LEGO® DNA/RNA
Booklet 2: Advanced DNA Topics

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There are 2 mats for the DNA nucleotides. There is only 1 mat for the RNA nucleotides. Which nucleotides have an orange brick? Which have a gray brick?

Note: This LEGO Kit has 12 of each DNA nucleotide, 6 of each RNA nucleotide, and 2 white markers.

Additional LEGO parts required for the activities in this booklet: 1 red 1x4 brick, 2 gray phosphate cylinders, and 2 gray connector clips.

This booklet assumes you have completed LEGO DNA/RNA Booklet 1: Structure, Replication, and Transcription.
Nucleotide Structure and DNA Synthesis

Summary: In this section, we focus on the key chemical features of nucleotides influencing DNA structure and synthesis. The key features of nucleotides are the 3’ and 5’ carbon positions on the sugars which orient the DNA strands in opposite directions, the triphosphates needed for DNA synthesis, and the hydrogen bonds that form between the bases.

Review the parts of a nucleotide: phosphate group, sugar, and base. In DNA, which bases are bigger? The bigger bases are purines and the smaller bases are pyrimidines.
To better understand nucleotide chemistry, we will look at the sugar, phosphate group, and base components one at a time. Focus on the sugar first.

Examine the carbon atoms numbered in pink. These carbons in the sugar are numbered with a prime mark to distinguish them from carbon atoms located in the base.

Notice the 3’ (or 3-prime) carbon and the 5’ (or 5-prime) carbon appear on opposite ends of the sugar. These carbons establish the nucleotide’s orientation and determine where DNA synthesis can occur. The 5’ end of the nucleotide is always attached to a phosphate group and the 3’ end is free. This 3’ end is the site where the next nucleotide can be attached.
Next we will examine the phosphate groups and their role in DNA synthesis.

DNA polymerases are enzymes that synthesize DNA. DNA polymerases can elongate a DNA strand by attaching single nucleotides to the free 3′ end. Look at the reaction below.

DNA nucleotides have three phosphates when polymerases attach them to a DNA strand. They are called deoxyribonucleoside triphosphates. Each time a polymerase attaches one of these nucleotides to the end of a DNA strand, a pyrophosphate (a group of two phosphates) is released. Releasing the pyrophosphate provides the energy to drive the reaction. Thus the DNA polymerase can synthesize long strands of DNA very quickly and efficiently.
Now synthesize a strand of DNA the way a DNA polymerase does. First build a deoxyribonucleoside triphosphate.

1. Find these extra nucleotide components: two phosphates (hollow gray cylinders) and two gray connector clips. Assemble the two extra phosphate groups as shown to the right.

2. Create a triphosphate nucleotide. Attach the extra two phosphates to the phosphate end of a G to create a guanosine triphosphate (a G with three phosphates).

Now model the DNA polymerase attachment reaction.

3. Find an A and remove the pyrophosphate from the G.

4. Attach the G to the A.

Remember that new DNA nucleotides are always added onto the 3’ end of the existing nucleotide or strand, in direction of the arrows on the bases.
5. Continue building this strand of DNA: 5’ - AGC TTC - 3’. Make each incoming nucleotide a triphosphate, then remove the pyrophosphate when you connect it to the strand, like the DNA polymerase does.

6. Check your final strand with the one in the photo below.
Lastly we will focus on the bases and how they interact.

DNA is usually double stranded. **Hydrogen bonds** hold the bases together in pairs (A-T) and (G-C) and connect the two strands of DNA. Hydrogen bonds are shown as dotted lines in the figure below between the A-T and G-C. In the LEGO model, they are represented by the black ball-and-socket joint. Hydrogen bonds are weak (easily made and easily broken) allowing the two DNA strands to separate temporarily for many important processes. Which base pair (A-T) or (G-C) has fewer hydrogen bonds and will separate more easily?

The black arrows on each LEGO nucleotide indicate the 3’ end of each subunit. Look carefully at the two strands. DNA is **antiparallel**. This means the strands are oriented in opposite directions (5’ to 3’ and 3’ to 5’) as shown with the pink arrows.
7. Place your previous DNA strand upside down with the 5’ A on the top left. We do this because scientists typically write DNA sequences with the 5’ end starting on the top left.

8. Create the complimentary DNA strand. Join the two strands by connecting the base pairs. Check that your new strand has its 3’ end on the bottom left. The DNA polymerase would bring in all nucleotides as triphosphates, but to make it easier for us to build, you can just use monophosphates (nucleotides with one phosphate).
9. Practice opening and closing the DNA by pinching and pulling up on the sides of the DNA double strands. The strands should pop apart easily.

10. Snap the two strands back together.

11. Join your DNA strands with the others around you (as your instructor directs) to create a long DNA molecule. Twist it and observe the double helix structure.
NEXT PAGE FOR ADVANCED REPLICATION
Advanced DNA Replication

Summary: The process of copying a DNA molecule is called DNA replication. DNA replication is not a symmetric process. Since DNA polymerases can only add nucleotides to the 3’ end of a strand when DNA is replicated, it has a leading strand and a lagging strand. We will model replication in bacteria. Replication in humans is slightly different.

1. Build the top strand of DNA: 5’ - ACG GTA CGC TAT - 3’. Note the arrows on the individual nucleotides mark the location of the 3’ end. On the top strand they point to the right. Make a complementary bottom strand of DNA using the base pairing rules and keep the arrows pointing to the left.

2. Add a white marker to the first A on the top strand and to the first T on the bottom strand. Both strands of the original DNA are now marked so that we can see what happens to them.

Notice the white markers on the original strands.
Now we begin the process of DNA replication!

3. Pinch open about eight DNA pairs from the left side, as shown in the photo.

Remember that the weak hydrogen bonds (represented by the ball-and-socket joint) allow the two DNA strands to separate easily. Opening the DNA requires two enzymes in our cells. Helicases unwind and separate the DNA strands, and topoisomerases relieve the twisting stress on the downstream DNA.

4. Base pair one nucleotide to the end of both strands. Check that the nucleotides are antiparallel.

5. Figure out which nucleotide can be added onto. Use the box below to help you.

Think About It!

Which nucleotide (A or T) can be added onto in the direction of the moving replication fork?

Remember:
• The DNA polymerase can only add nucleotides onto the 3’ end.
• The 3’ end has no phosphate group (as shown in the photo).

Make your guess before continuing on the next page.
6. Remove the T from the top strand. Replication cannot proceed on the top strand in the direction of the replication fork. We will proceed with replication on the bottom strand, called the leading strand, first.

Remember that nucleotides are actually deoxyribonucleoside triphosphates when they are being added to the DNA strand. We will simulate a couple of reactions with triphosphates for effect.

7. Make the incoming C a triphosphate. Add two connector clips and two more phosphate groups (hollow cylinders) to the existing C as shown in the photo.
8. Add the cytosine triphosphate to the leading strand by base pairing.

Cells have many DNA polymerases, not just one. They all perform specific functions. DNA polymerase I (Pol I) synthesizes the first few nucleotides of each new strand.

9. Release the pyrophosphate and create the sugar-phosphate bond on the 3’ end of the growing strand. Recycle the pyrophosphate and add it to the next incoming nucleotide.
10. Base pair the incoming guanine triphosphate, adding it to the leading strand as shown.

11. Release the pyrophosphate and create the sugar-phosphate bond.

For simplicity, we will no longer continue to simulate the incoming nucleotides as triphosphates (although they are all triphosphates when they are added). Join the nucleotides directly to each other in the rest of the steps.

12. Continue bringing in nucleotides and adding them to the leading strand until six base pairs have been completed.
13. Now we’ll start to replicate the top strand, or lagging strand. Add a nucleotide to the third nucleotide (G) on the lagging strand, as shown in the photo. Be sure to orient the 3’ and 5’ ends correctly on this nucleotide.

DNA polymerase I (Pol I) starts synthesizing both the leading and lagging strands. But after a small number of nucleotides, it is replaced by DNA polymerase III (Pol III). Pol III can add nucleotides more quickly, so it takes over synthesis of both strands.

14. Continue adding nucleotides to the lagging strand until the end of the strand.

15. Pinch open the replication fork further and continue replication on the leading strand (bottom strand) in the direction of the fork.
16. Add another nucleotide on the lagging strand, opposite the next C closer to the replication fork, as shown in the photo.

17. Add two more nucleotides to the lagging strand. Note that there is a gap, a missing base pair. This is what happens in cells, as different enzymes are required for different steps in DNA replication.

18. Pinch open the replication fork completely.
19. Complete DNA replication on the leading strand. Make one more fragment on the lagging strand, as shown below.

We replicated a very short segment of DNA (12 base pairs), but most chromosomes are millions of base pairs long! In cells, the DNA strands open in several different places along a chromosome, called replication origins, to complete DNA replication.

Think About It!

*Can you explain why one strand might be called “leading” and one strand called “lagging”? Which strand took longer to create?*
Finally, the lagging strand gaps are filled in and stitched together by special enzymes. Pol I adds the missing nucleotides to the lagging strand. DNA ligase joins the small fragments together by creating sugar-phosphate bonds. Because of these extra steps, the lagging strand takes longer to create.

20. Add the missing nucleotides and join the fragments together.

![Diagram of DNA replication](image)

Congratulations, DNA replication is complete!

21. Look carefully at your two molecules of DNA. Are both molecules identical? Notice the white markers on the molecules. Remember you marked the original DNA strands. Where did they end up?

DNA replication is called a **semi-conservative** process. One strand is conserved (or kept) in the copying process. In other words, there is one original strand in each new molecule.
DNA Damage

Summary: DNA is constantly damaged. During normal respiration in cells, reactive oxygen species are created. Reactive oxygen species are chemically reactive molecules containing oxygen atoms. Reactive oxygen species can alter or damage the molecules around them. In this activity, an oxygen atom will combine with a G to form a damaged nucleotide called 8-oxo-G. If DNA replication occurs before the 8-oxo-G has been repaired, the replication process will produce an A-T base pair instead of a G-C base pair at this site! We will model this process in human cells.

1. Build this DNA sequence: 5’- A T G G G G - 3’ Place the 5’ on the top left and create the complementary bottom strand. Add the 2 white markers to indicate the 2 original DNA strands in replication.

Breathing oxygen is harmful to your DNA! Cell processes such as cellular respiration produce reactive oxygen molecules that have unpaired oxygen atoms. These atoms readily bind to nearby molecules. Guess how many times per day your DNA is damaged? (The answer in the back of the booklet may surprise you.)
2. Add an extra oxygen atom (tall red brick) to the G as shown. This G is called an 8-oxo-guanine (8-oxo-G). The 8 refers to the oxygen’s exact binding site on the G.

Let’s see what happens if the 8-oxo-G is not repaired and DNA replication begins...

3. Pinch open 5 DNA pairs from the right, as shown in the photo. We will follow the replication fork going towards the left.

4. Place an A opposite the 8-oxo-G. Note the two LEGO nucleotides are too wide. Let them form an arch or tent-shaped connection.

In real life, the 8-oxo-G rotates around to create a better fit and acts more like a T than a G. This is why the DNA polymerase inserts an A here instead of a C.
5. Replicate both strands of DNA completely. Look for the white markers. One should be located on each new DNA molecule as shown to the right. We’ve named these DNA molecules alpha and beta.

6. Look closely at DNA molecule beta. Compare this DNA sequence with the original DNA sequence on page 21. The sequences should be the same. This DNA molecule has replicated correctly. It was copied from the undamaged strand of DNA. Set DNA molecule beta aside for the DNA Repair activity on page 25.

Now let’s observe DNA molecule alpha with the oxygen damaged G. Let’s discover what happens when this damaged DNA molecule undergoes replication for the second time.

7. Pinch open DNA molecule alpha and replicate the top strand completely. Remember to pair an A opposite the 8-oxo-G since this is the best match that the DNA polymerase can make.

8. Replicate the bottom strand completely. All the base pairs are normal here.
9. Look at your two new DNA molecules and observe the effects of this replication cycle. Notice that the A-T base pair on the right side of the bottom molecule is a normal base pair. It is entirely unremarkable. Which new DNA molecule, top or bottom, now contains a mutation that cannot be repaired?

10. Look again at your DNA models and imagine what will happen in future replication cycles. Note that the mutant A-T base pair on the bottom strand will now be passed on to each new DNA molecule every time replication occurs. When this cell divides from now on, it will only create cells with this mutation.

With this activity, you have seen how small changes in the structure of DNA bases can lead to mispairing. Mispairing of bases can lead to mutations, or changes in the DNA sequence. Fortunately, cells have special DNA repair proteins that remove the 8-oxo-G base pairs so these mutations won’t occur during replication. We will learn about them next.

Congratulations! You have just demonstrated one way a mutation is produced!

Think About It!

Some common reactive oxygen species include:
- Superoxide \( \text{O}_2^- \)
- Peroxide \( \text{O}_2^{-2} \)
- Hydrogen Peroxide \( \text{H}_2\text{O}_2 \)
- Hydroxyl ion \( \text{OH}^- \)

Reactive oxygen species (ROS) damage many cell structures, not just DNA. Antioxidants (such as Vitamin C and E) are molecules that help limit the damage done by ROS in cells.
DNA Repair

Summary: Now we’ll explore how the DNA repair protein human oxo-guanine glycosylase (hogg1) prevents mutations by removing 8-oxo-G damaged bases. We will model one example of base excision repair. Base excision repair is used to remove small structural damage to DNA nucleotides.

1. Find DNA molecule beta that you set aside in step 6 of the previous activity. Or you can build the original DNA molecule as shown in the photo above. Either way, we begin with an undamaged DNA strand, the same as our original strand.

2. Find an oxygen atom (tall red brick) and attach it to the 5th nucleotide on the top strand, a G. This is the damaged base that will need to be fixed.

The DNA repair protein hogg1 moves along the DNA and detects this damaged base by its odd shape. The repair protein then flips the 8-oxo-G nucleotide away from its base pair, moving the 8-oxo-G outside of the DNA ladder.

3. Disengage the LEGO 8-oxo-G from its base pair and flip the nucleotide so it points away from the DNA chain, as shown. The 8-oxo-G is now outside of the DNA helix and is positioned precisely inside the repair protein.
Next the repair protein functions as an enzyme, cutting out the 8-oxo-G base and moving on to check the rest of the strand. Other proteins will arrive to release the entire nucleotide. This leaves a gap in the DNA strand.

4. Remove the 8-oxo-G nucleotide from the top strand to leave a gap in the DNA sequence.

Additional repair enzymes will finish the repair. DNA polymerase beta (Pol β) will base pair a new G opposite the C. Then the 3’ and 5’ ends of the new G will be joined to the strand by DNA ligase.

5. Add a normal G into the gap. Base pair with the C and join the 5’ and 3’ ends into the strand.

Congratulations! The DNA repair has been successful.

Think About It!

One way to tell bacterial and human polymerases apart is by their names. Bacterial DNA polymerases have numbers: Pol I, Pol II, and Pol III. Human DNA polymerases have greek letters: Pol β, Pol δ, Pol ε (beta, delta, epsilon).
NEXT PAGE FOR DNA MUTATIONS
DNA Mutations

Summary: A mutation is defined as any change in the nucleotide sequence of DNA. This lesson will familiarize you with the two major types of mutations: 1) substitutions and 2) additions and deletions. Substitutions can be further classified into three more types: silent, missense, and nonsense mutations. The detrimental effects of these mutations and their resulting diseases will be described. However, do keep in mind that mutations are not all bad. Mutations produce a wealth of genetic diversity in nature, and this can be very beneficial for survival.

1. Build this short sequence of DNA nucleotides: 5’ - CCC GAG CAG - 3’ This sequence is part of a gene. Mark the 5’ end on the top left with a white marker.
This LEGO gene sequence will serve as the wild type gene. Wild type (wt) is any sequence that is a common or standard reference. You will mutate this DNA in several steps to create different proteins. The next steps will require use of a LEGO Protein Kit. If you do not have a LEGO Protein Kit available, you can write the protein sequences on a piece of paper instead.

2. Complete the double stranded DNA as shown below. Check the directions of 3’ and 5’ nucleotides: the top strand arrows should point to the right, the bottom strand arrows should point to the left.

   ![Diagram of DNA strands with codons labeled as Codon 1, Codon 2, and Codon 3.]

3. Use the DNA Codon Chart (page 41) to look up the amino acids for the three codons. Remember the top strand is the coding strand. You should only decode the top strand.

4. Place each amino acid below its codon. Then join the amino acids into a short chain. (Or write down the protein sequence on a sheet of paper.) This protein will serve as the wild type protein.
5. Check your protein sequence, it should look the same as the sequence below: Pro, Glu, Gln. Also check that you are keeping the amino end (black LEGO brick) to the left as you create the protein.

The 5’ end of the gene always codes for the first amino acid. The first amino acid (Pro in this chain) has a free amino group. This is called the amino end, or the N terminal end of the protein. The last amino acid (Gln in this chain) has a free acid group. This is called the acid end, or the C terminal end of the protein.

Keep this LEGO protein chain as a reference. It is the wild type protein, which was produced from the original (non-mutated) gene. Next we will see what happens to the protein after several mutations have occurred in the gene.
6. Separate the wild type (wt) gene into the three codons. This will help prepare for the three single nucleotide substitutions that you will make in the next step.

7. Substitute three T nucleotides as shown below in the pink boxes. Your DNA sequence should now read: 5′- CCT GTG TAG - 3′

8. Decode the new DNA sequence with its three mutations using the DNA Codon Chart (page 41). Place each amino acid below its codon. Join the amino acids to form a new protein chain.
9. Check your protein sequence, it should look the same as the sequence below: Pro, Val.

10. Compare this DNA sequence with the wild type DNA sequence in Step 4 (page 29). Remember you made three substitutions, or changes, in the original DNA sequence, one in each codon. These are called substitution mutations.
10. Arrange your two small protein chains as shown. Compare the wild type protein with the mutated protein.

Each of the three codons was mutated by a substitution of one nucleotide. Substitutions can be classified by their effects on the amino acid sequence.

11. Match each type of substitution with its effect. Use the box below to help you.

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**Think About It!**

*Which codons show the following types of mutations?*  
*(Hint: Compare the wild type and mutated sequences in the boxes above.)*

- **Missense Mutation** = A nucleotide substitution that changes one amino acid into another.
- **Nonsense Mutation** = A nucleotide substitution that creates an early STOP codon. During translation, the ribosome stops too early, creating a protein that is too short.
- **Silent Mutation** = A nucleotide substitution that does not change the amino acid sequence of the protein.

Make your guess before continuing on the next page.
12. Check your answers and read about the connections between mutations and human diseases below.

Codon 1 illustrates a silent mutation. The amino acid sequence of the final protein isn’t affected. In most cases, there will not be a problem with the protein, and it will not cause a disease. However, recent research shows that some silent mutations may have effects on protein folding, and therefore, protein function. Silent mutations may also affect splicing signals, creating changes in protein structure.

Codon 2 illustrates a well-known missense mutation that causes Sickle Cell Disease. The codon GAG becomes GTG and as a result, glutamic acid becomes valine in every beta hemoglobin protein. This causes the red blood cells to be deformed in low oxygen conditions.

Codon 3 illustrates a famous nonsense mutation that causes a different genetic disease, Thalassemia. This is another way a hemoglobin protein can be defective: the stop codon occurs too early. In codon 3 above, CAG becomes TAG. This single nucleotide substitution creates a stop signal too early in the gene sequence. The resulting hemoglobin protein is too short, which makes it non-functional.
You have now illustrated the first major type of mutations: substitutions. Next let’s create DNA examples of the second major type of mutations: **additions** and **deletions**.

13. Add one T (with its base pair, A) to the beginning of your gene as shown in the pink box below. Regroup the nucleotides into new groups of **three** as shown. There will be one base pair left over at the end.

An addition of one nucleotide will change the total number of nucleotides in the gene. All nucleotides following this addition will be rearranged into different triplets, or codons. This is called changing the **reading frame** of the gene.

14. Use the DNA Codon Chart (page 41) and build this protein.
15. Check your protein sequence, it should look the same as the sequence below: Ser, Cys, Val. Save this protein chain with the others.

Notice that changing the reading frame will produce different amino acids after the addition, creating a very different protein. This is called a frameshift mutation.
16. Another mutation that can cause drastic changes in a protein is a deletion. Compare the DNA sequence below with the DNA sequence that you have now (from Step 13). The deletion of one nucleotide occurred at the pink arrows.

Think About It!

Will an addition or deletion of three nucleotides change the reading frame of the gene?

17. Recreate this deletion in your LEGO DNA sequence. Remove the third nucleotide pair (C-G) from your DNA and regroup the nucleotides as shown above. The deletion of one nucleotide will also change the reading frame of the gene.

18. Use the DNA Codon Chart (page 41) and build this protein.
19. Check your protein sequence, it should look the same as the sequence below: Ser, Val. Save this protein chain with the others.

The deletion of one nucleotide will also change the reading frame of the gene, producing a very different protein. This deletion is also a frameshift mutation.

Most of the time, an addition or deletion of nucleotides will shift the reading frame. But if the addition or deletion is a multiple of three, amino acids will be added to or subtracted from the protein chain, but it will not cause a frameshift.
20. Arrange all your proteins as shown below and note the diversity of these simple protein products.

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<th>Codon Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<td>Protein resulting from 3 substitution mutations</td>
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<td>Protein resulting from 1 nucleotide deletion</td>
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<tr>
<td>(Step 18)</td>
<td>Ser</td>
<td>Val</td>
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Congratulations! You have successfully created all the sample mutations in this lesson.
Review: Remember that a mutation is defined as any change in the DNA sequence. You’ve now illustrated the two major types of mutations: 1) substitutions and 2) additions and deletions.

In one protein chain, you created the three types of substitution mutations: silent, missense, and nonsense. Remember that a missense mutation changes one amino acid to another, a nonsense mutation changes an amino acid to a STOP codon, and a silent mutation does not change the amino acid sequence at all.

Additions and deletions can cause even bigger changes in the resulting protein. Since our DNA is read three bases at a time, an addition or deletion that is a multiple of three will add or subtract amino acids from the protein chain. But an addition or deletion that is not a multiple of three will cause a shift in the reading frame of the gene. This will change the entire protein sequence after the shift!

Some of these mutations cause diseases, like cystic fibrosis, but occasionally mutations can be very beneficial for survival. Mutations provide the diversity by which natural selection can work in evolution.

Conclusion: Small DNA nucleotide changes in a gene can create huge changes in proteins or no changes at all!
## DNA Codons for Amino Acids

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<th>Amino Acid</th>
<th>Codons</th>
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<td>Lysine</td>
<td>AAA, AAG</td>
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<td>AAT, AAC</td>
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## RNA Codons for Amino Acids

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<td>Threonine</td>
</tr>
<tr>
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<td>C</td>
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<tr>
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</tr>
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<td>Tryptophan</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>G</td>
<td>C</td>
<td>Phenylalanine</td>
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Answer Key

Page 3: A (adenine) and G (guanine) are bigger bases, or purines.
Page 8: G-C base pairs have three hydrogen bonds and A-T base pairs have two hydrogen bonds. Therefore A-T base pairs are less stable and will separate more easily.
Page 13: Think About It! Only the A nucleotide can be added onto in the direction of the replication fork.
Page 19: Think About It! The lagging strand took longer to create because the gaps between fragments needed to be filled.
Page 20: Yes, both molecules are identical. One original strand ended up in each new DNA molecule.
Page 21: The current estimation is that our DNA is damaged about 100,000 times per day in every cell.
Page 24: The bottom DNA molecule has a mutation that cannot be repaired, because A-T is a normal base pair, but different than the original sequence.
Page 33: Think About It! Codon 1 = silent mutation, Codon 2 = missense mutation, Codon 3 = nonsense mutation.
Page 37: Think About It! An addition or deletion of three nucleotides will not change the reading frame of the gene, since nucleotides are read in groups of three.