator RNAs	321
11.21	MicroRNAs are regulators in many eukaryotes	322
11.22	RNA interference is related to gene silencing	323
11.23	Summary	325

#### 12 Phage strategies

12.1	Introduction	329
12.2	Lytic development is divided into two periods	330
12.3	Lytic development is controlled by a cascade	331
12.4	Two types of regulatory event control the lytic cascade	332
12.5	The T7 and T4 genomes show functional clustering	333
12.6	Lambda immediate early and delayed early genes are needed for both lysogeny and the lytic cycle	334
12.7	The lytic cycle depends on antitermination	335
12.8	Lysogeny is maintained by repressor protein	336
12.9	Repressor maintains an autogenous circuit	337
12.10	The repressor and its operators define the immunity region	338
12.11	The DNA-binding form of repressor is a dimer	339
12.12	Repressor uses a helix-turn-helix motif to bind DNA	340
12.13	The recognition helix determines specificity for DNA	340
12.14	Repressor dimers bind cooperatively to the operator	342
12.15	Repressor at <i>O<sub>R2</sub></i> interacts with RNA polymerase at <i>P<sub>RM</sub></i>	343
12.16	The <i>cII</i> and <i>cIII</i> genes are needed to establish lysogeny	344
12.17	A poor promoter requires cII protein	345
12.18	Lysogeny requires several events	346
12.19	The <i>cro</i> repressor is needed for lytic infection	347
12.20	What determines the balance between lysogeny and the lytic cycle?	349
12.21	Summary	350

## 13 The replicon

13.1 Introduction	353
13.2 Replicons can be linear or circular	355
13.3 Origins can be mapped by autoradiography and electrophoresis	355
13.4 The bacterial genome is a single circular replicon	356
13.5 Each eukaryotic chromosome contains many replicons	358
13.6 Replication origins can be isolated in yeast	359
13.7 D loops maintain mitochondrial origins	361
13.8 The ends of linear DNA are a problem for replication	362
13.9 Terminal proteins enable initiation at the ends of viral DNAs	363
13.10 Rolling circles produce multimers of a replicon	364
13.11 Rolling circles are used to replicate phage genomes	364
13.12 The F plasmid is transferred by conjugation between bacteria	366
13.13 Conjugation transfers single-stranded DNA	367
13.14 Replication is connected to the cell cycle	368
13.15 The septum divides a bacterium into progeny each containing a chromosome	370
13.16 Mutations in division or segregation affect cell shape	371
13.17 FtsZ is necessary for septum formation	372
13.18 <i>min</i> genes regulate the location of the septum	373
13.19 Chromosomal segregation may require site-specific recombination	374
13.20 Partitioning involves separation of the chromosomes	375
13.21 Single-copy plasmids have a partitioning system	377
13.22 Plasmid incompatibility is determined by the replicon	379
13.23 The ColE1 compatibility system is controlled by an RNA regulator	380
13.24 How do mitochondria replicate and segregate?	382
13.25 Summary	383

## 14 DNA replication

14.1 Introduction	387
14.2 DNA polymerases are the enzymes that make DNA	388
14.3 DNA polymerases have various nuclease activities	389
14.4 DNA polymerases control the fidelity of replication	390
14.5 DNA polymerases have a common structure	391
14.6 DNA synthesis is semidiscontinuous	392
14.7 The $\phi$ X model system shows how single-stranded DNA is generated for replication	393
14.8 Priming is required to start DNA synthesis	394
14.9 Coordinating synthesis of the lagging and leading strands	396
14.10 DNA polymerase holoenzyme has 3 subcomplexes	397
14.11 The clamp controls association of core enzyme with DNA	398
14.12 Okazaki fragments are linked by ligase	399
14.13 Separate eukaryotic DNA polymerases undertake initiation and elongation	400
14.14 Phage T4 provides its own replication apparatus	402
14.15 Creating the replication forks at an origin	404
14.16 Common events in priming replication at the origin	405
14.17 The primosome is needed to restart replication	407
14.18 Does methylation at the origin regulate initiation?	408
14.19 Origins may be sequestered after replication	409
14.20 Licensing factor controls eukaryotic rereplication	411
14.21 Licensing factor consists of MCM proteins	412
14.22 Summary	413

## 15 Recombination and repair

15.1 Introduction	419
15.2 Homologous recombination occurs between synapsed chromosomes	420
15.3 Breakage and reunion involves heteroduplex DNA	422
15.4 Double-strand breaks initiate recombination	424
15.5 Recombining chromosomes are connected by the synaptonemal complex	425

15.6 The synaptonemal complex forms after double-strand breaks	426
15.7 Pairing and synaptonemal complex formation are independent	428
15.8 The bacterial RecBCD system is stimulated by <i>chi</i> sequences	429
15.9 Strand-transfer proteins catalyze single-strand assimilation	431
15.10 The Ruv system resolves Holliday junctions	433
15.11 Gene conversion accounts for interallelic recombination	434
15.12 Supercoiling affects the structure of DNA	436
15.13 Topoisomerases relax or introduce supercoils in DNA	438
15.14 Topoisomerases break and reseal strands	440
15.15 Gyrase functions by coil inversion	441
15.16 Specialized recombination involves specific sites	442
15.17 Site-specific recombination involves breakage and reunion	444
15.18 Site-specific recombination resembles topoisomerase activity	445
15.19 Lambda recombination occurs in an intasome	446
15.20 Repair systems correct damage to DNA	447
15.21 Excision repair systems in <i>E. coli</i>	450
15.22 Base flipping is used by methylases and glycosylases	451
15.23 Error-prone repair and mutator phenotypes	452
15.24 Controlling the direction of mismatch repair	453
15.25 Recombination-repair systems in <i>E. coli</i>	455
15.26 Recombination is an important mechanism to recover from replication errors	456
15.27 RecA triggers the SOS system	457
15.28 Eukaryotic cells have conserved repair systems	459
15.29 A common system repairs double-strand breaks	460
15.30 Summary	462

## 16 Transposons

16.1 Introduction	467
16.2 Insertion sequences are simple transposition modules	468
16.3 Composite transposons have IS modules	470
16.4 Transposition occurs by both replicative and nonreplicative mechanisms	471
16.5 Transposons cause rearrangement of DNA	473
16.6 Common intermediates for transposition	474
16.7 Replicative transposition proceeds through a cointegrate	475
16.8 Nonreplicative transposition proceeds by breakage and reunion	476
16.9 TnA transposition requires transposase and resolvase	478
16.10 Transposition of Tn10 has multiple controls	480
16.11 Controlling elements in maize cause breakage and rearrangements	482
16.12 Controlling elements form families of transposons	483
16.13 Spm elements influence gene expression	486
16.14 The role of transposable elements in hybrid dysgenesis	487
16.15 P elements are activated in the germline	488
16.16 Summary	490

## 17 Retroviruses and retroposons

17.1 Introduction	493
17.2 The retrovirus life cycle involves transposition-like events	493
17.3 Retroviral genes code for polyproteins	494
17.4 Viral DNA is generated by reverse transcription	496
17.5 Viral DNA integrates into the chromosome	498
17.6 Retroviruses may transduce cellular sequences	499
17.7 Yeast Ty elements resemble retroviruses	500
17.8 Many transposable elements reside in <i>D. melanogaster</i>	502
17.9 Retroposons fall into three classes	504
17.10 The Alu family has many widely dispersed members	506
17.11 Processed pseudogenes originated as substrates for transposition	507
17.12 LINES use an endonuclease to generate a priming end	508
17.13 Summary	509

## 18 Rearrangement of DNA

18.1 Introduction	513
18.2 The mating pathway is triggered by pheromone-receptor interactions	514
18.3 The mating response activates a G protein	515
18.4 The signal is passed to a kinase cascade	516
18.5 Yeast can switch silent and active loci for mating type	517
18.6 The <i>MAT</i> locus codes for regulator proteins	519
18.7 Silent cassettes at <i>HML</i> and <i>HMR</i> are repressed	521
18.8 Unidirectional transposition is initiated by the recipient <i>MAT</i> locus	522
18.9 Regulation of HO expression controls switching	523
18.10 Trypanosomes switch the VSG frequently during infection	525
18.11 New VSG sequences are generated by gene switching	526
18.12 VSG genes have an unusual structure	528
18.13 The bacterial Ti plasmid causes crown gall disease in plants	529
18.14 T-DNA carries genes required for infection	530
18.15 Transfer of T-DNA resembles bacterial conjugation	532
18.16 DNA amplification generates extra gene copies	534
18.17 Transfection introduces exogenous DNA into cells	537
18.18 Genes can be injected into animal eggs	538
18.19 ES cells can be incorporated into embryonic mice	540
18.20 Gene targeting allows genes to be replaced or knocked out	541
18.21 Summary	542

## Part 5 The Nucleus

### 19 Chromosomes

19.1 Introduction	545
19.2 Viral genomes are packaged into their coats	546
19.3 The bacterial genome is a nucleoid	549
19.4 The bacterial genome is supercoiled	550
19.5 Eukaryotic DNA has loops and domains attached to a scaffold	551
19.6 Specific sequences attach DNA to an interphase matrix	552
19.7 Chromatin is divided into euchromatin and heterochromatin	553
19.8 Chromosomes have banding patterns	555
19.9 Lampbrush chromosomes are extended	556
19.10 Polytene chromosomes form bands	557
19.11 Polytene chromosomes expand at sites of gene expression	558
19.12 The eukaryotic chromosome is a segregation device	559
19.13 Centromeres have short DNA sequences in <i>S. cerevisiae</i>	560
19.14 The centromere binds a protein complex	561
19.15 Centromeres may contain repetitious DNA	562
19.16 Telomeres have simple repeating sequences	563
19.17 Telomeres seal the chromosome ends	564
19.18 Telomeres are synthesized by a ribonucleoprotein enzyme	565
19.19 Telomeres are essential for survival	566
19.20 Summary	567

### 20 Nucleosomes

20.1 Introduction	571
20.2 The nucleosome is the subunit of all chromatin	572
20.3 DNA is coiled in arrays of nucleosomes	573
20.4 Nucleosomes have a common structure	574
20.5 DNA structure varies on the nucleosomal surface	576
20.6 The periodicity of DNA changes on the nucleosome	577
20.7 The path of nucleosomes in the chromatin fiber	578
20.8 Organization of the histone octamer	579
20.9 The N-terminal tails of histones are modified	581
20.10 Reproduction of chromatin requires assembly of nucleosomes	582
20.11 Do nucleosomes lie at specific positions?	585

20.12 Are transcribed genes organized in nucleosomes?	587
20.13 Histone octamers are displaced by transcription	588
20.14 DNAase hypersensitive sites change chromatin structure	590
20.15 Domains define regions that contain active genes	592
20.16 An LCR may control a domain	593
20.17 Summary	594

### 21 Promoters and enhancers

21.1 Introduction	597
21.2 Eukaryotic RNA polymerases consist of many subunits	599
21.3 Promoter elements are defined by mutations and footprinting	600
21.4 RNA polymerase I has a bipartite promoter	601
21.5 RNA polymerase III uses both downstream and upstream promoters	602
21.6 TF <sub>IIIB</sub> is the commitment factor for pol III promoters	603
21.7 The startpoint for RNA polymerase II	605
21.8 TBP is a universal factor	606
21.9 TBP binds DNA in an unusual way	607
21.10 The basal apparatus assembles at the promoter	608
21.11 Initiation is followed by promoter clearance	610
21.12 A connection between transcription and repair	611
21.13 Short sequence elements bind activators	613
21.14 Promoter construction is flexible but context can be important	614
21.15 Enhancers contain bidirectional elements that assist initiation	615
21.16 Enhancers contain the same elements that are found at promoters	616
21.17 Enhancers work by increasing the concentration of activators near the promoter	617
21.18 Gene expression is associated with demethylation	618
21.19 CpG islands are regulatory targets	620
21.20 Insulators block the actions of enhancers and heterochromatin	621
21.21 Insulators can define a domain	622
21.22 Insulators may act in one direction	623
21.23 Insulators can vary in strength	624
21.24 What constitutes a regulatory domain?	625
21.25 Summary	626

### 22 Activating transcription

22.1 Introduction	631
22.2 There are several types of transcription factors	632
22.3 Independent domains bind DNA and activate transcription	633
22.4 The two hybrid assay detects protein-protein interactions	635
22.5 Activators interact with the basal apparatus	636
22.6 Some promoter-binding proteins are repressors	638
22.7 Response elements are recognized by activators	639
22.8 There are many types of DNA-binding domains	641
22.9 A zinc finger motif is a DNA-binding domain	642
22.10 Steroid receptors are activators	643
22.11 Steroid receptors have zinc fingers	644
22.12 Binding to the response element is activated by ligand-binding	645
22.13 Steroid receptors recognize response elements by a combinatorial code	646
22.14 Homeodomains bind related targets in DNA	647
22.15 Helix-loop-helix proteins interact by combinatorial association	649
22.16 Leucine zippers are involved in dimer formation	651
22.17 Summary	652

### 23 Controlling chromatin structure

23.1 Introduction	657
23.2 Chromatin can have alternative states	658
23.3 Chromatin remodeling is an active process	659
23.4 Nucleosome organization may be changed at the promoter	661
23.5 Histone modification is a key event	662
23.6 Histone acetylation occurs in two circumstances	663
23.7 Acetylases are associated with activators	665

23.8	Deacetylases are associated with repressors	666
23.9	Methylation of histones and DNA is connected	667
23.10	Chromatin states are interconverted by modification	668
23.11	Promoter activation involves an ordered series of events	668
23.12	Histone phosphorylation affects chromatin structure	669
23.13	Heterochromatin propagates from a nucleation event	670
23.14	Some common motifs are found in proteins that modify chromatin	671
23.15	Heterochromatin depends on interactions with histones	672
23.16	Polycomb and trithorax are antagonistic repressors and activators	674
23.17	X chromosomes undergo global changes	676
23.18	Chromosome condensation is caused by condensins	678
23.19	DNA methylation is perpetuated by a maintenance methylase	680
23.20	DNA methylation is responsible for imprinting	681
23.21	Oppositely imprinted genes can be controlled by a single center	683
23.22	Epigenetic effects can be inherited	683
23.23	Yeast prions show unusual inheritance	685
23.24	Prions cause diseases in mammals	687
23.25	Summary	689

## 24 RNA splicing and processing

24.1	Introduction	697
24.2	Nuclear splice junctions are short sequences	698
24.3	Splice junctions are read in pairs	699
24.4	pre-mRNA splicing proceeds through a lariat	701
24.5	snRNAs are required for splicing	702
24.6	U1 snRNP initiates splicing	704
24.7	The E complex can be formed by intron definition or exon definition	706
24.8	5 snRNPs form the spliceosome	707
24.9	An alternative splicing apparatus uses different snRNPs	709
24.10	Splicing is connected to export of mRNA	709
24.11	Group II introns autosplice via lariat formation	710
24.12	Alternative splicing involves differential use of splice junctions	712
24.13	<i>trans</i> -splicing reactions use small RNAs	714
24.14	Yeast tRNA splicing involves cutting and rejoining	716
24.15	The splicing endonuclease recognizes tRNA	717
24.16	tRNA cleavage and ligation are separate reactions	718
24.17	The unfolded protein response is related to tRNA splicing	719
24.18	The 3' ends of polI and polIII transcripts are generated by termination	720
24.19	The 3' ends of mRNAs are generated by cleavage and polyadenylation	721
24.20	Cleavage of the 3' end of histone mRNA may require a small RNA	723
24.21	Production of rRNA requires cleavage events	723
24.22	Small RNAs are required for rRNA processing	724
24.23	Summary	725

## 25 Catalytic RNA

25.1	Introduction	731
25.2	Group I introns undertake self-splicing by transesterification	732
25.3	Group I introns form a characteristic secondary structure	734
25.4	Ribozymes have various catalytic activities	735
25.5	Some group I introns code for endonucleases that sponsor mobility	737
25.6	Some group II introns code for reverse transcriptases	739
25.7	The catalytic activity of RNAase P is due to RNA	740
25.8	Viroids have catalytic activity	740
25.9	RNA editing occurs at individual bases	742
25.10	RNA editing can be directed by guide RNAs	743
25.11	Protein splicing is autocatalytic	746
25.12	Summary	747

## 26 Immune diversity

26.1	Introduction	751
26.2	Clonal selection amplifies lymphocytes that respond to individual antigens	753

26.3	Immunoglobulin genes are assembled from their parts in lymphocytes	754
26.4	Light chains are assembled by a single recombination	757
26.5	Heavy chains are assembled by two recombinations	758
26.6	Recombination generates extensive diversity	759
26.7	Immune recombination uses two types of consensus sequence	760
26.8	Recombination generates deletions or inversions	761
26.9	The RAG proteins catalyze breakage and reunion	762
26.10	Allelic exclusion is triggered by productive rearrangement	765
26.11	Class switching is caused by DNA recombination	766
26.12	Switching occurs by a novel recombination reaction	768
26.13	Early heavy chain expression can be changed by RNA processing	769
26.14	Somatic mutation generates additional diversity in mouse and man	770
26.15	Somatic mutation is induced by cytidine deaminase and uracil glycosylase	771
26.16	Avian immunoglobulins are assembled from pseudogenes	773
26.17	B cell memory allows a rapid secondary response	774
26.18	T cell receptors are related to immunoglobulins	775
26.19	The T cell receptor functions in conjunction with the MHC	777
26.20	The major histocompatibility locus codes for many genes of the immune system	778
26.21	Innate immunity utilizes conserved signaling pathways	781
26.22	Summary	783

## Part 6 Cells

### 27 Protein trafficking

27.1	Introduction	787
27.2	Oligosaccharides are added to proteins in the ER and Golgi	788
27.3	The Golgi stacks are polarized	790
27.4	Coated vesicles transport both exported and imported proteins	790
27.5	Different types of coated vesicles exist in each pathway	792
27.6	Cisternal progression occurs more slowly than vesicle movement	795
27.7	Vesicles can bud and fuse with membranes	796
27.8	The exocyst tethers vesicles by interacting with a Rab	797
27.9	SNARES are responsible for membrane fusion	798
27.10	The synapse is a model system for exocytosis	800
27.11	Protein localization depends on specific signals	800
27.12	ER proteins are retrieved from the Golgi	802
27.13	Brefeldin A reveals retrograde transport	803
27.14	Vesicles and cargos are sorted for different destinations	804
27.15	Receptors recycle via endocytosis	804
27.16	Internalization signals are short and contain tyrosine	806
27.17	Summary	807

### 28 Signal transduction

28.1	Introduction	811
28.2	Carriers and channels form water soluble paths through the membrane	813
28.3	Ion channels are selective	814
28.4	Neurotransmitters control channel activity	816
28.5	G proteins may activate or inhibit target proteins	817
28.6	G proteins function by dissociation of the trimer	818
28.7	Protein kinases are important players in signal transduction	819
28.8	Growth factor receptors are protein kinases	821
28.9	Receptors are activated by dimerization	822
28.10	Receptor kinases activate signal transduction pathways	823
28.11	Signaling pathways often involve protein-protein interactions	824
28.12	Phosphotyrosine is the critical feature in binding to an SH2 domain	825
28.13	Prolines are important determinants in recognition sites	826
28.14	The Ras/MAPK pathway is widely conserved	827
28.15	The activation of Ras is controlled by GTP	829
28.16	A MAP kinase pathway is a cascade	830
28.17	What determines specificity in signaling?	832

28.18	Activation of a pathway can produce different results	834
28.19	Cyclic AMP and activation of CREB	835
28.20	The JAK-STAT pathway	836
28.21	TGF $\beta$ signals through Smads	838
28.22	Summary	839

## 29 Cell cycle and growth regulation

29.1	Introduction	843
29.2	Cycle progression depends on discrete control points	844
29.3	Checkpoints occur throughout the cell cycle	845
29.4	Cell fusion experiments identify cell cycle inducers	846
29.5	M phase kinase regulates entry into mitosis	848
29.6	M phase kinase is a dimer of a catalytic subunit and a regulatory cyclin	849
29.7	Protein phosphorylation and dephosphorylation control the cell cycle	851
29.8	Many cell cycle mutants have been found by screens in yeast	853
29.9	Cdc2 is the key regulator in yeasts	854
29.10	Cdc2 is the only catalytic subunit of the cell cycle activators in <i>S. pombe</i>	855
29.11	<i>CDC28</i> acts at both START and mitosis in <i>S. cerevisiae</i>	856
29.12	Cdc2 activity is controlled by kinases and phosphatases	858
29.13	DNA damage triggers a checkpoint	861
29.14	The animal cell cycle is controlled by many cdk-cyclin complexes	863
29.15	Dimers are controlled by phosphorylation of cdk subunits and by availability of cyclin subunits	864
29.16	RB is a major substrate for cdk-cyclin complexes	866
29.17	G0/G1 and G1/S transitions involve cdk inhibitors	867
29.18	Protein degradation is important in mitosis	868
29.19	Cohesins hold sister chromatids together	869
29.20	Exit from mitosis is controlled by the location of Cdc14	871
29.21	The cell forms a spindle at mitosis	871
29.22	The spindle is oriented by centrosomes	873
29.23	A monomeric G protein controls spindle assembly	874
29.24	Daughter cells are separated by cytokinesis	875
29.25	Apoptosis is a property of many or all cells	876
29.26	The Fas receptor is a major trigger for apoptosis	876
29.27	A common pathway for apoptosis functions via caspases	878
29.28	Apoptosis involves changes at the mitochondrial envelope	879
29.29	Cytochrome <i>c</i> activates the next stage of apoptosis	880
29.30	There are multiple apoptotic pathways	882
29.31	Summary	882

## 30 Oncogenes and cancer

30.1	Introduction	889
30.2	Tumor cells are immortalized and transformed	890
30.3	Oncogenes and tumor suppressors have opposite effects	892
30.4	Transforming viruses carry oncogenes	893
30.5	Early genes of DNA transforming viruses have multifunctional oncogenes	893
30.6	Retroviruses activate or incorporate cellular genes	895
30.7	Retroviral oncogenes have cellular counterparts	896
30.8	Quantitative or qualitative changes can explain oncogenicity	898
30.9	Ras oncogenes can be detected in a transfection assay	899
30.10	Ras proto-oncogenes can be activated by mutation at specific positions	900
30.11	Nondefective retroviruses activate proto-oncogenes	901
30.12	Proto-oncogenes can be activated by translocation	902
30.13	The Philadelphia translocation generates a new oncogene	904
30.14	Oncogenes code for components of signal transduction cascades	905
30.15	Growth factor receptor kinases can be mutated to oncogenes	907
30.16	Src is the prototype for the proto-oncogenic cytoplasmic tyrosine kinases	909
30.17	Src activity is controlled by phosphorylation	910
30.18	Oncoproteins may regulate gene expression	912
30.19	RB is a tumor suppressor that controls the cell cycle	915
30.20	Tumor suppressor p53 suppresses growth or triggers apoptosis	917

30.21	p53 is a DNA-binding protein	919
30.22	p53 is controlled by other tumor suppressors and oncogenes	921
30.23	p53 is activated by modifications of amino acids	922
30.24	Telomere shortening causes cell senescence	923
30.25	Immortalization depends on loss of p53	925
30.26	Different oncogenes are associated with immortalization and transformation	926
30.27	p53 may affect ageing	929
30.28	Genetic instability is a key event in cancer	930
30.29	Defects in repair systems cause mutations to accumulate in tumors	931
30.30	Summary	932

## 31 Gradients, cascades, and signaling pathways

31.1	Introduction	939
31.2	Fly development uses a cascade of transcription factors	940
31.3	A gradient must be converted into discrete compartments	941
31.4	Maternal gene products establish gradients in early embryogenesis	943
31.5	Anterior development uses localized gene regulators	945
31.6	Posterior development uses another localized regulator	946
31.7	How are mRNAs and proteins transported and localized?	948
31.8	How are gradients propagated?	949
31.9	Dorsal-ventral development uses localized receptor-ligand interactions	950
31.10	Ventral development proceeds through Toll	951
31.11	Dorsal protein forms a gradient of nuclear localization	953
31.12	Patterning systems have common features	955
31.13	TGF $\beta$ /BMPs are diffusible morphogens	956
31.14	Cell fate is determined by compartments that form by the blastoderm stage	957
31.15	Gap genes are controlled by bicoid and by one another	959
31.16	Pair-rule genes are regulated by gap genes	960
31.17	Segment polarity genes are controlled by pair-rule genes	961
31.18	Wingless and engrailed expression alternate in adjacent cells	963
31.19	The wingless/wnt pathway signals to the nucleus	964
31.20	Complex loci are extremely large and involved in regulation	965
31.21	The <i>bithorax</i> complex has <i>trans</i> -acting genes and <i>cis</i> -acting regulators	968
31.22	The homeobox is a common coding motif in homeotic genes	972
31.23	Summary	975

Glossary	981
----------	-----

Index	1003
-------	------