MBoC6 MEDICAL TOPICS GUIDE

KEY:

- Medical conditions are in dark red.
- Organisms, viruses, and other infectious agents are in orange.
- Nucleic acid sequences, DNA, RNA, genes, and chromosomes are in dark blue.
- Proteins, amino acids, and protein-containing molecular complexes are in green.
- In Chapters 20 and 23 only, concept headings are included as grid entries, in their original lighter blue. The red/orange/dark-blue/green color-coding is NOT used within the concept headings.

Chapter	Page	TOPIC
		PART I - INTRODUCTION TO THE CELL
01	001	CELLS AND GENOMES
1	13	Fig 1-14 ***Vibrio cholerae*** and ***Escherichia coli*** are two examples of prokaryotes that are important human pathogens
1	19	**Horizontal gene transfers** occur frequently between different species of prokaryotes, producing new and sometimes dangerous strains. Examples include penicillin-resistant strains of ***Neisseria gonorrhoeae*** the bacterium that causes **gonorrhea**.
1	21	Genetic and biochemical studies of **mutant organisms** help reveal gene functions.
1	32	The yeast ***Saccharomyces cerevisiae*** serves as a minimal **model eukaryote**.
1	39	**Model organisms** play a key part in revealing universal genetic mechanisms of animal development.
02	43	CELL CHEMISTRY AND BIOENERGETICS
2	86	**Essential amino acids**: about half of the 20 amino acids found in proteins cannot be synthesized by vertebrates and are therefore an essential part of the vertebrate diet.
2	88	Metabolism is highly organized and regulated, and **metabolic homeostasis** is amazingly stable.
03	109	PROTEINS
3	119	**Protein function** depends upon correct overall conformation, which in turn depends on correct amino acid sequence. The change of even a few atoms in one amino acid can sometimes disrupt the structure of the whole molecule.
3	121	Amino acid **sequence relationships** first indicated that certain genes that cause mammalian cells to become cancerous encode protein kinases (discussed in Chapter 20).
3	130-131	**Amyloid fibrils** can form from many proteins. They feature in some normal cell functions, but can also contribute to human diseases when not controlled. Amyloid fibrils cause pathologies in several sites in the body, most severe being **neurodegenerative diseases**, for example, **Alzheimer's** and **Parkinson's** diseases.
3	130-131	**Prion diseases** are a special type of 'infectious' amyloid pathologies. A set of closely related diseases—**scrapie** in sheep, **Creutzfeldt–Jakob disease (CJD)**

		in humans, **Kuru** in humans, and **bovine spongiform encephalopathy (BSE)** "mad cow disease" in cattle—are caused by a misfolded, aggregated form of a particular protein called **PrP** (for prion protein).
	132	Figure 3–33 Certain protein aggregates cause **prion diseases**.
3	132	New drugs that specifically disrupt the **fibrous networks formed by bacterial amyloids** have promise for treating human infections.
3	144	The fit between an **enzyme** and its **substrate** needs to be precise. A small genetic change can have a profound effect.
3	147	Many **vitamins** and their derivatives are critical **coenzymes** for human cells. Some cannot be synthesized by humans and must therefore be part of the diet.
3	147	Table 3–2 Many **vitamin derivatives** are critical **coenzymes** for human cells.
3	148	The efficiency of **enzymes** in accelerating chemical reactions is crucial to the maintenance of life.
3	155	The **Src family of protein kinases**, if deregulated, can give rise to **sarcomas**.
3	163	The study of **ABC transporters** is of intense interest in clinical medicine, because the overproduction of proteins in this class contributes to the **drug resistance** of tumor cells to chemotherapeutic drugs.
3	163	PROBLEM 3-12 **Rous sarcoma virus (RSV)** carries a **Src oncogene**, which encodes a continuously active protein tyrosine kinase that leads to unchecked cell proliferation.
		PART II - BASIC GENETIC MECHANISMS
04	173	DNA, CHROMOSOMES, AND GENOMES
4	182	Chromosome painting: changes in the pattern of chromosome painting can be used to detect **inherited chromosome abnormalities** and to reveal the **chromosome rearrangements** that occur in cancer cells as they progress to malignancy (discussed in Chapter 20).
4	224	Figure 4–71 In humans, mutation of the **huntingtin gene** causes **Huntington's disease**, an inherited neurodegenerative disorder.
4	233-234	**SNPs** and **CNVs**: Even a single nucleotide change in a protein can cause a serious disease, as for example in sickle-cell anemia, which is caused by a mutation in hemoglobin. Also, **gene dosage**—a doubling or halving of the copy number of some genes—can have a profound effect on development. Some of the many differences between any two human beings will have substantial effects on human health, physiology, behavior, and physique.
4	234	The genomes of any two humans will differ from each other both because of nucleotide substitutions (**single-nucleotide polymorphisms**, or **SNPs**) and because of inherited DNA gains and DNA losses that cause **copy number variations (CNVs)**. Understanding the effects of these differences will improve both medicine and our understanding of human biology.
05	237	DNA REPLICATION, REPAIR, AND RECOMBINATION
5	237	A **mutation** can destroy an organism if it occurs in a vital position in the DNA sequence.

5	238-239	**Nucleotide changes** in somatic cells can give rise to variant cells, some of which proliferate rapidly at the expense of the rest of the organism. In an extreme case, the result is **cancer** (discussed in Chapter 20).
5	250-251	Individuals who inherit one defective copy of a **mismatch repair gene** (along with a functional gene on the other copy of the chromosome) have a marked **predisposition** for certain types of cancers.
5	250-251	Most cancers arise in cells that have accumulated **multiple mutations**, and cells deficient in **mismatch proofreading** therefore have a greatly enhanced chance of becoming cancerous.
5	264	**Replicative cell senescence** resulting from **telomere depletion** could, in theory, provide a safeguard against the uncontrolled cell proliferation of abnormal cells in somatic tissues, thereby helping to protect us from cancer.
5	265	Humans with the genetic disease **dyskeratosis congenita** carry one functional and one nonfunctional copy of the telomerase RNA gene; they have prematurely shortened telomeres and typically die of progressive bone marrow failure. They also develop lung scarring and liver cirrhosis and show abnormalities in various epidermal structures including skin, hair follicles, and nails.
5	266	**DNA repair** is vital to genetic stability, and many human diseases are linked with decreased DNA repair (Table 5–2).
5	266	Defects in a human gene whose product normally functions to repair the mismatched base pairs resulting from DNA replication errors can lead to an inherited **predisposition to cancers** of the colon and some other organs
5	267	In **xeroderma pigmentosum (XP)**, individuals have an extreme sensitivity to ultraviolet radiation because they are unable to repair certain DNA photoproducts. This repair defect results in an increased mutation rate that leads to serious skin lesions and an increased susceptibility to skin cancers.
5	267	Mutations in the ***Brca1*** and ***Brca2* genes** compromise **homologous recombination DNA repair**, and are a cause of hereditary breast and ovarian cancer.
5	266	Table 5–2 Some inherited human syndromes with **defects in DNA repair**. [See table.]
5	280-281	Errant homologous recombination may result, though rarely, in **loss of heterozygosity**. This in turn is a critical step in the formation of many cancers (discussed in Chapter 20).
5	281-282	Mutations in the components that carry out and regulate homologous recombination are responsible for several inherited forms of cancer. Mutant forms of the **Brca1** or **Brca2 proteins**, for example, lead to a greatly increased frequency of breast cancers.
5	290	**Transposition** has a key role in the life cycle of many viruses. Most notable are the retroviruses, which include the human AIDS virus, HIV.
	288	A large fraction of the human genome is composed of **nonretroviral retrotransposons**, a few of which still retain the ability to move, and in doing so may result in human disease. A type of **hemophilia**, for instance, results from an L1 insertion into the gene encoding the blood-clotting

		protein Factor VIII (see Figure 6–24).
06	299	HOW CELLS READ THE GENOME: FROM DNA TO PROTEIN
6	300-301	Figure 6-2: Inherited human conditions that are caused by **mutations** of genes in the **X chromosome** include: • disorders of cognition and movement consequent to **neuron demyelination** (*Abcd1* gene) • **Incontinentia pigmenti** • **Hemophilia A** (Factor VIII gene) Most of these conditions affect only males; females that inherit one of these defective genes are often asymptomatic.
6	318	From figure 6-24: The most prevalent form of **hemophilia** results from mutations in the Factor VIII gene.
6	323-324	Mutations that affect **RNA splicing** can be severely detrimental to the organism. Examples of human pathologies caused or exacerbated by aberrant splicing include **β thalassemia**, **cystic fibrosis**, **frontotemporal dementia**, **Parkinson's disease**, **retinitis pigmentosa**, **spinal muscular atrophy**, **myotonic dystrophy**, **premature aging**, and **cancer**.
6	351	Fungally-produced inhibitors of prokaryotic protein synthesis are useful as **antibiotics**, and humans can take high dosages of some of these compounds without undue toxicity.
6	351	Figure 6–75: Three **mechanisms of antibiotic activity**: Hygromycin B induces errors in **translation**, spectinomycin blocks t-RNA **translocation**, and streptogramin B prevents **elongation** of nascent peptides.
6	352	TABLE 6-4 The specific **antibiotic effects** of the following inhibitors of protein or RNA synthesis are listed: Tetracycline, Streptomycin, Chloramphenicol, Erythromycin, Rifamycin, Puromycin, Actinomycin D, Cycloheximide, Anisomycin, α-Amanitin.
6	353	**Nonsense-mediated surveillance decay** serves as a quality control mechanism to prevent translation of damaged mRNAs, thus mitigating the symptoms of many inherited human diseases.
6	355	**Molecular chaperones** help guide the folding of most proteins, thus preventing the formation of protein aggregates that might otherwise cause severe pathologies.
6	367	Problem 6-10: (answer) **Single-nucleotide substitution** in a gene is often harmless, but if it does change the amino acid coded for, the consequences may be deleterious or benign.
6	367	Problem 6-11: (answer) A **broken mRNA** when translated could produce a harmful protein.
07	369	CONTROL OF GENE EXPRESSION
7	405	One reflection of the importance of **DNA methylation** to humans is the widespread involvement of "incorrect" DNA methylation patterns in **cancer**

		progression (discussed in Chapter 20).
7	410	A **gene-dosage compensation mechanism** operates to ensure the correct ratio of X chromosome to autosome gene products. Mutations that interfere with this dosage compensation are generally lethal.
7	414	HIV highjacks a normal **transcription attenuation mechanism** in infected cells, thus promoting transcription of the viral genome.
7	420	Figure 7–62 Once the HIV genome is incorporated into the human genome, it is transcribed into a large RNA transcript that can be spliced in many ways, giving rise to different viral proteins.
7	420	Regulation of **nuclear export by Rev** has important consequences for HIV growth and pathogenesis.
7	421	Figure 7–63 The **HIV Rev protein** regulates nuclear export.
7	426	Some viruses use **internal ribosome entry sites (IRESs)** to get their own mRNA molecules translated, simultaneously blocking normal translation of host mRNAs.
7	429	**Noncoding RNAs** play widespread roles in regulating gene expression and in protecting the genome from viruses and transposable elements.
7	431	**RNA interference** machinery doubles as a cell defense mechanism, helping to keep transposable elements and viruses in check.
7	437	Problem 7-6 The **patterns of mRNA abundance** are so characteristic of cell type that they can be used to determine the tissue of origin of cancer cells, even though the cells may have metastasized to different parts of the body.
		PART III - WAYS OF WORKING WITH CELLS
08	439	ANALYZING CELLS, MOLECULES, AND SYSTEMS
8	444	**Monoclonal antibodies** produced by hybridoma cell lines provide useful cell biology tools, and aid the diagnosis and treatment of certain diseases, including rheumatoid arthritis and cancer.
8	474	**PCR (polymerase chain reaction)** can be used to detect invading pathogens at very early stages of infection.
8	475	Figure 8–38 **PCR** can detect trace amounts of virus in a sample of blood or tissue. HIV and many other viruses that infect humans are now detected in this way.
8	479	Rapid **second-generation DNA sequencing** technologies have had major impacts on all branches of biology and medicine, allowing, for example, the identification of mutations that increase the risk of various diseases, from cancer to autism.
8	493	**Monogenic (Mendelian) mutations** that give rise to clearly defined abnormalities such as albinism, hemophilia, or congenital deafness, can often be easily identified, and individuals who inherit the causative mutation will exhibit the abnormality irrespective of environmental factors such as diet or exercise.
8	493	**Multigenic (non-Mendelian) conditions** — such as diabetes, coronary

		artery disease, rheumatoid arthritis, and depression — have complex genetic roots, and environmental factors often have strong influences on the severity of the disorder.
8	494	A number of different **loss-of-function mutations**, each individually rare, have been found to increase greatly the predisposition to **autism** and **schizophrenia**.
8	497	Figure 8–54 **Trichothiodystrophy** in humans — a premature aging condition characterized by brittle hair, skeletal abnormalities, and a very reduced life expectancy — is mimicked in transgenic mice that have been engineered to express a mutant DNA helicase.
8	506	**Recombinant DNA** methods contribute greatly to human health, in areas including: • development of pharmaceuticals (e.g. insulin, human growth hormone, blood-clotting factors, and interferon) • prediction of disease susceptibility • prediction of drug response • genetic targeting of anticancer treatments • identification of deleterious mutations • creation of transgenic animals
8	526	Problem 8–14 **Gain-of-function mutations** and **dominant-negative mutations** are both usually dominant.
8	526	Problem 8–15 The quest to understand and alleviate human disease is a principal driving force in biomedical research. The study of **diabetes** is an ancient example.
09	529	VISUALIZING CELLS
9	562	**Combined images** from multiple **microscopy techniques** reveal the detailed structures of biomedical entities, from individual molecules to whole cells and tissues.
		PART IV - INTERNAL ORGANIZATION OF THE CELL
10	565	MEMBRANE STRUCTURE
10	576	Some **glycolipids** provide entry points for bacterial toxins and viruses, for example **cholera toxin** and **polyomaviruses**.
10	591	Humans with genetic **spectrin abnormalities** have fragile spherical red cells, and are anemic; the severity of the anemia increases with the degree of spectrin deficiency.
11	597	MEMBRANE TRANSPORT OF SMALL MOLECULES AND THE ELECTRICAL PROPERTIES OF MEMBRANES
11	598-599	Mutations in **membrane transport proteins** cause various inherited diseases; **cystinuria** (causing kidney stones) is one example.
11	610	The **multidrug resistance (MDR) protein**, also called **P-glycoprotein**, is an ABC transporter that is present at elevated levels in many human cancer cells, and makes cells simultaneously resistant to a variety of chemically unrelated cytotoxic drugs that are widely used in cancer chemotherapy.
11	610	Some strains of ***Plasmodium falciparum***, which causes **malaria**, have

		developed resistance to the antimalarial drug **chloroquine** by amplifying a gene encoding an ABC transporter that pumps out the chloroquine.
11	611	**Cystic fibrosis** is caused by a mutation in the gene encoding **CFTR (cystic fibrosis transmembrane conductance regulator protein)**, a member of the ABC transporter family.
11	611	[The three previous entries could be cut and replaced with this summary:] The **superfamily of ABC transporters** is especially important clinically. It includes proteins that are responsible for cystic fibrosis, for drug resistance in both cancer cells and malaria-causing parasites, and for pumping pathogen-derived peptides into the ER for cytotoxic lymphocytes to reorganize on the surface of infected cells.
11	625	**Multiple sclerosis** is a demyelinating disease in which the immune system destroys myelin sheaths in some regions of the central nervous system, thus impairing nerve impulse propagation.
11	627	Humans who inherit mutant genes encoding **ion channels** can suffer from a variety of nerve, muscle, brain, or heart diseases, depending in which cells the channel encoded by the mutant gene normally functions. Mutations affecting voltage-gated Na+ channels in skeletal muscle cells, can cause **myotonia**; mutations that affect Na+ or K+ channels in the brain can cause **epilepsy**.
11	627	Many **psychoactive drugs** act at synapses. Categories include • muscle relaxants used during surgery (curare) • anti-insomnia drugs • anti-anxiety drugs • anti-depression drugs • anti-schizophrenia drugs • other mental illness conditions
12	641	INTRACELLULAR COMPARTMENTS AND PROTEIN SORTING
12	662	**Mitochondria** containing mutant forms of **hsp70** fail to import precursor proteins into the matrix space.
13	695	INTRACELLULAR MEMBRANE TRAFFIC
13	704	Human mutations in genes encoding **COPII** and other packaging proteins result in **collagen defects** with severe consequences, such as skeletal abnormalities and other developmental defects.
	709	Some viruses, such as HIV, enter a cell by **fusion** of the viral membrane with the plasma membrane of the cell. Other viruses, such as the influenza virus, first enter the cell by **receptor-mediated endocytosis**.
13	712	Humans with an inherited lack of a particular cargo-receptor **lectin** have lowered serum levels of **blood-clotting Factors V and VIII**, and therefore bleed excessively.
13	712	The predominant mutations that cause **cystic fibrosis** result in a slightly misfolded plasma membrane protein that would function normally, but quality control mechanisms result in it being retained in the ER and degraded.
13	726	**Autophagy** degrades unwanted proteins and organelles during normal cell growth, in development, and also in adaptive responses to stresses such as

		starvation and **infection**.
13	726	**Defects in autophagy** may contribute to diseases ranging from infectious disorders to neurodegeneration and cancer.
13	726	**Selective autophagy** mediates the degradation of unwanted organelles, and can also be used to destroy invading microbes.
13	727	Mutations in the protein kinase Pink1 or the ubiquitin ligase Parkin cause a form of **early-onset Parkinson's disease**.
13	728	Genetic defects that affect one or more of the lysosomal hydrolases cause a number of human **lysosomal storage diseases**. Two examples are **Hurler's disease** and **inclusion-cell disease (I-cell disease)**.
	733	If cholesterol uptake into cells is blocked, **cholesterol** accumulates in the blood and can contribute to the formation of **atherosclerotic plaques**. There is a strong genetic predisposition for atherosclerosis.
	733	The receptor-mediated endocytosis pathway for **cholesterol uptake** is disrupted in individuals who inherit defective genes encoding LDL receptors.
13	737	Mutant cells compromised in **ESCRT** (endosomal sorting complexes required for transport) function feature overactive receptors and prolonged signaling, which can lead to uncontrolled cell proliferation and cancer.
13	739	**Macrophages** and **neutrophils** ingest invading microorganisms to defend us against infection. Macrophages also scavenge senescent cells and cells that have died by apoptosis.
14	753	ENERGY CONVERSION: MITOCHONDRIA AND CHLOROPLASTS
14	760 ¶2	Cancer cells are frequently mutated in ways that enhance **growth and proliferation pathways**, as part of their program of **abnormal growth** (see Figure 20–26).
14	760	Nuclear **genome instability**, a hallmark of cancer, is sometimes linked to decreased function in cell proteins that contain iron–sulfur clusters.
14	804	The parasites ***Plasmodium falciparum*** and ***Leishmania tarentolae***, which spend most of their life cycles inside cells of their host organisms, have retained only two or three **mitochondrially-encoded proteins**.
14	804	The mitochondrial DNA in ***Plasmodium falciparum*** (the human **malaria** parasite) has less than 6000 nucleotide pairs.
14	807	Mutations in **mitochondrial DNA** can cause numerous inherited diseases, some of them severe; muscle and the nervous system are most at risk.
14	807	**Inheritance of mitochondrial diseases**: Diseases arising from mutations in mitochondrial DNA pass from affected mothers to both daughters and sons, with the daughters but not the sons producing children with the disease.
14	808	Some mitochondrial diseases are caused by mutations in nuclear-encoded mitochondrial proteins; these diseases follow regular **Mendelian inheritance** patterns.
14	808	There is typically a 100-fold higher occurrence of deletions and point mutations in mitochondrial DNA than in nuclear DNA, and the **accumulation of mutations in mitochondrial DNA** contributes to both aging and disease.

14		Problem 14-8 **Dinitrophenol**, an inhibitor of oxidative phosphorylation, was once promoted as a diet drug to aid in weight loss, but is no longer prescribed because its use led to several deaths.
15	813	CELL SIGNALLING
15	834	**Stimulatory G proteins (Gs)** and **inhibitory G proteins (Gi)**, are both targets for medically important **bacterial toxins**. Examples include **cholera toxin** (causing cholera) and **pertussis toxin** (causing whooping cough).
15	834	Individuals with genetic defects in the **G protein subunit Gsα** show decreased responses to certain hormones, resulting in metabolic abnormalities, abnormal bone development, and mental retardation.
15	837-838	**Prostaglandins** have many biological activities, including roles in pain and inflammatory responses; many **anti-inflammatory drugs** (such as aspirin, ibuprofen, and cortisone) act in part by inhibiting their synthesis.
15	845	Humans with a mutation that inactivates the gene encoding **rhodopsin kinase (RK)** have a prolonged light response.
15	847	**Nitroglycerine**, which is converted to **nitric oxide (NO)** and is a blood vessel relaxant, has been used for about 100 years to treat patients with **angina**.
15	847	The drug **Viagra®** and its relatives increase the amount of time that penile blood vessels remain relaxed, thereby increasing the time that the penis remains erect.
	853	Mutations that inactivate c-Cbl-dependent receptor tyrosine kinase **(RTK) down-regulation** cause prolonged **RTK signaling** and thereby promote the development of cancer.
15	854	Hyperactive mutant forms of the GTPase **Ras** promote the development of cancer, and are present in 30% of human tumors.
15	859	Mutations in the gene encoding **PTEN** are found in many cancers: by prolonging signaling by PI 3-kinase, they promote uncontrolled cell growth.
15	861	Figure 15–54 The genetic disease **tuberous sclerosis** is associated with benign tumors that contain abnormally large cells.
15	864	The signal protein **Interferon-α (IFNα)** increases cell resistance to viral infection
15	865	Proteins belonging to the **transforming growth factor-β (TGFβ) superfamily** regulate a wide range of biological functions, including, in adults, tissue repair and immune regulation.
15	867-868	When the **Delta-Notch signaling** process is defective, a huge and lethal excess of neural cells is produced at the expense of epidermal cells.
15	868	Mutations in the gene encoding **Presenilin**, an essential protease complex subunit, are a frequent cause of **early-onset, familial Alzheimer's** disease, a form of presenile dementia. The protease complex is thought to contribute to this and other forms of Alzheimer's disease.
15	870	The gene encoding the scaffold protein **adenomatous polyposis coli (APC)** is often mutated in a type of benign tumor (**adenoma**) of the colon; the tumor can eventually become malignant.

15	871	Mutations of the ***Apc* gene** promote the development of cancer, and occur in 80% of human colon cancers (discussed in Chapter 20).
15	873	The **NFκB proteins** are central to many stressful, inflammatory, and innate immune responses. An excessive or inappropriate **inflammatory response** can also damage tissue and cause severe pain, and **chronic inflammation** can lead to cancer. Excessive **NFκB signaling** is found in a number of human cancers.
16	889	THE CYTOSKELETON
16	897	The bacterial actin homolog **ParM** is encoded by a gene on the bacterial plasmid that also carries genes responsible for **antibiotic resistance** and causes the spread of **multidrug resistance (MDR)** in epidemics.
16	904	**Polymer-stabilizing** and **polymer-destabilizing chemicals** both inhibit the functions of **actin** filaments, and are dramatically toxic to cells. Such compounds include cytochalasins, Latrunculin, and phalloidins.
16	913	Figure 16–24 **Periventricular heterotopia**, caused by mutation in the filamin A gene, features neurons that fail to migrate to the cortex during brain development. The intelligence of affected individuals is frequently normal or only mildly compromised, and the major clinical syndrome is **epilepsy**.
16	913	Bacteria can hijack the host **actin cytoskeleton**; certain bacteria and viruses use components of the host-cell actin cytoskeleton to move through the cytoplasm.
16	913	***Listeria monocytogenes*** causes a rare but serious form of food poisoning.
16	917	Figure 16–29 **Rigor mortis**, the rigidity of death, results when the heads of the myosin molecules that normally 'walk' along actin filaments become locked tightly onto actin filaments in the 'rigor conformation'.
16	923	Subtle changes in **cardiac-specific contractile proteins**—changes that would not cause any noticeable consequences in other tissues—can cause serious heart disease.
16	925	Mutations in a particular human ***β -tubulin* gene** give rise to a paralytic eye-movement disorder due to loss of ocular nerve function.
16	925	Numerous human neurological diseases have been linked to specific mutations in different **tubulin genes**.
16	929	**Polymer-stabilizing** and **polymer-destabilizing drugs** both inhibit **microtubule** functions, and preferentially kill dividing cells. Examples include colchicine, nocodazole, and Taxol.
16	929	Some polymer-stabilizing and polymer-destabilizing drugs efficiently kill certain types of human tumor cells, although not without toxicity to rapidly dividing normal cells. **Taxol** in particular has been widely used to treat cancers of the breast and lung, and it is frequently successful in treatment of tumors that are resistant to other chemotherapeutic agents.
16	935	The tubulin-sequestering protein **Stathmin** (also called **Op18**) has been implicated in the regulation of both cell proliferation and cell death.
16	939	Many viruses take advantage of **microtubule motor-based transport** during infection and use **kinesin** to move from their site of replication and

		assembly to the plasma membrane, from which they are poised to infect neighboring cells.
16	939	A particular **amino-acid motif** that mediates binding to **kinesin-1 light chain** and transport along microtubules is present in an outer-membrane protein of Vaccinia virus and is also found in over 450 human proteins, one-third of which are associated with human diseases.
16	939	Defects in **microtubule-based transport** have been linked to human neurological diseases such as **lissencephaly**, or smooth brain, in which cells fail to migrate to the cerebral cortex of the developing brain.
16	942	In humans, hereditary defects in axonemal dynein cause **primary ciliary dyskinesia** or **Kartagener's syndrome**.
16	943	**Bardet-Biedl syndrome** produces defects in intraflagellar transport (IFT), the cilium, or the basal body; and patients with the disorder suffer multiple consequences including inability to smell, retinal degeneration, hearing loss, polycystic kidney disease, diabetes, obesity, and polydactyly.
16	946	The diversity in **keratins** is clinically useful in the diagnosis of epithelial cancers (carcinomas), as the particular set of keratins expressed gives an indication of the epithelial tissue in which the cancer originated.
16	947	Mutations in keratin genes cause several human genetic diseases, including **epidermolysis bullosa simplex**, and other types of **blistering diseases** of the mouth, esophageal lining, and cornea of the eye.
16	947	The usually fatal neurodegenerative disease **amyotrophic lateral sclerosis (ALS,** or **Lou Gehrig's disease)** is associated with an accumulation and abnormal assembly of neurofilaments in motor neurons, although a causative link between neurofilament pathology and ALS has not been firmly established.
16	948	In humans, mutations in the genes encoding the intermediate filament protein **desmin** are associated with various forms of **muscular dystrophy** and **cardiac myopathy**.
16	949	Mutations in the gene coding for **plectin** (a cross-linking plakin protein) cause a devastating human disease that combines epidermolysis bullosa, muscular dystrophy, and neurodegeneration.
16	951	**Cell crawling** plays a role in many cancers: cells in a primary tumor invade neighboring tissues, crawl into blood vessels or lymph vessels, and emerge at other sites in the body to form metastases.
16	957	Human patients deficient in the WASp protein family suffer from **Wiskott-Aldrich Syndrome**, a severe form of immunodeficiency.
16	957	Neutrophils demonstrate **chemotactic movement** toward a source of bacterial infection.
17	963	THE CELL CYCLE
17	973	**Table 17–2** The cell cycle regulatory protein **p16** is frequently inactivated in cancer.
17	1010	**Down syndrome** mental retardation results from a nondisjunction event that causes the developing individual to have an extra copy of **chromosome 21**

17	1014	An **accumulation of genetic damage** in cells that lack the **DNA damage response** leads to an increased frequency of cancer-promoting mutations.
17	1014	Mutations in the ***p53* gene** occur in at least half of all human cancers (discussed in Chapter 20).
17	1015	**Ataxia telangiectasia** is caused by a defect in the protein kinase **ATM (ataxia telangiectasia mutated)**; patients with this disease are very sensitive to x-rays and suffer from increased rates of cancer.
17	1015	The **apoptosis**-promoting function of p53 is apparently most important in protecting us against cancer.
17	1016	Most cancer cells have regained the ability to maintain **telomere function**; as a result, they do not undergo **replicative cell senescence**.
17	1016	Abnormal **proliferation signals** cause **cell-cycle arrest** or **apoptosis**, except in cancer cells
17	1016	Many of the components of **mitogenic signaling pathways** are encoded by genes that, if mutated, contribute to the development of cancer. Such genes include those coding for **Ras** and **Myc**.
17	1016	Cancer-promoting mutations may stimulate normal cells to increase **Arf** and **p53** production, thereby preventing further cell division; but this protective system is often inactivated in cancer cells.
17	1019	Problem 17-13 **Down syndrome (trisomy 21)** and **Edwards syndrome (trisomy 18)** are the most common autosomal trisomies seen in human infants. The most common trisomy – **trisomy 16** –occurs in more than 1% of pregnancies, but the affected fetuses do not survive.
18	1021	CELL DEATH
18	1021	Either excessive or insufficient **apoptosis** can contribute to human disease.
18	1022	After helping to destroy invading infectious microbes, most of the **lymphocytes** activated by an infection are subsequently eliminated by apoptosis.
18	1022	**DNA damage** can produce cancer-promoting mutations; cells have various ways of detecting DNA damage, and undergo apoptosis if they cannot repair it.
18	1031	**Excessive apoptosis**: There are many human disorders in which excessive numbers of cells undergo apoptosis and thereby contribute to tissue damage. After heart attacks and strokes, for instance, some of the less affected cells die apparently needlessly by apoptosis.
18	1031	Mutations that prevent the normal death of some lymphocytes cause these cells to accumulate in excessive numbers in the spleen and lymph —— leading in many cases to **autoimmune disease**.
18	1033	Problem 18–3 One important role of **Fas** and **Fas ligand** is to mediate the elimination of tumor cells by **killer lymphocytes**.
18	1033	When tumor cells overproduce so-called **decoy receptors**, they insulate themselves against Fas-mediated attack by killer lymphocytes.
18	1033	When human cancer cells are exposed to **ultraviolet (UV) light** at 90

		mJ/cm2, most of the cells undergo apoptosis within 24 hours.
18	1033	**Autoimmune lymphoproliferative syndrome (ALPS)** is associated with dominant mutations in **Fas**.
		PART V - CELLS IN THEIR SOCIAL CONTEXT
19	1035	CELL JUNCTIONS AND THE EXTRACELLULAR MATRIX
19	1035	Defects in the apparatus of **cell junctions** and the **extracellular matrix** underlie an enormous variety of diseases.
19	1042	**Epithelial–mesenchymal transitions** occur as pathological events in cancer.
19	1042	Most cancers originate in epithelia but become dangerously **malignant** only when the cancer cells escape from the epithelium of origin and invade other tissues.
19	1046	In some forms of the skin disease **pemphigus**, affected individuals make antibodies against one of their own desmosomal cadherin proteins, resulting in a severe blistering of the skin, with leakage of body fluids into the loosened epithelium.
19	1049	A mutation in the gene encoding **claudin** results in excessive loss of Mg2+ in the urine.
19	1055	At sites of **inflammation**, endothelial cells switch on expression of **selectins** that recognize the oligosaccharides on white blood cells and platelets, flagging the cells down to help deal with the local emergency.
19	1058	A genetic defect in the production of **glycosaminoglycans (GAGs)** leads to dermatan sulfate disaccharide deficiency. Affected individuals have a short stature, a prematurely aged appearance, and generalized defects in their skin, joints, muscles, and bones.
19	1063	Table 19–2 Mutant phenotypes of **collagen** family proteins cause severe **connective tissue pathologies**, including: osteogenesis imperfecta, dwarfism (chondrodysplasia), Ehlers–Danlos syndrome, myopia, blindness, osteoarthritis, glomerulonephritis), deafness, skin blistering, detached retina, and hydrocephalus.
19	1066	Mutations in the fibrillin gene result in **Marfan's syndrome**.
19	1069	Genetic defects in certain basal lamina proteins or in a special type of collagen cause **junctional epidermolysis bullosa**, a severe and sometimes lethal blistering condition.
19	1071	**Alport syndrome**, a hereditary kidney disorder, is caused by mutations in a type IV collagen gene.
	1071	When cells in tissues such as muscles, nerves, and epithelia are damaged or killed, the **basal lamina** often survives and provides a scaffold along which regenerating cells can migrate.
19	1072	After a nerve or muscle injury, the basal lamina at the **synapse** has a central role in reconstructing the synapse at the correct location.
19	1072	Defects in components of the basal lamina at the synapse are responsible for some forms of **muscular dystrophy**.
19	1076	Figure 19–56

		Defects in any of the components of **hemidesmosomes** can give rise to a blistering disease of the skin. One example is the autoimmune disease **bullous pemphigoid**.
19	1076	**Integrin defects** are responsible for many genetic pathologies. Examples listed in Table 19-3 include: embryo death; blood vessel defects, somites, neural crest; impaired leucocyte recruitment, bleeding; Glanzmann's disease; severe skin blistering; other epithelia defects; leucocyte adhesion deficiency (LAD); impaired inflammatory responses; recurrent life-threatening infections; mild osteopetrosis; severe skin blistering.
19	1077	People with the genetic disease **leucocyte adhesion deficiency** fail to synthesize functional β2 subunits, and they suffer repeated bacterial infections.
19	1077	Humans with **Glanzmann's disease** are genetically deficient in β3 integrins, and suffer from defective clotting and excessive bleeding.
19	1087	Problem 19–7 The food-poisoning bacterium ***Clostridium perfringens*** makes a toxin that binds to members of the claudin family of proteins, which are the main constituents of tight junctions.
20	1091	CANCER
20	1092	Cancer cells bypass normal proliferation controls and colonize other tissues
20	1092	A **neoplasm** is a new growth.
20	1092	A **benign tumor** is a non-invasive neoplasm.
20	1092	A **malignant tumor** is an invasive neoplasm.
20	1092	**Metastases** are secondary invasive neoplasms.
20	1092	**Carcinomas** are cancers arising from epithelial cells.
20	1092	**Sarcomas** are cancers arising from connective tissue or muscle cells.
20	1092	**Leukemias** and **lymphomas** are cancers derived from white blood cells and their precursors (hemopoietic cells).
20	1092	**Adenomas** and **adenocarcinomas** are, respectively, benign and malignant glandular tumors.
20	1092	**Chondromas** and **chondrosarcomas** are, respectively, benign and malignant tumors of cartilage.
20	1092	**Basal-cell carcinoma** is derived from a keratinocyte stem cell in the skin.
20	1092	**Melanoma** is derived from a pigment cell in the skin.
20	1092	Figure 20–1 Metastasis **Non-Hodgkin's lymphoma (NHL)**
20	1093	Most cancers derive from a single abnormal cell
20	1093	A **primary tumor** is the original tumor of a cancer.
20	1093	**Chronic myelogenous leukemia (CML)**
20	1093	The **Philadelphia chromosome** is an abnormal chromosome created by a translocation between the long arms of chromosomes 9 and 22; it is a hallmark of CML.
20	1093	Figure 20–2 **Cancer incidence** and mortality in the United States. skin melanoma, myelomas, leukemias, lymphomas

20	1094	Cancer cells contain somatic mutations
20	1094	**Somatic mutations**: Abnormalities are present in the DNA sequence of tumor cells that are not present in normal cells. They help drive cancer.
20	1094	**Epigenetic changes** are persistent, heritable changes in gene expression that result from modifications of chromatin structure without alteration of the cell's DNA sequence. These changes also help to drive cancer.
20	1094	**Carcinogenesis** (the generation of cancer) can be linked to **mutagenesis** (the production of a change in the DNA sequence). Factors that cause genetic changes tend to provoke the development of cancer.
20	1094	**Chemical carcinogens** provoke the development of cancer typically by causing local changes in the DNA nucleotide sequence.
20	1094	**Radiation** provokes the development of cancer typically by causing chromosome breaks and translocations or specific DNA base alterations.
20	1094	**Xeroderma pigmentosum**
20	1094	A single mutation is not enough to change a normal cell into a cancer cell
20	1094	Figure 20–5 Chronic myelogenous leukemia Philadelphia chromosome
20	1095	Cancers develop gradually from increasingly aberrant cells
20	1095	**Tumor progression** - An initial mild disorder of cell behavior evolves gradually into a full-blown cancer.
20	1095	Philadelphia chromosome
20	1095	Figure 20–6 Cancer incidence as a function of age Colon cancer
20	1095	Figure 20–7 Smoking and the onset of lung cancer.
20	1096	Tumor progression involves successive rounds of random inherited change followed by natural selection
20	1096	Figure 20–8 Cancer of the epithelium of the uterine cervix Intraepithelial neoplasia, malignancy
20	1097	Human cancer cells are genetically unstable
20	1097	**Genetic instability**: A prominent feature of cancer cells is that they accumulate genetic changes at an abnormally rapid rate
20	1098	Cancer cells display an altered control of growth
20	1098	**Transformed phenotype**: Cancer cells in culture and *in vivo* are abnormal in looks and behavior. Their shape, motility, growth, and responses to their substratum and to one another are all abnormal.
20	1098	Cancer cells have an altered sugar metabolism
20	1098	The **Warburg effect** is an abnormally high glucose uptake and altered sugar metabolism that is typical of cancer cells.
20	1099	Cancer cells have an abnormal ability to survive stress and DNA damage
20	1099	**Cell stress (homeostatic imbalance)** normally provokes repair, senescence, or apoptosis - but cancer cells evade normal safety mechanisms and survive with dangerous features.
20	1099	Human cancer cells escape a built-in limit to cell proliferation

20	1100	Figure 20–12 The Warburg effect
20	1100	**Replicative cell senescence** is avoided by cancer cells by (a) maintaining telomerase activity, or (b) using ALT to elongate chromosome ends.
20	1100	**ALT** is a mechanism for elongating chromosome ends that is based on homologous recombination and that allows a cancer cell to avoid replicative cell senescence.
20	1100	The tumor microenvironment influences cancer development
20	1100	Figure 20–14 **Colon adenocarcinoma** Colorectal cancer
20	1101	Cancer cells must survive and proliferate in a foreign environment
20	1101	**Metastasis** is a multistep process by which cancer cells establish new colonies at distant sites in the body. It is the most deadly—and least understood—aspect of cancer. Most of the molecular mechanisms involved are not yet clear.
20	1102	**Circulating tumor cells (CTCs)** are cancer cells that enter blood vessels from an invasive tumor, either directly or first via a lymphatic vessel.
20	1102	**Micrometastases** are formed when CTCs leave the blood circulation to colonize new tissue sites. A micrometastasis may die or may develop into an established metastasis.
20	1102	Figure 20–16 Steps in the process of **metastasis**.
20	1103	Many properties typically contribute to cancerous growth
20	1104	Passenger mutations
20	1104	Driver mutations
20	1104	**Cancer-critical genes** - all genes whose alteration contributes to the causation or evolution of cancer by driving tumorigenesis.
20	1104	The identification of gain-of-function and loss-of-function cancer mutations has traditionally required different methods
20	1104	**Proto-oncogenes** are genes in which a gain-of-function mutation can drive a cell toward cancer.
		Oncogenes are mutant genes whose products can act in a dominant fashion to help make a cell cancerous. They are overactive or overexpressed mutant forms of proto-oncogenes.
20	1104	**Tumor suppressor genes** appear to help prevent cancer; a loss-of-function mutation in a tumor suppressor gene can contribute to cancer.
20	1104	**Genome maintenance genes** are genes whose alteration results in genomic instability. They represent a subclass of cancer-critical genes
20	1105	Retroviruses can act as vectors for oncogenes that alter cell behavior
20	1105	Tumor viruses
20	1105	*Rous sarcoma virus*
20	1105	*RNA tumor viruses*
20	1105	Retrovirus
20	1105	Figure 20–17 **Cancer-critical mutations**
20	1106	Different searches for oncogenes converged on the same gene—*Ras*
20	1106	Ras

20	1106	Genes mutated in cancer can be made overactive in many ways
20	1107	Epidermal growth factor (EGF)
20	1107	Myc protein
20	1107	Burkitt's lymphoma
20	1107	Studies of Rare Hereditary Cancer Syndromes First Identified Tumor Suppressor Genes
20	1107	Retinoblastoma
20	1107	Figure 20–19 Mutation of the epidermal growth factor (EGF) receptor
20	1108	*Rb* gene
20	1108	Rb protein
20	1108	Figure 20–20 **Retinoblastoma**
20	1108	Both genetic and epigenetic mechanisms can inactivate tumor suppressor genes
20	1109	Dangerous **inactivation of tumor suppressor genes** can occur in many ways, including: • small chromosomal deletion • point mutation • errors in chromosome segregation • **mitotic recombination** • **gene conversion**
20	1109	Systematic sequencing of cancer cell genomes has transformed our understanding of the disease
20	1111	Many cancers have an extraordinarily disrupted genome
20	1111	Breast cancers
20	1111	Figure 20–24 breast cancer
20	1111	Many mutations in tumor cells are merely passengers
20	1112	**Driver mutations** of cancer are causal mutations in the development of the disease.
20	1112	**Passenger mutations** are mutations that happen to have occurred in the same cell as the driver mutations but are irrelevant to the development of the disease.
20	1112	About one percent of the genes in the human genome are cancer-critical
20	1112	Figure 20–25 **colorectal cancer**
20	1113	Disruptions in a handful of key pathways are common to many cancers
20	1113	**Glioblastoma** is the commonest type of human brain tumor.
20	1113	The **Rb pathway** consists of Rb and the genes that directly regulate Rb, and governs initiation of the cell-division cycle.
20	1113	The **RTK/Ras/PI3K pathway** serves to transmit signals for cell growth and cell division from the cell exterior into the heart of the cell
20	1113	The **p53 pathway** regulates responses to stress and DNA damage.
20	1114	Mutations in the PI3K/Akt/mTOR Pathway drive cancer cells to grow
20	1114	The **PI 3-kinase/Akt/mTOR intracellular signaling pathway** is critical for cell

		growth control.
20	1115	***PTEN*** is a common tumor-suppressor gene.
20	1115	Mutations in the p53 Pathway enable cancer cells to survive and proliferate despite stress and DNA damage
20	1115	***p53* gene** is a cancer-critical gene that is mutated in about 50% of all cases of cancer.
20	1116	Genome instability takes different forms in different cancers
20	1116	Ovarian cancers
20	1116	***Brca1*** and ***Brca2* genes**
20	1116	Colorectal cancers
20	1117	Figure 20–27 Modes of action of the p53 tumor suppressor. The p53 protein is a cell-stress sensor.
20	1117	Cancers of specialized tissues use many different routes to target the common core pathways of cancer
20	1117	Glioblastoma
20	1117	Prostate cancer
20	1117	T cell acute lymphocytic leukemias
20	1117	Studies using mice help to define the functions of cancer-critical genes
20	1118	Cancers become more and more heterogeneous as they progress
20	1119	The changes in tumor cells that lead to metastasis are still largely a mystery
20	1120	Epithelial–mesenchymal transition (EMT)
20	1120	E-cadherin gene
20	1120	Angiogenesis
20	1120	Vascular endothelial growth factor (VEGF)
20	1120	A small population of cancer stem cells may maintain many tumors
20	1121	Transit amplifying cell
20	1121	**Cancer stem cells** are capable of dividing indefinitely
20	1121	The cancer stem-cell phenomenon adds to the difficulty of curing cancer
20	1121	Figure 20–32 Cancer stem cells can be responsible for tumor growth and yet remain only a small part of the tumor-cell population.
20	1122	Breast cancers and leukemias
20	1122	Colorectal cancers evolve slowly via a succession of visible changes
20	1122	Colorectal cancer
20	1123	Polyp, adenomatous polyps
20	1123	A few key genetic lesions are common to a large fraction of colorectal cancers
20	1123	**Familial adenomatous polyposis coli (FAP)** - a rare type of hereditary predisposition to colorectal cancer
20	1124	**Wnt signaling pathway**
20	1124	β-catenin
20	1124	Some colorectal cancers have defects in DNA mismatch repair
20	1124	**Hereditary nonpolyposis colorectal cancer (HNPCC)** - an hereditary

		predisposition to colon carcinoma
20	1124	DNA mismatch repair system
20	1124	Figure 20–34 Colon of familial adenomatous polyposis coli patient
20	1125	The steps of tumor progression can often be correlated with specific mutations
20	1125	Figure 20–35 Chromosome complements (**karyotypes**) of colon cancers showing different kinds of genetic instability.
20	1126	Oncogenes and tumor suppressor genes = two classes of cancer-critical genes:
20	1126	Genome maintenance genes belong to a subclass of tumor suppressors; their normal role is to help maintain genome integrity.
20	1126	Inactivation of the p53 pathway
20	1126	Inactivation of the Rb pathway
20	1126	Driver mutations
20	1126	Tumor progression
20	1126	Passenger mutations
20	1126	**Cancer stem cells** are much more dangerous than other cancer cells.
20	1126	Figure 20–36 Colorectal carcinoma, adenoma, carcinoma invasion, metastasis
20	1127	Epidemiology reveals that many cases of cancer are preventable
20	1127	Sensitive assays can detect those cancer-causing agents that damage DNA
20	1128	Chemical carcinogens
20	1128	**Ames test** - for mutagenicity
20	1128	Cytochrome P-450 oxidases
20	1128	Benzo[a]pyrene, a cancer-causing chemical present in coal tar and tobacco smoke
20	1128	Aflatoxin B1 - a fungal toxin
20	1128	Fifty percent of cancers could be prevented by changes in lifestyle
20	1128	Figure 20–37 **Cancer incidence** is related to environmental influences. Burkitt's lymphoma Hodgkin's disease
20	1129	Viruses and other infections contribute to a significant proportion of human cancers
20	1129	Cancer of the uterine cervix is associated with papillomavirus
20	1129	Liver cancer is associated with hepatitis-B virus infections
20	1129	Figure 20–38 Some known carcinogens. • VINYL CHLORIDE: liver angiosarcoma • BENZENE: acute leukemias • ARSENIC: skin carcinomas, bladder cancer • ASBESTOS: mesothelioma • RADIUM: osteosarcoma Aflatoxin is an important cause of liver cancer in the tropics.
20	1129	Figure 20–39 Age-adjusted **cancer death rates,** United States, 1930–2008.

		Lung cancer, tobacco smoking Stomach cancer, *Helicobacter pylori*
20	1130	Hepatitis-C virus, development of liver cancer.
20	1130	DNA tumor viruses
20	1130	Table 20–2 Viruses Associated with Human Cancers Cancers associated with DNA viruses: • Warts (benign) • Carcinoma of the uterine cervix • Liver cancer (hepatocellular carcinoma) • Burkitt's lymphoma (cancer of B lymphocytes) • Nasopharyngeal carcinoma • Kaposi's sarcoma Cancers associated with RNA viruses: • Adult T-cell leukemia/lymphoma • Kaposi's sarcoma (via human herpesvirus 8) • Liver cancer (hepatocellular carcinoma)
20	1130	Hepatitis-B virus Liver cancer (hepatocellular carcinoma)
20	1131	Cancers of the uterine cervix can be prevented by vaccination against human papillomavirus
20	1131	Papillomaviruses - DNA tumor viruses, warts, cervical cancer
20	1131	Human papillomaviruses (HPV)
20	1131	Intraepithelial neoplasia
20	1131	Cervical cancer
20	1131	Figure 20–40 Papillomaviruses are thought to give rise to cancer of the uterine cervix.
20	1132	Infectious agents can cause cancer in a variety of ways
20	1132	Papillomaviruses E6 and E7
20	1132	Hepatitis-B and hepatitis-C viruses,
20	1132	**Hepatitis** - chronic inflammation of the liver
20	1132	Human immunodeficiency virus (HIV)
20	1132	Kaposi's sarcoma
20	1132	Human herpesvirus (HHV-8)
20	1132	*Helicobacter pylori*
20	1132	The search for cancer cures is difficult but not hopeless
20	1132	Hodgkin's lymphoma
20	1132	Testicular cancer
20	1132	Choriocarcinoma
20	1132	Leukemias
20	1132	Cancers of childhood
20	1132	Traditional therapies exploit the genetic instability and loss of cell-cycle checkpoint responses in cancer cells
20	1133	New drugs can kill cancer cells selectively by targeting specific mutations
20	1133	**Synthetic lethality** occurs with a treatment that is cell-lethal in combination

		with a genetic lesion that is present in cancer cells, but harmless to cells where this lesion is absent.
20	1133	PARP Inhibitors kill cancer cells that have defects in Brca1 or Brca2 genes
20	1134	Individuals who inherit one mutant copy of ***Brca1*** or ***Brca2*** develop tumors that have inactivated the second copy of the same gene.
20	1134	**Brca1** and **Brca2** - important for the repair of DNA double-strand breaks
20	1134	**PARP (polyADP-ribose polymerase)** - important for single-strand break repair. Drugs that block PARP activity kill Brca-deficient cells with extraordinary selectivity.
20	1134	**PARP inhibitors** also appear to be applicable to cancers with mutations other than *Brca1* and *Brca2* that also cause defects in the cell's homologous recombination machinery.
20	1134	Figure 20–41 How a tumor's genetic instability can be exploited for cancer therapy. PARP protein, *Brca1*, *Brca2*
20	1135	Small molecules can be designed to inhibit specific oncogenic proteins
20	1135	**Oncogene dependence**: Once a cancer cell has undergone an oncogenic mutation, it will often undergo further changes that make it reliant on the initial oncogene.
20	1135	Chronic myelogenous leukemia (CML)
20	1135	Philadelphia chromosome
20	1135	Chimeric Bcr-Abl protein
20	1135	**Imatinib** (trade name **Gleevec®**)
20	1135	Figure 20–42 The conversion of the *Abl* proto-oncogene into an oncogene in patients with Chronic myelogenous leukemia. Philadelphia chromosome
20	1136	**Blast crisis**: acute phase of myeloid leukemia
20	1136	**Chronic myelogenous leukemia (CML)**—at least in the chronic (early) stage—may be on its way to becoming a curable disease.
20	1136	Once we understand precisely what genetic lesions have occurred in a cancer, we can begin to design effective **rational treatments**.
20	1136	Melanomas
20	1136	Many cancers lack an oncogenic mutation in a protein kinase. But most tumors contain **inappropriately activated signaling pathways**, for which a target somewhere in the pathway can hopefully be found.
20	1136	Figure 20–43 How imatinib (Gleevec) blocks the activity of Bcr-Abl protein and halts chronic myelogenous leukemia.
20	1137	Many cancers may be treatable by enhancing the immune response against the specific tumor
20	1137	**Immunological therapy** for cancer, at its simplest, is to inject the patient with antibodies that target the cancer cells.
20	1137	Breast cancers
20	1137	**Trastuzumab** (trade name **Herceptin®**) is a monoclonal antibody that inhibits Her2

20	1137	Antibodies can be used to deliver poisons to the cancer cells.
20	1137	Figure 20–44 Some **anticancer drugs** and **drug targets** in the Ras–MAP-kinase signaling pathway. RTK inhibitors • Trastuzumab • Gefitinib • Erlotinib • Cetuximab • Bevacizumab B-Raf inhibitors • Dabrafenib • Vemurafenib Raf inhibitors • Regorafenib • Sorafenib Mek inhibitors • Refametinib • Selumetinib • Trametinib
20	1138	**Ipilimumab** is a monoclonal antibody that blocks CTLA4 (cytotoxic T-lymphocyte-associated protein 4).
20	1138	Figure 20–45 Therapies designed to remove the immunosuppressive microenvironment in tumors.
20	1139	**Personalized immunotherapy** for cancer may become possible, in which an individual patient's tumor is molecularly analyzed, and treatment is tailored to that tumor's particular mechanisms of immunosuppression.
20	1139	Cancers evolve resistance to therapies
20	1139	**Multidrug resistance** is a phenomenon in which cancer cells that are exposed to one anticancer drug evolve a resistance not only to that drug but also to other drugs to which they have never been exposed.
20	1139	Combination therapies may succeed where treatments with one drug at a time fail
20	1140	We now have the tools to devise combination therapies tailored to the individual patient
20	1140	Figure 20–46 Multidrug treatments can be more effective than sequential treatments.
20	1141	Problem 20–1 Dimethylbenz[a]anthracene (DMBA)
20	1142	Problem 20–5 Colon cancer, osteosarcoma
20	1142	Problem 20–6 Lung cancer
20	1142	Problem 20–8 Acute promyelocytic leukemia (APL)
20	1143	Problem 20–10 Cancer of the breast and ovary

20	1143	Problem 20–11 **Natural transmission of cancer:** A malignant oral–facial tumor in Tasmanian Devils, and a venereal disease in dogs are the only known examples of natural transmission of cancer by tumor cells.
21	1145	DEVELOPMENT OF MULTICELLULAR ORGANISMS
21	1154	2 to 5% of all human babies are born with **anatomical abnormalities**,
21	1169	Human **embryonic stem cells** can generate the specific cell types needed for regenerative medicine (discussed in the next chapter).
21	1186	Mutations in the gene for endothelin-3 or its receptor cause **aberrant neural-crest-cell migration**, and widespread death of the migrating crest cells. Albino patches of skin result, as well as a condition called **megacolon**, a potentially lethal distention of the large intestine.
21	1187	Individuals with mutations in genes coding for either **Kit** or **Steel** factors have deficits in pigmentation, blood cells, and germ cells (Figure 21–47).
21	1196	Excessive production of growth hormone leads to **gigantism**, and too little leads to **dwarfism** (Figure 21–61). **Pituitary dwarfs** have bodies and organs that are proportionately small, unlike **achondroplastic dwarfs**, whose limbs are disproportionately short.
21	1212-1213	Neural networks are subject to **activity-dependent synaptic changes**; if, before about 5 years of age in humans, one eye is deprived it of visual stimulation, while the other eye is allowed normal stimulation, the deprived eye becomes almost entirely, and irreversibly, blind.
22	1217	STEM CELLS AND TISSUE RENEWAL
22	1220	Mutations in the ***Apc (adenomatous polyposis coli)* gene** predispose individuals to colorectal cancer.
22	1220	In advance of the invasive colorectal cancer, individuals with mutations in *Apc* develop large numbers of small precancerous tumors (**adenomas**) in the lining of the large intestine.
22	1226	Loss of pancreatic β cells (through autoimmune attack) is responsible for **type 1 (juvenile-onset) diabetes**; they are also a significant factor in the **type 2 (adult-onset) diabetes**.
22	1227	The **auditory epithelium** and the **retinal epithelium** lack stem cells; if their sensory receptor cells are destroyed—the sensory hair cells in the ear, or the photoreceptors in the retina— the loss is permanent.
22	1232	Disturbance of the balance between osteoblast and osteoclast activity can lead to **osteoporosis**, or to the opposite condition, **osteopetrosis**.
22	1234	In one form of **muscular dystrophy**, a genetic defect in the cytoskeletal protein **dystrophin** damages differentiated skeletal muscle cells.
22	1234	A decline of **capacity for repair** contributes to the weakening of muscle in the elderly.
22	1235	**Quiescent myoblasts** are the stem cells of skeletal muscle; exhaustion of their regenerative capacity is responsible for some forms of muscular dystrophy as well as for the decline of muscle mass in old age.
22	1235	Cancerous tissue is as dependent on a **blood supply** as is normal tissue.

22	1236	**Lymphatic vessels** provide a path by which cancer cells escape from a primary tumor to invade other tissues.
22	1237	Wounds, local irritants, infections, and tumors are all capable of inducing a proliferation of **new capillaries**.
22	1238	Embryonic mutants lacking the signal protein **platelet-derived growth factor-B (PDGF-B)** or its receptor, develop microaneurysms—microscopic pathological dilatations—that eventually rupture, as well as other abnormalities.
22	1240	The **inflammatory response** is governed by many different signal molecules produced locally by mast cells, nerve endings, platelets, and white blood cells, as well as by the activation of complement (discussed in Chapter 24).
22	1241	Some bacterial infections cause a selective increase in **neutrophils**; some protozoan infections and other parasitic infections cause a selective increase in **eosinophils**.
22	1241	**Erythrocyte** production is selectively increased in response to **anemia** due to blood loss, and in the process of **high-altitude acclimatization** .
22	1242	Bone marrow contains **multipotent hematopoietic stem cells**, able to give rise to all classes of blood cells; bone marrow transplantation is used in the treatment of leukemia.
22	1246	Mutations that inhibit **cell death** by causing excessive production of the intracellular apoptosis inhibitor **Bcl2** promote the development of cancer in B lymphocytes.
22	1246	Many cases of **leukemia** arise through mutations that confer the capacity for unlimited self-renewal on committed hematopoietic precursor cells.
22	1247	In most parts of the human brain, nerve cells that die, as in **Alzheimer's**, are not replaced.
22	1247	When **heart muscle** dies for lack of oxygen, as in a heart attack, the muscle is replaced by scar tissue.
22	1249	Patients with some forms of **leukemia** or **lymphoma** can be irradiated or chemically treated to destroy their cancerous cells along with the rest of their hematopoietic tissue, and then can be rescued by a transfusion of healthy, noncancerous hematopoietic stem cells.
22	1250	Repair of the skin after **extensive burns** can be accomplished using cultured epidermal stem cells derived from undamaged regions of the burned patient's own skin.
22	1250	**Neural stem cells** can be grafted into an adult brain; it might be possible to develop neural stem cell treatments for **neurodegenerative diseases**, such as **Parkinson's**, and for **CNS injuries**, such as accidents that sever the spinal cord.
22	1259	The advent of **induced pluripotent stem cells (iPS cells)** and **direct transdifferentiation**, appears at least in principle to solve the problem of **immune rejection**.
22	1259	**iPS and transdifferentiated cells** can be generated from a small sample of the patient's own tissue and so should escape immune attack when transplanted back into the same individual.
22	1259	**Embryonic stem (ES)**, **induced pluripotent stem (iPS)**, and

		transdifferentiated cells can be used to generate large, homogeneous populations of specialized cells of any chosen type in culture; these can serve for investigation of disease mechanisms and in the search for new drugs acting on a specific cell type (Figure 22–47).
22	1259	iPS cells can be derived from sufferers of a genetic disease and used to produce the specific cell types that malfunction, to investigate how the malfunction occurs, and to screen for drugs. **Timothy syndrome** provides an example.
22	1259	iPS cells can be prepared from an individual patient, differentiated into the relevant cell type, and used to test **candidate drugs** in vitro.
23	1263	PATHOGENS AND INFECTION
23	1263	Tuberculosis
23	1263	Malaria
23	1263	AIDS (acquired immune deficiency syndrome)
23	1263	*Helicobacter pylori*
23	1264	The **human microbiota** is a complex ecological system that is important for our development and health.
23	1264	Dysbiosis is a microbiota imbalance.
23	1264	*Clostridium difficile* can cause colitis.
23	1264	Pathogens interact with their hosts in different ways
23	1264	Figure 23–1 Parasitism at many levels. Blacklegged tick or deer tick (*Ixodes scapularis*) *Borrelia burgdorferi* causes Lyme disease.
23	1265	*Vibrio cholerae* causes cholera.
23	1265	Variola virus causes smallpox.
23	1265	Influenza viruses cause flu.
23	1265	*Mycobacterium tuberculosis* can cause the lung infection tuberculosis.
23	1265	*Ascaris* is an intestinal worm.
23	1265	**Opportunistic pathogens** cause disease only if our immune systems are weakened or if they gain access to a normally sterile part of the body.
23	1265	**Pathogenesis** refers to the mechanisms by which pathogens cause disease.
23	1265	Pathogens can contribute to cancer, cardiovascular disease, and other chronic illnesses
23	1265	*Rous sarcoma virus* causes sarcomas in chickens.
23	1265	*Human papillomavirus* causes genital warts, and is responsible for more than 90% of cervical cancers.
23	1265	*H. pylori* can be a major contributor to stomach cancer, as well as to gastric ulcers.
23	1265	**Atherosclerosis** is the accumulation of fatty deposits in blood vessel walls.
23	1266	**Atherosclerotic plaques** in blood vessels are hallmark of early atherosclerosis. Clumps of macrophages called foam cells recruit other white blood cells into the forming atherosclerotic plaque.
23	1266	*Chlamydia pneumoniae* - a bacterial pathogen - causes pneumonia and is a significant risk factor for atherosclerosis.

23	1266	*Porphyromonas gingivalis* are bacteria usually associated with teeth and gums, and are also implicated in atherosclerosis.
23	1266	Pathogens can be viruses, bacteria, or eukaryotes
23	1266	AIDS
23	1266	Smallpox
23	1266	Common cold
23	1266	*Ascaris lumbricoides* is a nematode worm that infects the gut.
23	1266	*Caenorhabditis elegans* is a harmless nematode and serves as a research model organism.
23	1266	Figure 23–2 Pathogens in many forms. Poliovirus causes poliomyelitis *Vibrio cholerae* causes cholera *Trypanosoma brucei* causes African sleeping sickness *Ascaris* nematodes infect the gut.
23	1267	Bacteria are diverse and occupy a remarkable variety of ecological niches
23	1267	**Gram-staining** properties reflect differences in the structure of the bacterial cell wall.
23	1267	**Gram-positive** bacteria have a thick peptidoglycan cell wall outside their inner (plasma) membrane.
23	1267	**Gram-negative** bacteria have a thinner peptidoglycan cell wall.
23	1267	**Pathogen-associated molecular patterns (PAMPs)** are microbe-associated molecules that are recognized by pattern recognition receptors (PRRs) in or on cells of the innate immune system.
23	1267	Figure 23–3 Bacterial shapes and cell-surface structures. Bacterial shapes: spirillum, spirochete, coccus, coccobacillus, vibrio, bacillus Bacteria are classified as Gram positive or Gram negative *Streptococcus, Staphylococcus, Salmonella, Escherichia coli (E. coli)*
23	1268	**Facultative pathogens** only cause disease if they happen to encounter a susceptible host.
23	1268	**Obligate pathogens** can only replicate inside the body of their host.
23	1268	*Shigella flexneri* causes epidemic dysentery (bloody diarrhea).
23	1268	*Salmonella enterica* is a common cause of food poisoning.
23	1268	*Pseudomonas aeruginosa* can cause disease in a wide variety of plants and animals.
23	1268	Bacterial pathogens carry specialized virulence genes
23	1268	**Virulence genes** are genes that contribute to the ability of an organism to cause disease
23	1268	**Virulence factors** are the proteins encoded by virulence genes.
23	1268	**Pathogenicity islands** are clusters of virulence genes on the bacterial chromosome.
23	1268	*Bacteriophages* are viruses that infect bacteria.
23	1268	**Transposons** are transposable elements, segments of DNA, that can move from one genome position to another by transposition.
23	1268	**Virulence plasmids** are plasmids containing virulence genes.

23	1268	**Horizontal gene transfer** is gene transfer by means other than vertical parent-to-offspring transfer. This can occur by one of three mechanisms: natural transformation by released naked DNA, transduction by bacteriophages, or sexual exchange by conjugation.
23	1268	**Transformation** is natural horizontal gene transfer by released naked DNA.
23	1268	**Transduction** is horizontal gene transfer by bacteriophages.
23	1268	**Conjugation** is horizontal gene transfer by sexual exchange.
23	1268	Figure 23–4 Genetic differences between pathogenic and nonpathogenic bacteria. *E. coli, Shigella flexneri, Salmonella enterica, E. coli, Salmonella enterica* Virulence plasmid, virulence genes, pathogenicity islands DNA-containing virus (bacteriophage) Plasmid, horizontal gene transfer Natural transformation / transduction / conjugation
23	1269	*Escherichia coli*
23	1269	The **core genome** includes the genes common to all isolates (strains) within a species. The core genome of a species is a subset of the pan genome of that species.
23	1269	The **pan-genome** includes all genes present in the full spectrum of isolates (strains) of a given species.
23	1269	*Vibrio cholerae* is a Gram-negative bacterium that causes the epidemic diarrheal disease cholera.
23	1269	CTXφ is a mobile bacteriophage infecting the *V. Cholerae* strains that cause pandemic human disease.
23	1269	Classical *V. Cholerae* strains display the O1 surface antigen
23	1269	El Tor *V. Cholerae* strain display O1 plus two bacteriophages and at least two new pathogenicity islands.
23	1269	O139 *V. Cholerae* strain
23	1269	Bacterial virulence genes encode effector proteins and secretion systems to deliver effector proteins to host cells
23	1269	Figure 23–5 Evolution of pathogenic *Vibrio cholerae* strains. *V. cholerae* progenitor *V. cholerae* O1 serogroup, Classical *V. cholerae* O1 serogroup, El Tor *V. cholerae* O139 serogroup CTXφ bacteriophage RS1φ bacteriophage Pathogenicity islands (VSP1 and VSP2) O139 antigen O1 antigen New pathogenicity island (SXT)
23	1269	Extracellular bacterial pathogens are pathogenic bacteria that live outside of host cells.
23	1270	**Toxins** are secreted poisons.
23	1270	*Vibrio cholerae*

23	1270	*Bacillus anthracis*
23	1270	Figure 23–6 Bacterial toxin entry into host cells. *Bacillus anthracis* Vibrio cholerae toxin, Bordetella pertussis toxin, anthrax toxin, cholera toxin, pertussis toxin
23	1271	**Edema** is an accumulation of extracellular fluid in the skin or lung.
23	1271	**Secretion systems** are specialized bacterial systems that secrete effector proteins. They include • **general secretion systems** • **accessory secretion systems (types I–VI)**, a subset of which are c**ontact-dependent secretion systems**.
23	1271	**Effector proteins** interact with host cells.
23	1271	**Contact-dependent secretion systems** are present in many bacteria that contact or live inside host cells.
23	1271	Fungal and protozoan parasites have complex life cycles involving multiple forms
23	1271	**Antifungal** and **antiparasitic drugs** are often less effective and more toxic to the host than are antibiotics that target bacteria.
23	1271	*Saccharomyces cerevisiae* , 'baker's yeast', is used to bake bread, and serves as a model organism for cell biology research.
23	1271	*Schizosaccharomyces pombe* , 'fission yeast', is used to brew beer, and serves as a model organism for cell biology research.
23	1271	Figure 23–7 Type III secretion systems
23	1272	*Histoplasma capsulatum* is a mold at low temperature in the soil, but adopts a yeast form when inhaled into the lung, where it can cause histoplasmosis.
23	1272	**Protozoan parasites** are single-celled eukaryotes, with more elaborate life cycles than fungi. They frequently require more than one host.
23	1272	**Malaria** is a protozoal disease caused by four species of *Plasmodium*
23	1272	Female *Anopheles* mosquito is the malaria vector.
23	1272	Figure 23–8 Dimorphism in the pathogenic fungus Histoplasma capsulatum.
23	1272	Figure 23–9 Life cycle of malaria parasites. *Plasmodium falciparum*
23	1273	*Plasmodium falciparum* causes the most serious form of malaria.
23	1273	All aspects of viral propagation depend on host cell machinery
23	1273	A **virus** is a particle consisting of nucleic acid (RNA or DNA) enclosed in a protein coat. It is capable of replicating within a host cell and spreading from cell to cell. Most clinically important human viruses have double-stranded DNA or single-stranded RNA.
23	1273	**Table 23–1 Viruses that cause human disease** Herpes simplex virus 1 - Recurrent cold sores Epstein–Barr virus (EBV) - Infectious mononucleosis Varicella-zoster virus - Chickenpox and shingles Smallpox virus (Variola) - Smallpox Human papillomavirus - Warts, cancer

		Adenovirus - Respiratory disease Hepatitis-B virus - Hepatitis B Human immunodeficiency virus (HIV-1) - Acquired immune deficiency syndrome (AIDS) Poliovirus - Poliomyelitis Rhinovirus - Common cold Hepatitis-A virus - Hepatitis A Hepatitis-C virus - Hepatitis C Yellow fever virus - Yellow fever Coronavirus - Common cold, respiratory disease Rabies virus - Rabies Mumps virus - Mumps Measles virus - Measles Influenza virus type A - Respiratory disease (flu)
23	1274	Virion is a single virus particle.
23	1274	Pandoraviruses are giant viruses of amoebae, with the largest known virions (700 nm). Their double-stranded DNA genomes have over 2,000,000 nucleotide pairs.
23	1274	Poxvirus virions are 250–350 nm long, with a double-stranded DNA genome of about 270,000 nucleotide pairs.
23	1274	Parvovirus virions are less than 30 nm in diameter, and have a single-stranded DNA genome of fewer than 5000 nucleotides.
23	1274	Nonenveloped viruses are packaged just in a protein coat, called a **capsid**.
23	1274	Enveloped viruses are packaged in a protein capsid, which is further enclosed by a lipid bilayer membrane, or **envelope**.
23	1274	Figure 23–10 A simple viral life cycle. No known virus is this simple.
23	1274	Figure 23–11 Viral morphology. DNA VIRUSES • poxvirus • herpesvirus • adenovirus • papillomavirus RNA VIRUSES • poliovirus • HIV (AIDS virus) • influenza virus • coronavirus (common cold) • rabies virus • mumps virus
23	1275	Smallpox
23	1275	Poliomyelitis
23	1275	Figure 23–12 Acquisition of a viral envelope Semliki forest virus
23	1275	Figure 23–13 Effective control of a viral disease through vaccination. Poliomyelitis Salk vaccine (inactivated virus given by injection)

		Sabin vaccine (live attenuated virus given orally)
23	1276	Pathogens overcome epithelial barriers to infect the host
23	1276	*Staphylococci*
23	1276	*Streptococci*
23	1276	*Staphylococcus aureus*, and MRSA (methicillin-resistant *Staphylococcus aureus*)
23	1276	Papillomaviruses
23	1276	Insect vectors
23	1276	*Plasmodium* protozoan
23	1276	yellow fever
23	1276	Dengue fever
23	1276	Viral encephalitis (inflammation of the brain)
23	1276	*Yersinia pestis* is the bacterium that causes bubonic plague
23	1276	Pathogens that colonize an epithelium must overcome its protective mechanisms
23	1276	Figure 23–14 Plague bacteria *Yersinia pestis*
23	1276	*E. coli*
23	1276	*H. pylori* is the major cause of stomach ulcers and some stomach cancers.
23	1276	Chronic inflammation
23	1276	Stomach cancer
23	1277	Extracellular pathogens disturb host cells without entering them
23	1277	*Bordetella pertussis* is the bacterium that causes whooping cough.
23	1277	Figure 23–15 Pathogenic E. coli Uropathogenic *E. coli* is a common cause of bladder infections and kidney infections.
23	1278	Pertussis toxin, like cholera toxin, has an A subunit.
23	1278	*B. pertussis* causes severe coughing.
23	1278	Enteropathogenic *E. coli* (EPEC) causes diarrhea in young children.
23	1278	Vaccinia virus is the virus that was used as a vaccine to eradicate smallpox.
23	1278	Intracellular pathogens have mechanisms for both entering and leaving host cells
23	1278	**Intracellular pathogens** include all viruses and many bacteria and protozoa. They are not accessible to antibodies.
23	1278	Figure 23–16 Interaction of enteropathogenic *E. coli* (EPEC) with host intestinal epithelial cells.
23	1279	Viruses bind to virus receptors at the host cell surface
23	1279	*E. coli*
23	1279	Bacteriophage lambda
23	1279	Herpes simplex virus
23	1279	Simian virus 40 (SV40)
23	1279	Influenza virus

23	1279	HIV- 1
23	1279	Figure 23–17 Receptor and co-receptors for HIV.
23	1280	Viruses enter host cells by membrane fusion, pore formation, or membrane disruption
23	1280	Enveloped viruses
23	1280	Poxviruses
23	1280	HIV-1
23	1280	Influenza A virus
23	1280	Figure 23–18 Four virus entry strategies. HIV (AIDS virus), influenza virus, poliovirus, adenovirus
23	1281	Nonenveloped viruses
23	1281	Poliovirus causes poliomyelitis
23	1281	Adenovirus
23	1281	Bacteria enter host cells by phagocytosis
23	1281	*M. tuberculosis*
23	1281	*Yersinia pseudotuberculosis* is a bacterium that causes diarrhea and is a close relative of the plague bacterium *Y. pestis*.
23	1281	*Listeria monocytogenes* causes food poisoning
23	1281	*Salmonella enterica*
23	1282	Intracellular eukaryotic parasites actively invade host cells
23	1282	*Toxoplasma gondii* is a cat parasite that also causes occasional serious human infections.
23	1282	Malaria parasites
23	1282	Figure 23–19 Mechanisms used by bacteria to induce phagocytosis by host cells that are normally nonphagocytic SPI1 (Salmonella pathogenicity island 1) *Salmonella enterica, Salmonella bacteria*
23	1283	*Trypanosoma cruzi* is a protozoan that causes Chagas disease.
23	1283	The protozoan *Trypanosoma cruzi* , which causes Chagas disease in Mexico and Central and South America, uses two alternative invasion strategies.
23	1283	Figure 23–20 The life cycle of *Toxoplasma gondii*
23	1283	Figure 23–21 The two alternative strategies that *Trypanosoma cruzi* uses to invade host cells
23	1284	Some intracellular pathogens escape from the phagosome into the cytosol
23	1284	*Trypanosoma cruzi*
23	1284	*Listeria monocytogenes*
23	1284	Listeriolysin O is a protein secreted by *L. monocytogenes*.
23	1284	Many pathogens alter membrane traffic in the host cell to survive and replicate
23	1284	Figure 23–22 Choices that an intracellular pathogen faces *Trypanosoma cruzi, Listeria monocytogenes, Shigella flexneri, Mycobacterium tuberculosis, Legionella pneumophila, Salmonella enterica, Coxiella burnetii, Leishmania*

23	1284	Figure 23–23 Escape of *Listeria monocytogenes* by selective destruction of the phagosomal membrane
23	1285	*M. tuberculosis*
23	1285	*Salmonella enterica*
23	1285	*Legionella pneumophila* is the cause of Legionnaire's disease (pneumonia).
23	1285	Figure 23–24 Modifications of membrane traffic in host cells by bacterial pathogens *Mycobacterium tuberculosis, Salmonella enterica, Legionella pneumophila*
23	1285	Figure 23–25 *Salmonella enterica*
23	1286	*L. pneumophila*
23	1286	HIV-1
23	1286	Vaccinia virus
23	1286	Viruses and bacteria use the host-cell cytoskeleton for intracellular movement
23	1286	Figure 23–26 *Legionella pneumophila* *Borrelia burgdorferi* causes Lyme disease. *Leishmania, Candida albicans*
23	1287	*Listeria monocytogenes*
23	1287	*Shigella flexneri*
23	1287	*Rickettsia rickettsii* causes Rocky Mountain spotted fever.
23	1287	*Burkholderia pseudomallei* causes melioidosis, characterized by severe respiratory symptoms.
23	1287	Baculovirus is an insect virus.
23	1287	Figure 23–27 Complex strategies for viral envelope acquisition. *Herpesvirus, Vaccinia virus*
23	1288	*L. monocytogenes*
23	1288	baculovirus
23	1288	*S. flexneri*
23	1288	*Rickettsia*
23	1288	*Neurotropic alpha herpesviruses* infect neurons.
23	1288	Chickenpox
23	1288	Viruses can take over the metabolism of the host cell
23	1288	*Poliovirus*
23	1288	Figure 23–28 The **actin-based movement of bacterial pathogens** within and between host cells. *Listeria monocytogenes, Shigella flexneri, Rickettsia rickettsii, Burkholderia pseudomallei*
23	1289	Adenovirus
23	1289	Poxviruses
23	1289	Mimivirus
23	1289	Influenza virus
23	1289	Measles virus

23	1289	Retroviruses such as HIV-1
23	1289	Reverse transcriptase enzyme
23	1289	Pathogens can evolve rapidly by **antigenic variation**
23	1289	Poliovirus
23	1289	Figure 23–29 Molecular mechanisms for actin nucleation by various bacterial pathogens. *Listeria monocytogenes, Shigella flexneri, Rickettsia rickettsii*
23	1290	**Antigenic variation** is the ability that many pathogens have to change the antigens displayed on the cell surface, enabling them to evade attack by the adaptive immune system.
23	1290	*Trypanosoma brucei* is a protozoan parasite that causes African sleeping sickness and is spread by tsetse flies.
23	1290	*T. cruzi*
23	1290	**Variant-specific glycoprotein (VSG)** coats *T. Brucei*, the causative agent of African sleeping sickness. At any one time only one of about 1000 *Vsg* genes in the trypanosome genome is expressed. *T. Brucei* employs antigenic variation to repeatedly change the VSG protein displayed on its surface, leading to chronic cyclic infection.
23	1290	*Salmonella enterica*
23	1290	**Phase variation** in bacteria is the use of conservative site-specific recombination to control the expression of particular genes.
23	1290	*Neisseria*
23	1290	Figure 23–30 Antigenic variation in trypanosomes. *Trypanosoma brucei*
23	1291	*Neisseria meningitidis*
23	1291	Error-prone replication dominates viral evolution
23	1291	HIV infection
23	1291	*Env* gene
23	1291	Simian immunodeficiency virus (SIV)
23	1291	HIV, HIV-1,
23	1291	Avian influenza
23	1291	Spanish flu - catastrophic pandemic of 1918
23	1291	Influenza pandemics
23	1291	H1N1 swine virus
23	1291	Drug-resistant pathogens are a growing problem
23	1291	**Antibiotic drugs** are either bactericidal or bacteriostatic, and have been enormously successful curing bacterial infections. However, bacteria continuously evolve resistant strains, often within a few years of the introduction of a new drug.
23	1291	**Penicillin** was one of the first antibiotics.
23	1291	Figure 23–31 Diversification of HIV-1, HIV-2, and related strains of SIV.
23	1292	**Selective toxicity**: Antibacterial drugs can be designed that specifically inhibit replication, transcription, translation, and metabolic processes in

		bacteria without disrupting these processes in the eukaryote hosts.
23	1292	The virus population in an HIV-infected person treated with the reverse transcriptase inhibitor AZT will acquire complete **AZT-resistance** within a few months.
23	1292	The current protocol for **treatment of HIV infections** involves the simultaneous use of three drugs.
23	1292	**Spread of drug-resistance**: Newly acquired or mutated genes that confer drug-resistance are frequently spread throughout a pathogen population by horizontal gene transfer. The transfer may even be between different species.
23	1292	**Vancomycin** is an antibiotic of last resort for many severe, hospital-acquired, Gram-positive bacterial infections that are resistant to most other known antibiotics. Vancomycin resistance is, however, increasing.
23	1292	Figure 23–32 Model for the **evolution of pandemic strains of influenza virus** by recombination.
23	1293	**Drug-resistance genes** acquired by horizontal transfer frequently come from environmental microbial reservoirs.
23	1293	**Penicillin** is an antibiotic made by the mold Penicillium.
23	1293	*Streptomyces*
23	1293	Figure 23–33 **Antibiotic targets** include: • cell membrane - polymixins • DNA gyrase - quinolones • RNA polymerase - rifampin • cell wall synthesis - vancomycin, penicillins, cephalosporins • protein synthesis, 30S ribosome inhibitors - tetracycline, streptomycin • protein synthesis, 50S ribosome inhibitors - erythromycin, chloramphenicol • folic acid biosynthesis - trimethoprim, sulfonamides
23	1293	Figure 23–34 Three general **mechanisms of antibiotic resistance**. (1) alter the drug's target enzyme (2) degrade or covalently modify the drug (3) express or up-regulate an efflux pump that ejects the drug from the bacterial cytoplasm Multidrug resistance **(MDR) efflux pumps**, are capable of exporting a wide variety of structurally dissimilar drugs. Upregulation of an MDR pump can render a bacterium resistant to a very large number of different antibiotics in a single step.
23	1294	Problem 23–7 *Clostridium difficile*
23	1294	Problem 23–8 The three general **mechanisms for horizontal gene transfer** are natural transformation by released naked DNA, transduction by bacteriophage, and sexual exchange by conjugation.
23	1294	Problem 23–9 *Yersinia pestis* is the causative agent of plague.
23	1295	Problem 23–10 *Salmonella typhimurium* causes gastroenteritis.
23	1295	Problem 23–11 John Snow, father of modern epidemiology, studied a cholera epidemic in London in 1854.

23	1295	Problem 23–12 Influenza epidemics
23	1295	Problem 23–13 influenza virus, Rift Valley fever virus, Hantavirus, Lassa virus
23	1295	Problem 23–14 Avian influenza viruses, human influenza viruses
23	1295	Problem 23–17 penicillin, influenza
24	1297	THE INNATE AND ADAPTIVE IMMUNE SYSTEMS
24	1297	A person who recovers from measles or is vaccinated against it is protected for life against measles by the **adaptive immune system**, but not against other common viruses.
24	1300	Individuals who are homozygous for a particular mutant allele of the NLR gene ***NOD2*** have a greatly increased risk of developing **Crohn's disease**.
24	1298	Activated **pattern recognition receptors (PRRs)** trigger an inflammatory response at sites of infection.
24	1301	Nod-like receptor (NLR)-dependent **inflammasome** assembly can be triggered in the absence of infection if cells are damaged or stressed, for example in **arthritis**.
24	1303	The bacterium ***Neisseria gonorrhoeae***, causative agent of **gonorrhea**, coats itself with a layer of sialic acid to effectively hide from the complement system.
24	1305	**Natural killer (NK) cell** killing activity is stimulated when various activating receptors on the NK cell surface recognize specific proteins that are greatly increased on the surface of virus-infected cells and some cancer cells.
24	1314	**Self-tolerance mechanisms** sometimes fail, causing T or B cells (or both) to react against the animal's own molecules; **Myasthenia gravis** is an example of such an **autoimmune disease**.
24	1315	In **juvenile (type 1) diabetes**, adaptive immune reactions against **insulin-secreting β cells** in the pancreas kill these cells, leading to severe insulin deficiency.
24	1317	The release of amines from mast cells and basophils is largely responsible for the symptoms of such **allergic reactions** as hay fever, asthma, and hives.
24	1331	25% of West African individuals have a specific **MHC** (major histocompatibility complex) **allele** (**HLA□B53**) that confers a reduced susceptibility to a severe endemic form of malaria. This allele is rare elsewhere.
24	1332	**AIDS** patients are susceptible to infection by microbes that are not normally dangerous because HIV depletes helper T cells.
24	1333	Mutations that inactivate the ***AIRE* gene** (autoimmune regulator gene) cause a severe multiorgan autoimmune disease.