Genetics and Genomics in Medicine Chapter 9 Questions

Multiple Choice Questions

Question 9.1

Which, if any, of the following can be classified as a type of augmentation therapy?

a) Treatment using a small molecule drug to bind a target protein and prevent it working.
b) A bone marrow transplant.
c) Corrective surgery for cleft lip and palate.
d) Insulin treatment in diabetes.

Question 9.2

With regard to treatment of inborn errors of metabolism (IEM), which of the following statements, if any, is false?

a) IEMs are all single gene disorders that have been studied for many decades, leading to the development of successful treatment in all cases.
b) IEMs can be treated by augmentation therapy, treatment to inhibit positively harmful effects, or by prevention therapy.
c) Treatment for some individual IEMs can involve both augmentation therapy plus treatment to inhibit positively harmful effects.
d) Treatment of some IEMs involves artificially forcing an increase in a minor metabolic pathway to counteract a build-up in a toxic metabolite produced by a metabolic block in a major metabolic pathway.

Question 9.3

Concerning the efficacy of small molecule drugs, which, if any, of the following statements is true?

a) At the level of clinical trials drugs can vary widely in how effective they are.
b) Once a drug has received regulatory approval, we can be sure that it will be effective in all patients, although some people will receive more benefit from it than others.
c) Drugs used to treat psychiatric disorders are particularly effective.
d) Stains and beta blockers that were meant to reduce the risk of heart disease are good examples of drugs that are largely ineffective.

Question 9.4

Which of the following descriptions, if any, is false? A person's ability to absorb or metabolize a drug that is intended to treat a genetic disorder

a) is entirely due to genetic factors.
b) depends on a person's lifestyle.
c) is not modified by having a bacterial infection.
d) is independent of a person's diet.

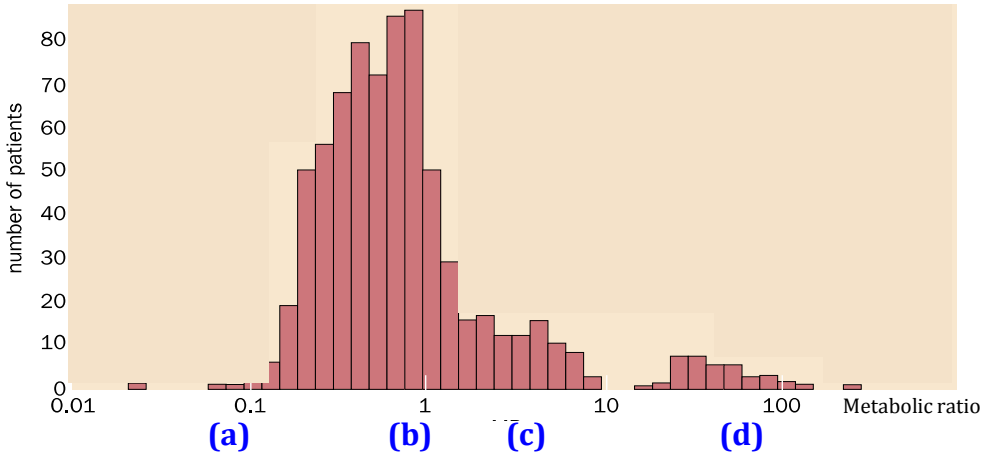
Question 9.5

With regard to drug metabolism, which, if any, of the following statements, is true?

a) The therapeutic window is simply the range of plasma drug concentrations in which the drug has therapeutic benefit.
b) Each individual drug molecule is metabolized by a specific drug-metabolizing enzyme that is dedicated to the metabolism of that drug.
c) An ultrafast metabolizer is a person who metabolizes a drug too quickly and so is at risk of an overdose
d) A poor metabolizer is a person who cannot metabolize a drug properly and is at risk of an underdose.

Question 9.6

The diagram below shows the urinary metabolic ratio as a measure of CYP2D6 enzyme activity in a total of about 700 individuals. After individuals were given a standard dose of a drug known to be metabolized by CYP2D6 the metabolic ratio was obtained by measuring the urinary concentration of the substrate drug and dividing it by the concentration of the metabolic product resulting from CYP2D6 acting on the drug. Classify individuals with metabolic ratios in the four ranges shown as (a) to (d) in terms of their drug-metabolizing abilities and describe the expected genotypes associated with each group.



Question 9.7

Which of the following statements, if any, is false?

a) Monoclonal antibodies are made by identical immune cells and so will recognize and bind just one specific epitope on a target molecule.
b) Monoclonal antibodies of rodent origin are far from ideal therapeutic agents because of their short half-life in human serum and the potential for immune responses by the recipient.
c) Humanized antibodies are hybrid antibodies that have constant regions of human origin but variable regions of rodent origin.
d) An intrabody is an artificial constructs with just a single chain that is linked to variable domains and, unlike regular antibodies with four polypeptide chains, has the potential to work inside cells.

Question 9.8

Which of the following statements, if any, is false?

a) Gene therapy involves the direct genetic modification of the cells of a person (or animal model) to achieve a therapeutic goal.
b) Current gene therapy is directed at modifying somatic cells.
c) The only successful gene therapies are those in which cells are removed from a patient, genetically modified, and then returned to the patient.
d) Gene therapy successes have largely involved treatment of recessively inherited disorders.

Question 9.9

Concerning stem cells, which of the following statements is incorrect?

a) Stem cells occur frequently in our bodies.
b) A stem cell can divide asymmetrically to give a daughter stem cell plus a daughter transit amplifying cell that can undergo a series of differentiation steps to give rise to a differentiated cell.
c) If for any reason, stem cells are depleted, a stem cell can divide symmetrically to regenerate the stem cell population.
d) In an adult person, stem cells are normally multipotent or unipotent.

Question 9.10

Concerning transport of genes into human (or animal) cells, which, if any, of the following statements is false?

a) Transduction means using viruses to transfer DNA into human (or other animal) cells.
b) Tropism refers to the ability of certain viruses to transduce only certain types of cell, such as hepatocytes, but not neurons.
c) Tropism depends on a virus being able to recognize a specific receptor molecule on the surface of the cell.
d) Transfection means transferring DNA into the cells by any means other than using viruses.

Question 9.11

Concerning gene transfer into human cells, which, if any, of the following statements is false?

a) Integrating viruses can insert genes into the chromosomes of a host cell.
b) Most integrating viruses insert their DNA into a specific location within the genome.
c) The great value of integrating viruses is that they allow foreign (and therefore, therapeutic) DNA to be stably inherited so that it passes to all descendant cells of the transduced cell.
d) Because non-integrating viruses cannot insert their DNA into the chromosomes of a cell, the transduced DNA is quickly destroyed by enzymes within the host cell.

Question 9.12

Concerning animal models of human disease, which, if any, of the following statements is false?

a) Primates should be the best animal models, but for mostly practical reasons, rodent models have been preferred.
b) Rats have been the preferred disease models because they offer the best balance between rapid breeding, size and the cost of maintaining colonies.

c) Rodent models are especially suited to modelling neuropsychiatric disorders.
d) All animal models have limitations regarding how far we can make inferences to help understand human disease.

Question 9.13

Concerning making animal models of human disease, which, if any, of the following statements is false?

a) Pronuclear microinjection is a general way of making a transgenic animal and involves microinjection of foreign DNA into a fertilized egg cell.
b) Pronuclear microinjection is best suited to modelling recessively inherited single gene disorders.
c) Gene targeting using embryonic stem cells depends on having well-characterized embryonic stem cell lines that can readily allow transmission through the germ line.
d) Gene targeting using embryonic stem cells in mice is a popular way of modelling disease phenotypes that result from a gain-of-function.

Question 9.14

Which, if any, of the following statements is false?

a) Hematopoietic stem cells are multipotent because they can give rise to a variety of different cell types.
b) Mammalian embryonic stem cell lines are pluripotent because they can give rise to all types of cell in the body.
c) Transdifferentiation is a type of epigenetic reprogramming in which a differentiated cell is induced to become pluripotent.
d) A transit amplifying cell is a cell produced by asymmetric division of a stem cell and has the potential to give rise to differentiated cells.

Question 9.15

Which, if any, of the following statements is false?

a) Transdifferentiation means reprogramming of a differentiated cell so that it acquires the characteristics of another type of differentiated cell.
b) In dedifferentiation a differentiated cell is artificially reprogrammed so that it behaves as a pluripotent cell.
c) Human induced pluripotent stem (iPS) cell lines are usually generated by artificial dedifferentiation of readily accessible human cells, such as skin cells.
d) Human iPS cell technologies do not offer clinical applications but they are of value for studying pathways of cellular differentiation

Question 9.16

Which, if any, of the following statements is true?

a) Autologous cell transplantation is involved in *in vivo* gene therapies: cells from an individual are genetically modified and then returned to that individual.
b) Adenovirus vectors have the advantage that they offer very high level expression and are well suited to gene therapy for blood disorders.
c) Adenovirus vectors have a better safety profile than adeno-associated virus vectors and have a larger insert size capacity.
d) Adeno-associated virus vectors are well suited to gene therapy for blood disorders but have a low insert size capacity

Question 9.17

Which, if any, of the following statements is false?

a) The great majority of clinical gene therapy trials have had limited success
b) The only successful gene therapies have been for recessive blood disorders.
c) The only successful gene therapies have been *ex vivo* gene therapies.
d) Gene therapy for inherited disorders represents a minority of clinical gene therapy trials.

Question 9.18

Which, if any, of the following statements is false?

a) RNA interference (RNAi) is a cellular defense mechanism that is triggered by the presence in cells of unnatural double-stranded RNA, as can occur after viral infections.
b) RNAi therapy is a type of RNA-targeted therapy in which specific double-stranded RNA constructs are engineered to appear in diseased cells in order to incite the cells to destroy any RNA that contains the same sequence.
c) By destroying RNAs that are related to a specifically introduced genetic construct, artificial RNAi is effectively a type of gene-specific silencing.
d) RNAi therapy is best suited to silencing genes so as to replicate a phenotype caused by loss-of-function mutations.

Question 9.19

Which, if any, of the following statements is false?

a) Genome editing means making a predetermined change to the nucleotide sequence at just one locus within an intact cell.
b) The specificity of genome editing depends on an initial site-specific cleavage of double-stranded DNA following base pairing with specifically designed nucleotide sequences.

c) Genome editing has the potential to permit specific "gene correction" in which a mutant sequence in a cell is restored to the normal sequence.
d) Genome editing might also have therapeutic potential by specifically inactivating a gene in some cases.

Question 9.20

Which, if any, of the following descriptions is false?

a) Zinc fingers are elements of protein secondary structure in which the polypeptide chain folds back upon itself after co-ordination of a Zn^{2+} ion with selected amino acids, often a pair of cysteines and a pair of histidines.
b) Zinc finger nucleases are natural proteins containing a sequence of zinc fingers that can bind to specific sequences in DNA.
c) After zinc finger nucleases bind to both DNA strands at a specific DNA sequence they attract cellular DNA cleavage enzymes, inducing them to make a double-stranded break at just that one position in the genome.
d) The CRISPR-Cas system also allows genome editing but in this case the target DNA sequences are recognized by guide RNA sequences rather than proteins.

Fill in the Blanks Questions

Question 9.21

Fill in the blanks with single words.

In some diseases the problem is the loss of some function and a type of ____1_____ therapy is used to supplement the resulting deficiency. It may be a deficiency in some normal aspect of the ____2_____, such as deafness, a deficiency of organs or ____3____ , or a deficiency of molecules (which might be at the level of ____4_____ , ____5_____ , or downstream factors). Sometimes, however, disease is not due to a deficiency; instead, the problem is that there is some positively _____6_____ effect produced at some level (at the level of the phenotype, ____3_____ or ____4_____), that cannot be supplemented. Here treatment is possible by seeking to eliminate, correct or ____ 7_____ the agent causing the positively _____6_____ effect. The treatment might seek to kill dangerous _____3____ , for example, or to ____7_____ a _____6_____ _____4_____ or a _____7_____ _____6_____. In the latter case, the treatment might often be to use some kind of _____8_____ , such as a conventional ____9_____ molecule ____8_____ that usually works by binding to a cleft in the _____6_____ _____5_____ and thereby ____7____ its ____6____ effect. A third class of disease treatment seeks to use a ____8____ in order to alter a person's ______10_______ to the disease, or to alter exposure to some _____11_____ factor.

Question 9.22

Fill in the missing blanks with single words.

In the recent past, virus vectors used in gene therapy trials were often based on a type of retrovirus called a ______1_______retrovirus. They had the advantage of allowing a _____2_____ DNA to be stably inserted into the _____3____ DNA of cells. For cells that are short-lived, such as blood cells, the hope was that a certain percentage of _____4_____ cells might be successfully transduced so that there was a self-renewing population of cells carrying the desired _____2_____ DNA. Unfortunately, vectors based on ______1_______retroviruses have a poor safety profile: there is little control over where they ______5_______ into the _____3____ DNA and sometimes when they _____5_____ they activate a neighboring _____6_____, causing _____7_____. As a result, in modern gene therapy trials it is now commonplace to use self-_____8______ strains of a class of retrovirus vectors known as _____9____ that are much safer to use.

Question 9.23

Fill in the missing blanks with single words.

Genome _____1_____ means artificially introducing a specific change in the DNA sequence at a unique, pre-determined location within the genome of an ____2____ cell. The method relies on some form of recognition of specific sequences on both DNA strands at a locus that then allows an artificially introduced _____3____-stranded DNA break at this location. In response to the _____3____-stranded DNA break, DNA repair is carried out by the cell but after using non_____4_____ end joining DNA repair, errors can be made in the repair that can occasionally result in a desired specific DNA change. In one system genetically engineered _____5_____ _____6_____ nucleases are used in which a DNA is constructed to code for a specific sequence of _____5_____ _____6_____ and is then ligated to a DNA sequence that will specify a DNA _____7_____ domain. A plasmid containing the resulting DNA construct can encode a _____5_____ _____6_____ nuclease when transfected into a cell. Using this technology, a pair of _____5_____ _____6_____ nucleases can be designed to bind to specific sequences on the opposite DNA strands at a desired unique position in the genome and the adjoining DNA cleavage domains work to produce the required ____3_____–strand DNA break.

Essay and Listing Questions

Question 9.24
There are three broad classes to disease treatment. Give a brief outline of the three classes.

Question 9.25
Four stages are often identified in drug development: a preclinical stage plus three clinical trial stages. What is involved in these?

Question 9.26
Many of the genes that produce the enzymes and other proteins involved in handling drugs are polymorphic. Why should that be?

Question 9.27
What distinguishes phase I and phase II reactions in the metabolism of small molecule drugs?

Question 9.28
Using the example of genes encoding cytochrome P450 enzymes, illustrate how genetic variation in drug-metabolizing enzymes can often stem from gene copy number variation.

Question 9.29
In some cases, genetic variation at multiple loci is known to affect the response to a specific drug. What is known about genetic variation that affects our responses to the anticoagulant warfarin?

Question 9.30
Sometimes, a prescribed drug can be dangerous, and occasionally deadly, according to a patient's genotype. Give three examples of such.

Question 9.31

The *CFTR* gene that underlies cystic fibrosis was isolated by positional cloning in 1989. Twenty years later, Jack Riordan, one of the major contributors to this historic achievement, was quoted as saying "the disease has contributed much more to science than science has contributed to the disease". What did he mean by this, and what important developments have occurred in treating cystic fibrosis since 2009?

Question 9.32

There are two broad principles regarding the technological aim of somatic gene therapy: (a) genetically modifying disease cells (without killing them), and (b) killing disease cells either directly or indirectly. Explain what is involved in the two strategies.

Question 9.33

In mammals, pluripotent cells occur naturally in the early embryo but pluripotent cell lines can also be artificially created. The first approach was to make embryonic stem cell lines from cells isolated from early embryos. More recently, pluripotent cell lines have been made by artificially changing the epigenetic settings of differentiated cells. What is involved in the latter case?

Question 9.34

Describe the characteristics of two viral vectors based on RNA genomes and two viral vectors based on DNA genomes that are used in gene therapy.

Question 9.35

Hematopoietic stem cells can be important target cells in gene therapy for blood disorders and some other disorders, including certain brain disorders. Explain the significance of hematopoietic stem cells and how they are exploited in gene therapy.

Question 9.36

What possible clinical applications might be derived from induced pluripotent stem cell technologies?

Question 9.37

Molecular therapeutic strategies sometimes target RNA instead of DNA. What is involved in RNA interference therapy, and how useful has it been?

Question 9.38

How has exon skipping therapy been applied to treat Duchenne muscular dystrophy?

Question 9.39

Genome editing is being used in an attempt to cure HIV-AIDS. What is the experimental strategy towards achieving that goal?

Question 9.40

How might a form of germ-line gene therapy be used to treat severe mitochondrial diseases?