MHCC Biology 112: Biology for Health Professions

MHCC Biology 112: Biology for Health Professions

LISA BARTEE AND JACK BROOK

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Part VII. Protein Synthesis

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Introduction

BI112 Course Description: This course is an introduction to the science of biology for students intending to take Anatomy and Physiology (BI231-233). The physical and chemical concepts as they apply to the study of life are introduced. BI112 lecture includes the principles of the scientific method, basic cell structure and function, respiration, cell division, Mendelian and non-Mendelian genetics and molecular genetics. Laboratory will require group collaboration in hands-on demonstration of the physical, chemical and genetic concepts.

Course and Student Learning Outcomes

1. Answer biological questions by applying the scientific method; collecting, analyzing, and interpreting reliable data; and forming a conclusion
2. Communicate information using appropriate biological terminology in multiple formats
3. Use evidence to develop informed opinions on issues affecting human health such as stem cells, cloning, and genetic engineering, while considering cultural and ethical implications
4. Discuss and apply biological theories and key concepts about cellular form and function including cell structure and metabolic processes
5. Discuss and apply biological theories and key concepts about cell division including mitosis and meiosis

6. Discuss and apply biological theories and key concepts to solve problems related to classical and molecular genetics, including pedigree analysis
7. Discuss the structure and function of DNA, including the potential implications of mutations on protein production and function at a cellular and organismal level
8. Describe the purpose of and mechanisms through which gene expression is regulated

PART I

THE PROCESS OF SCIENCE

THE PROCESS OF SCIENCE

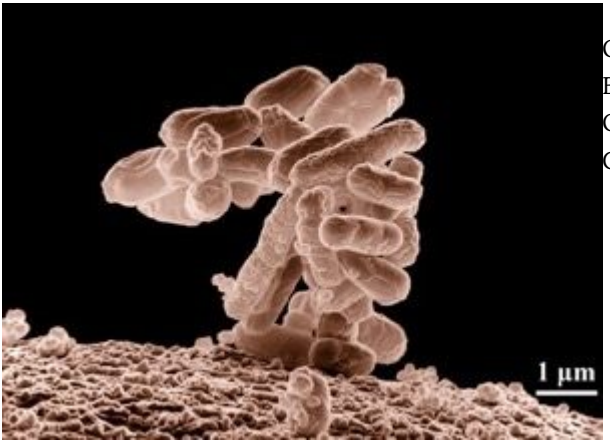
Learning Objectives

Course Objective for this section: Understand the process of scientific inquiry in order to apply the scientific method to biological questions by designing experiments and using the resulting data to form a conclusion

- Design a controlled experiment to answer a biological question.
- Predict the outcome of an experiment.
- Collect, manipulate, and analyze quantitative and qualitative data
- Answer a biological question using data.

Like geology, physics, and chemistry, **biology** is a science that gathers knowledge about the natural world. Specifically, biology is the study of life. The discoveries of biology are made by a community of researchers who work individually and together using agreed-on methods. In this sense, biology, like all sciences is a social enterprise like politics or the arts. The methods of science include careful observation, record keeping, logical and mathematical reasoning, experimentation, and submitting conclusions to the scrutiny of others. Science also requires considerable imagination and creativity; a well-designed experiment is commonly described

as elegant, or beautiful. Like politics, science has considerable practical implications and some science is dedicated to practical applications, such as the prevention of disease (see Figure 1.1). Other science proceeds largely motivated by curiosity. Whatever its goal, there is no doubt that science, including biology, has transformed human existence and will continue to do so.



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1. Hypothesis Testing

Biology is a science, but what exactly is science? What does the study of biology share with other scientific disciplines? **Science** (from the Latin scientia, meaning "knowledge") can be defined as knowledge about the natural world.

Biologists study the living world by posing questions about it and seeking science-based responses. This approach is common to other sciences as well and is often referred to as the **scientific method**. The scientific process was used even in ancient times, but it was first documented by England's Sir Francis Bacon (1561–1626) (**Figure 1**), who set up inductive methods for scientific inquiry. The scientific method is not exclusively used by biologists but can be applied to almost anything as a logical problem solving method.

Figure 1*Sir Francis Bacon (1561–1626) is credited with being the first to define the scientific method. (credit: Paul van Somer)*

Question

The scientific process typically starts with an **observation** (often a problem to be solved) that leads to a **question.** Science is very good at answering questions having to do with observations about the natural world, but is very bad at answering questions having to do with purely moral questions, aesthetic questions, personal opinions, or what can be generally categorized as spiritual questions. Science has cannot investigate these areas because they are outside the realm of material phenomena, the phenomena of matter and energy, and cannot be observed and measured.

Questions that can be answered using science	**Questions that cannot be answered using science**
• What is the optimum temperature for the growth of E. coli bacteria?	• How tall is Santa Claus?
• Do birds prefer bird feeders of a specific color?	• Do angels exist?
• What is the cause of this disease?	• Which is better: classical music or rock and roll?
• How effective is this drug in treating this disease?	• What are the ethical implications of human cloning?

Let's think about a simple problem that starts with an observation and apply the scientific method to solve the problem. Imagine that one morning when you wake up and flip a the switch to turn on your bedside lamp, the light won't turn on. That is an observation that also describes a problem: the lights won't turn on. Of course, you would next ask the question: "Why won't the light turn on?"

Hypothesis

A **hypothesis** is a suggested explanation that can be tested. A

hypothesis is NOT the question you are trying to answer – it is what you think the answer to the question will be ***and why***. Several hypotheses may be proposed as answers to one question. For example, one hypothesis about the question "Why won't the light turn on?" is "The light won't turn on because the bulb is burned out." There are also other possible answers to the question, and therefore other hypotheses may be proposed. A second hypothesis is "The light won't turn on because the lamp is unplugged" or "The light won't turn on because the power is out." A hypothesis should be based on credible background information. A hypothesis is NOT just a guess (not even an educated one), although it can be based on your prior experience (such as in the example where the light won't turn on). In general, hypotheses in biology should be based on a credible, referenced source of information.

A hypothesis must be *testable* to ensure that it is valid. For example, a hypothesis that depends on what a dog thinks is not testable, because we can't tell what a dog thinks. It should also be *falsifiable*, meaning that it can be disproven by experimental results. An example of an unfalsifiable hypothesis is "Red is a better color than blue." There is no experiment that might show this statement to be false. To test a hypothesis, a researcher will conduct one or more experiments designed to eliminate one or more of the hypotheses. This is important: *a hypothesis can be disproven, or eliminated, but it can never be proven.* If an experiment fails to disprove a hypothesis, then that explanation (the hypothesis) is supported as the answer to the question. However, that doesn't mean that later on, we won't find a better explanation or design a better experiment that will disprove the first hypothesis and lead to a better one.

Variables

A variable is any part of the experiment that can vary or change

during the experiment. Typically, an experiment only tests one variable and all the other conditions in the experiment are held constant.

- The variable that is being changed or tested is known as the **independent variable**.
- The **dependent variable** is the thing (or things) that you are measuring as the outcome of your experiment.
- A **constant** is a condition that is the same between all of the tested groups.
- A **confounding variable** is a condition that is not held constant that could affect the experimental results.

Let's start with the first hypothesis given above for the light bulb experiment: the bulb is burned out. When testing this hypothesis, the independent variable (the thing that you are testing) would be changing the light bulb and the dependent variable is whether or not the light turns on.

- HINT: You should be able to put your identified independent and dependent variables into the phrase "dependent depends on independent". If you say "whether or not the light turns on depends on changing the light bulb" this makes sense and describes this experiment. In contrast, if you say "changing the light bulb depends on whether or not the light turns on" it doesn't make sense.

It would be important to hold all the other aspects of the environment constant, for example not messing with the lamp cord or trying to turn the lamp on using a different light switch. If the entire house had lost power during the experiment because a car hit the power pole, that would be a confounding variable.

You may have learned that a hypothesis can be phrased as an "If..then..." statement. Simple hypotheses can be phrased that way (but they must always also include a "because"), but more

complicated hypotheses may require several sentences. It is also very easy to get confused by trying to put your hypothesis into this format. Don't worry about phrasing hypotheses as "if...then" statements – that is almost never done in experiments outside a classroom.

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Results

The **results** of your experiment are the data that you collect as the

outcome. In the light experiment, your results are either that the light turns on or the light doesn't turn on. Based on your results, you can make a conclusion. Your **conclusion** uses the results to answer your original question.

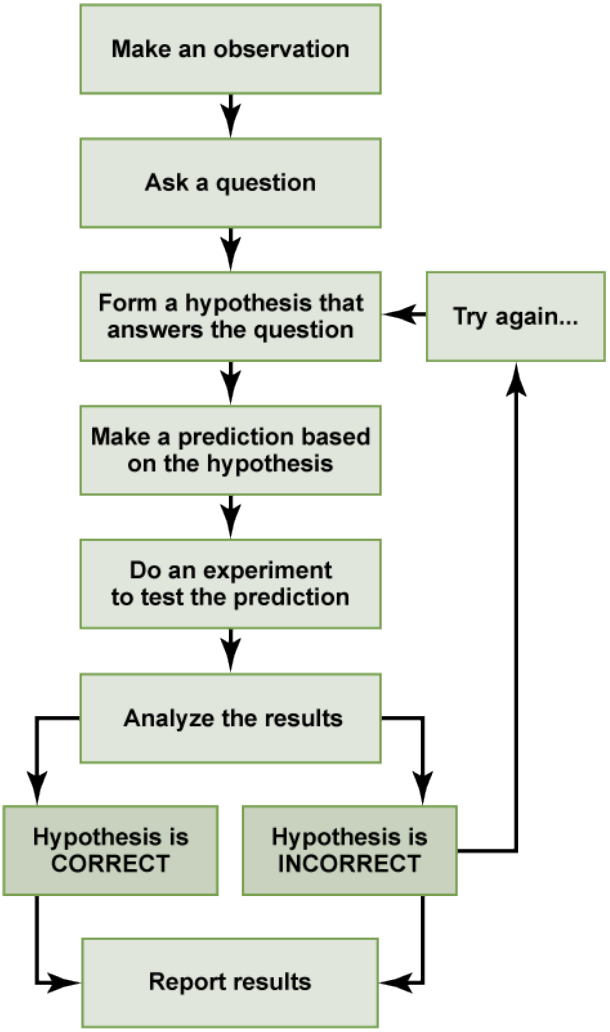


Figure 2 *The basic process of the scientific method. This is what science looks like in a simplified world.*

We can put the experiment with the light that won't go in into the figure above:

1. Observation: the light won't turn on.
2. Question: why won't the light turn on?
3. Hypothesis: the lightbulb is burned out.
4. Prediction: if I change the lightbulb (independent variable), then the light will turn on (dependent variable).
5. Experiment: change the lightbulb while leaving all other variables the same.
6. Analyze the results: the light didn't turn on.
7. Conclusion: The lightbulb isn't burned out. The results do not support the hypothesis, time to develop a new one!
8. Hypothesis 2: the lamp is unplugged.
9. Prediction 2: if I plug in the lamp, then the light will turn on.
10. Experiment: plug in the lamp
11. Analyze the results: the light turned on!
12. Conclusion: The light wouldn't turn on because the lamp was unplugged. The results support the hypothesis, it's time to move on to the next experiment!

In practice, the scientific method is not as rigid and structured as it might at first appear. Sometimes an experiment leads to conclusions that favor a change in approach; often, an experiment brings entirely new scientific questions to the puzzle. Many times, science does not operate in a linear fashion; instead, scientists continually draw inferences and make generalizations, finding patterns as their research proceeds. Scientific reasoning is more complex than the scientific method alone suggests.

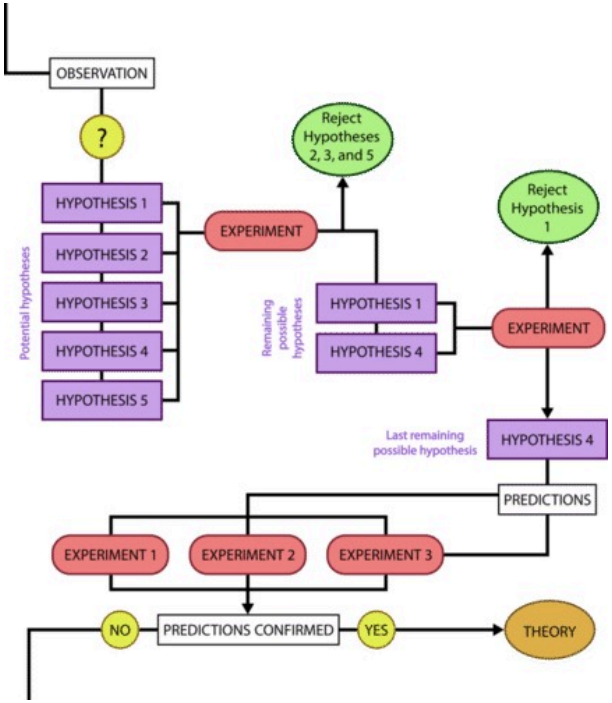


Figure 3 *The actual process of using the scientific method. "The general process of scientific investigations" by Laura Guerin, CK-12 Foundation is licensed under CC BY-NC 3.0*

Control Groups

Another important aspect of designing an experiment is the presence of one or more control groups. A **control group** allows you to make a comparison that is important for interpreting your results. Control groups are samples that help you to determine that differences between your experimental groups are due to your treatment rather than a different variable – they eliminate alternate explanations for your results (including experimental error and experimenter bias). They increase reliability, often through the comparison of control measurements and measurements of the experimental groups. Often, the control group is a sample that is not treated with the independent variable, but is otherwise treated

the same way as your experimental sample. This type of control group is treated the same way as the experimental group except it does not get treated with the independent variable. Therefore, if the results of the experimental group differ from the control group, the difference must be due to the change of the independent, rather than some outside factor. It is common in complex experiments (such as those published in scientific journals) to have more control groups than experimental groups.

Example 1

Question: Which fertilizer will produce the greatest number of tomatoes when applied to the plants?

Hypothesis: If I apply different brands of fertilizer to tomato plants, the most tomatoes will be produced from plants watered with Brand A because Brand A advertises that it produces twice as many tomatoes as other leading brands.

Experiment: Purchase 10 tomato plants of the same type from the same nursery. Pick plants that are similar in size and age. Divide the plants into two groups of 5. Apply Brand A to the first group and Brand B to the second group according to the instructions on the packages. After 10 weeks, count the number of tomatoes on each plant.

Independent Variable: Brand of fertilizer.

Dependent Variable: Number of tomatoes.

- *The number of tomatoes produced depends on the brand of fertilizer applied to the plants.*

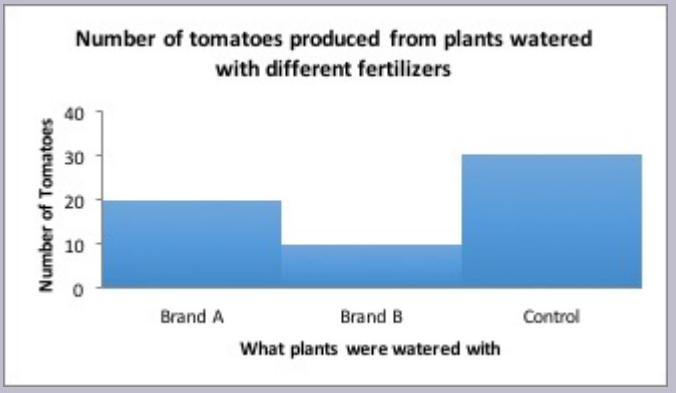
Constants: amount of water, type of soil, size of pot,

amount of light, type of tomato plant, length of time plants were grown.

Confounding variables: any of the above that are not held constant, plant health, diseases present in the soil or plant before it was purchased.

Results: Tomatoes fertilized with Brand A produced an average of 20 tomatoes per plant, while tomatoes fertilized with Brand B produced an average of 10 tomatoes per plant.

You'd want to use Brand A next time you grow tomatoes, right? But what if I told you that plants grown without fertilizer produced an average of 30 tomatoes per plant! Now what will you use on your tomatoes?



Results including control group: Tomatoes which received no fertilizer produced more tomatoes than either brand of fertilizer.

Conclusion: Although Brand A fertilizer produced more tomatoes than Brand B, neither fertilizer should be used

because plants grown without fertilizer produced the most tomatoes!

More examples of control groups:

- **You read an article in the NY Times that says some spinach is contaminated with Salmonella.** You want to test the spinach you have at home in your fridge, so you wet a sterile swab and wipe it on the spinach, then wipe the swab on a nutrient plate (petri plate).
    - *You observe growth.* Does this mean that your spinach is really contaminated? Consider an alternate explanation for growth: the swab, the water, or the plate is contaminated with bacteria. You could use a control group to determine which explanation is true. If you wet one of the swabs and wiped on a nutrient plate, do bacteria grow?
    - *You don't observe growth.* Does this mean that your spinach is really safe? Consider an alternate explanation for no growth: Salmonella isn't able to grow on the type of nutrient you used in your plates. You could use a control group to determine which explanation is true. If you wipe a known sample of Salmonella bacteria on the plate, do bacteria grow?
- **In a drug trial, one group of subjects are given a new drug, while a second group is given a placebo drug** (a sugar pill; something which appears like the drug, but doesn't contain the active ingredient). Reduction in disease symptoms is measured.
    - *You see a reduction in disease symptoms:* you might expect a reduction in disease symptoms purely because the person knows they are taking a drug so they believe

should be getting better. If the group treated with the real drug does not show more a reduction in disease symptoms than the placebo group, the drug doesn't really work. The placebo group sets a baseline against which the experimental group (treated with the drug) can be compared.
    - *You don't see a reduction in disease symptoms*: your drug doesn't work. You don't need an additional control group for comparison.
- **The preference of birds for various types of food is determined.** You place different types of food in several different feeders and measure how many birds visit each feeder.
    - You would want a "placebo feeder". This would be the same type of feeder, but with no food in it. Birds might visit a feeder just because they are interested in it; an empty feeder would give a baseline level for bird visits.
- **Testing the effect of pH on the function of an enzyme.** You add solutions of various pH to an enzyme and observe how well the enzyme functions.
    - You would want a control group where you knew the enzyme would function. This would be a tube where you did not change the pH. You need this control group so you know your enzyme is working: if you didn't see a reaction in any of the tubes with the pH adjusted, you wouldn't know if it was because the enzyme wasn't working at all or because the enzyme just didn't work at any of your tested pH values.
    - You would also want a control group where you knew the enzyme would not function (no enzyme added). You need the negative control group so you can ensure that there is no reaction taking place in the absence of enzyme: if the reaction proceeds without the enzyme, your results are meaningless.

References

Text adapted from: OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:RD6ERYiU@5/The-Process-of-Science.

2. Types of Data

There are different types of data that can be collected in an experiment. Typically, we try to design experiments that collect objective, quantitative data.

Objective data is fact-based, measurable, and observable. This means that if two people made the same measurement with the same tool, they would get the same answer. The measurement is determined by the object that is being measured. The length of a worm measured with a ruler is an objective measurement. The observation that a chemical reaction in a test tube changed color is an objective measurement. Both of these are observable facts.

Subjective data is based on opinions, points of view, or emotional judgment. Subjective data might give two different answers when collected by two different people. The measurement is determined by the subject who is doing the measuring. Surveying people about which of two chemicals smells worse is a subjective measurement. Grading the quality of a presentation is a subjective measurement. Rating your relative happiness on a scale of 1-5 is a subjective measurement. All of these depend on the person who is making the observation – someone else might make these measurements differently.

Quantitative measurements gather numerical data. For example, measuring a worm as being 5cm in length is a quantitative measurement.

Qualitative measurements describe a quality, rather than a numerical value. Saying that one worm is longer than another worm is a qualitative measurement.

	Objective	Subjective
Quantitative	The chemical reaction has produced 5cm of bubbles.	The chemical reaction has produced a lot of bubbles.
Qualitative	I give the amount of bubbles a score of 7 on a scale of 1-10.	I think the bubbles are pretty.

Example Experiment

An experiment might be conducted to test the **hypothesis** that phosphate limits the growth of algae in freshwater ponds. A series of artificial ponds are filled with water and half of them are treated by adding phosphate each week, while the other half are treated by adding a salt that is known not to be used by algae. The i**ndependent variable** here is the phosphate (or lack of phosphate). The **experimental** or treatment cases are the ponds with added phosphate and the **control ponds** are those with the salt that is known to not be used by algae. Just adding something is also a control against the possibility that adding extra matter to the pond has an effect. If the treated ponds show lesser growth of algae, then we have found support for our hypothesis. If they do not, then we reject our hypothesis. Be aware that rejecting one hypothesis does not determine whether or not the other hypotheses can be accepted; it simply eliminates one hypothesis that is not valid. Using the scientific method, the hypotheses that are inconsistent with experimental data are rejected.

- This experiment is collecting objective, quantitative data because algae growth is a measurable, observable fact.

How many times should you perform your test? How many samples should be in each test? The answer is "as many as is feasible". For the purposes of educational laboratory experiences, that answer is typically around three times. However, if you were testing a new

drug, you would need many more than three samples in order to show that the drug was safe and effective!

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3. Reporting Scientific Work

Whether scientific research is basic science or applied science, scientists must share their findings for other researchers to expand and build upon their discoveries. Communication and collaboration within and between sub disciplines of science are key to the advancement of knowledge in science. For this reason, an important aspect of a scientist's work is disseminating results and communicating with peers. Scientists can share results by presenting them at a scientific meeting or conference, but this approach can reach only the limited few who are present. Instead, most scientists present their results in peer-reviewed articles that are published in scientific journals.

In addition, important scientific work must be shared with people who do not read peer-reviewed articles in scientific journals. This means that scientific results must be rewritten using language that the general population understands.

Types of Sources

Whether conducting research in the social sciences, humanities (especially history), arts, or natural sciences, the ability to distinguish between **primary** and **secondary source material** is essential. Basically, this distinction illustrates the degree to which the author of a piece is removed from the actual event being described. This means whether the author is reporting information *first hand* (or is first to record these immediately following an event), or conveying the experiences and opinions of others—that is, *second hand*. In biology, the distinction would be between the person (or people) who conducted the research and someone who didn't actually do the research, but is merely reporting on it.

Primary sources

These are contemporary accounts of an event, written by someone who experienced or witnessed the event in question. In general, these original documents (i.e., they are not about another document or account) are often diaries, letters, memoirs, journals, speeches, manuscripts, interviews, photographs, audio or video recordings, or original literary or theatrical works.

In science, a "primary source" or the "primary literature" refers to the original publication of a scientist's new data, results, and conclusions. These articles are written for other experts in a specific scientific field.

You've probably done a writing assignment or other project during which you have participated in a **peer review** process. During this process, your project was critiqued and evaluated by people of similar competence to yourself (your peers). This gave you feedback on which to improve your work. Scientific articles typically go through a much more stringent peer review process before they are published in an academic journal. In scientific peer review, the article is reviewed (usually anonymously) by other experts in the specific field about which the paper is written. These peers are qualified individuals, often other experts in the same research area, who judge whether or not the scientist's work is suitable for publication. This allows other scientists to critique experimental design, data, and conclusions before that information is published in an academic journal. Often, the scientists who did the experiment and who are trying to publish it are required to do additional work or edit their paper before it is published. The goal of the scientific peer review process is to ensure that published primary articles contain the best possible science.

There are many journals and the popular press that do not use a peer-review system. A large number of online open-access journals, journals with articles available without cost, are now available many of which use rigorous peer-review systems, but some of which do

not. Results of any studies published in these forums without peer review are not reliable and should not form the basis for other scientific work. It is important to evaluate whether or not you are looking at a peer reviewed source before you decide if the information is credible.

Secondary sources

The function of a **secondary source** is to interpret the primary source**.** A secondary source can be described as at least one step removed from the event or phenomenon under review. Secondary source materials interpret, assign value to, conjecture upon, and draw conclusions about the events reported in primary sources. These are usually in the form of published works such as magazine articles or books, but may include radio or television documentaries, or conference proceedings. For example, a NY Times article reporting about a new drug treatment for breast cancer is a secondary source. The academic journal article presenting the data from the drug trial is the primary source.

Popular vs. Scholarly Sources

POPULAR	SCHOLARLY
Broad range of topics, presented in shorter articles	Specific, narrowly focused topics in lengthy, in-depth articles
Articles offer overview of subject matter; interpretation, rather than original research; sometimes contain feature articles and reports on current social issues and public opinion	Articles often contain previously unpublished research and detail new developments in field
Intended to attract a general readership without any particular expertise or advanced education	Intended for specialist readership of researchers, academics, students and professionals
Written by staff (not always attributed) or freelance writers using general, popular language	Written by identified specialists and researchers in subject area, usually employing technical, subject-specific language and jargon
Edited and approved for publication in-house (not peer-reviewed)	Critically evaluated by peers (fellow scholars) in field for content, scholarly soundness, and academic value
Articles rarely contain references or footnotes and follow no specific format	Well-researched, documented articles nearly always follow standard format: abstract, introduction, literature review, methodology, results, conclusion, bibliography/ references
Designed to attract eye of potential newsstand customers: usually filled with photographs or illustrations, printed on glossier paper	Sober design: mostly text with some tables or graphs accompanying articles; usually little or no photography; negligible, if any, advertising; rarely printed on high-gloss paper
Each issue begins with page number '1'	Page numbers of issues *within a volume* (*year*) are usually consecutive (i.e., first page of succeeding issue is number following last page number of previous issue)
Presented to entertain, promote point of view, and/or sell products	Intended to present researchers' opinions and findings based on original research

Examples: *Newsweek*, *Rolling Stone*, *Vogue*	Examples: *Science*, Nature, *Journal of Microbial and Biochemical Technology*

In science, it is often extremely difficult to read and understand primary articles unless you are an expert in that specific scientific field. Secondary sources are typically easier to read and can give you the important information from a primary source, but only if the secondary source has interpreted the information correctly! It is always better to go to the primary source if possible because otherwise you are relying on someone else's interpretation of the information. However, it is always better to use a source that you can read and understand rather than a source that you can't. For this reason, it is very important to be able to identify credible secondary sources.

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PART II

PROPERTIES OF LIVING THINGS

Learning Objectives

By the end of this chapter, you will be able to:

- Describe characteristics that can be used to determine if something is living.

Figure 1 This NASA image is a composite of several satellite-based views of Earth. To make the whole-Earth image, NASA scientists combine observations of different parts of the planet. (credit: modification of work by NASA)

Viewed from space, Earth (**Figure 1**) offers few clues about the diversity of life forms that reside there. The first forms of life on Earth are thought to have been microorganisms that existed for billions of years before plants and animals appeared. The mammals,

birds, and flowers so familiar to us are all relatively recent, originating 130 to 200 million years ago. Humans have inhabited this planet for only the last 2.5 million years, and only in the last 200,000 years have humans started looking like we do today.

Biology is the science that studies life. What exactly is life? This may sound like a silly question with an obvious answer, but it is not easy to define life. For example, a branch of biology called virology studies viruses, which exhibit some of the characteristics of living entities but lack others. It turns out that although viruses can attack living organisms, cause diseases, and even reproduce, they do not meet the criteria that biologists use to define life.

From its earliest beginnings, biology has wrestled with four questions: What are the shared properties that make something "alive"? How do those various living things function? When faced with the remarkable diversity of life, how do we organize the different kinds of organisms so that we can better understand them? And, finally—what biologists ultimately seek to understand—how did this diversity arise and how is it continuing? As new organisms are discovered every day, biologists continue to seek answers to these and other questions.

All groups of living organisms share several key characteristics or functions:

- Order / Organization
- Sensitivity / response to stimuli
- Reproduction
- Evolution / Adaptation
- Growth and development
- Energy processing
- Homeostasis

When viewed together, these eight characteristics serve to define life. Let's examine what each of these characteristics means in a scientific sense.

Order / Organization

Organisms, in the most basic form, consist of highly organized structures that are made up of one or more cells. Even very simple, single-celled organisms are remarkably complex. Inside each cell, atoms make up molecules. These in turn make up cell components or organelles. Multicellular organisms, which may consist of millions of individual cells, have an advantage over single-celled organisms in that their cells can be specialized to perform specific functions.

Figure 1 A toad represents a highly organized structure consisting of cells, tissues, organs, and organ systems. (credit: "Ivengo(RUS)"/Wikimedia Commons)

Sensitivity / Response to Stimuli

Organisms respond to diverse stimuli. For example, plants can bend toward a source of light or respond to touch (Figure 2). Even tiny bacteria can move toward or away from chemicals (a process called chemotaxis) or light (phototaxis). Movement toward a stimulus is considered a positive response, while movement away from a stimulus is considered a negative response.

Figure 3: The leaves of this sensitive plant (Mimosa pudica) will instantly droop and fold when touched. After a few minutes, the plant returns to its normal state. (credit: Alex Lomas)

Reproduction

Single-celled organisms reproduce by duplicating their DNA (deoxyribonucleic acid, the genetic material) and then dividing it equally as the cell prepares to divide to form two new cells.

Many multicellular organisms produce specialized reproductive cells that will form new individuals. When reproduction occurs, DNA is passed along to an organism's offspring. Genes, made up of DNA, are the basic units by which traits are passed from parent to offspring. DNA, and the information that it encodes in genes, is the reason that offspring will belong to the same species as parents and will have similar characteristics.

Evolution / Adaptation

All living organisms exhibit a "fit" to their environment. Biologists refer to this fit as adaptation and it is a consequence of evolution

by natural selection, which operates in every lineage of reproducing organisms. Examples of adaptations are diverse and unique, from heat-resistant Archaea that live in boiling hot springs to the tongue length of a nectar-feeding moth that matches the size of the flower from which it feeds. All adaptations enhance the reproductive potential of the individual exhibiting them, including their ability to survive to reproduce. Adaptations are not constant. As an environment changes, natural selection causes the characteristics of the individuals in a population to track those changes.

Growth and Development

Organisms grow and develop according to specific instructions coded for by their genes. These genes provide instructions that will direct cellular growth and development, ensuring that a species' young (Figure 4) will grow up to exhibit many of the same characteristics as its parents.

Figure 4 Although no two look alike, these kittens have inherited genes from both parents and share many of the same characteristics. (credit: Pieter & Renée Lanser)

Even the smallest organisms are complex and require multiple

regulatory mechanisms to coordinate internal functions, such as the transport of nutrients, response to stimuli, and coping with environmental stresses. For example, organ systems such as the digestive or circulatory systems perform specific functions like carrying oxygen throughout the body, removing wastes, delivering nutrients to every cell, and cooling the body.

Energy Processing

All organisms (such as the California condor shown in Figure 5) use a source of energy for their metabolic activities. Some organisms capture energy from the Sun and convert it into chemical energy in food; others use chemical energy from molecules they take in.

Figure 5 A lot of energy is required for a California condor to fly. Chemical energy derived from food is used to power flight. California condors are an endangered species; scientists have strived to place a wing tag on each bird to help them identify and locate each individual bird. (credit: Pacific Southwest Region U.S. Fish and Wildlife)

Homeostasis

To function properly, cells require appropriate conditions such as proper temperature, pH, and concentrations of diverse chemicals. These conditions may, however, change from one moment to the next. Organisms are able to maintain internal conditions within a narrow range almost constantly, despite environmental changes, through a process called homeostasis or "steady state"—the ability of an organism to maintain constant internal conditions. For example, many organisms regulate their body temperature in a process

known as thermoregulation. Organisms that live in cold climates, such as the polar bear (Figure 6), have body structures that help them withstand low temperatures and conserve body heat. In hot climates, organisms have methods (such as perspiration in humans or panting in dogs) that help them to shed excess body heat.

Figure 6 Polar bears and other mammals living in ice-covered regions maintain their body temperature by generating heat and reducing heat loss through thick fur and a dense layer of fat under their skin. (credit: "longhornda ve"/Flickr)

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4. Spotlight on Homeostasis

Maintaining homeostasis requires that the body continuously monitor its internal conditions. From body temperature to blood pressure to levels of certain nutrients, each physiological condition has a particular set point. A **set point** is the physiological value around which the normal range fluctuates. A **normal range** is the the normal, healthful, and stable fluctuation around the set point. For example, the set point for normal human body temperature is approximately 37°C (98.6°F) and the normal range is roughly 97°F to 99°F.

Control centers in the brain and other parts of the body monitor and react to deviations from the normal range using negative feedback. **Negative feedback** is a mechanism that reverses a deviation from the set point. In other words, when there is a change from the set point out of the normal range, negative feedback brings the body parameter back to the set point. Therefore, negative feedback maintains body parameters within their normal range. The maintenance of homeostasis by negative feedback goes on throughout the body at all times, and an understanding of negative feedback is therefore fundamental to an understanding of human physiology.

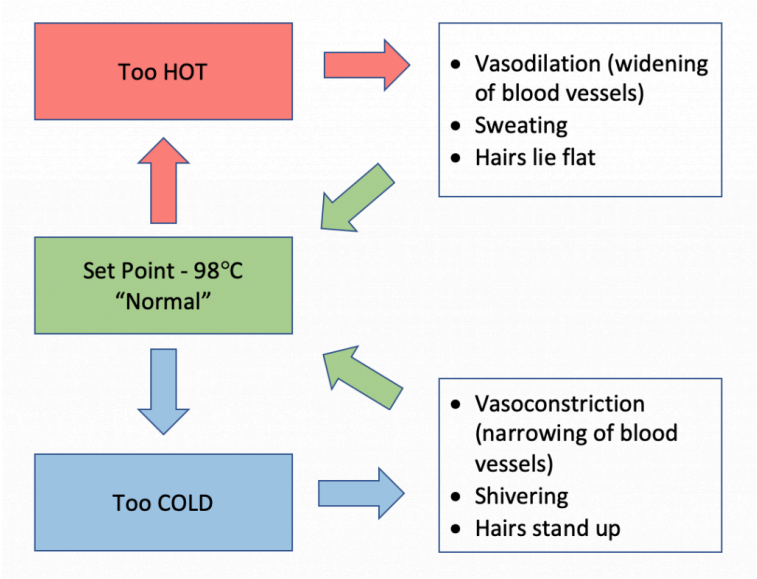

Figure 7 Body temperature regulation is an example of homeostasis.

Negative Feedback Loop

In order to set the system in motion, something must drive a physiological parameter beyond its normal range (for example, blood glucose becomes too high because you ate three chocolate donuts). This stimulus is detected by the body. In the control of blood glucose, specific cells in the pancreas detect excess glucose (the stimulus) in the bloodstream. These pancreatic cells respond to the increased level of blood glucose by releasing the hormone insulin into the bloodstream. The insulin signals skeletal muscle fibers, fat cells, and liver cells to take up the excess glucose, removing it from the bloodstream. As glucose concentration in the

bloodstream drops, the decrease in concentration—the actual negative feedback—is detected by other cells in the pancreases and insulin release stops. This prevents blood sugar levels from continuing to drop below the normal range.

Humans have a similar temperature regulation feedback system that works by promoting either heat loss or heat gain. When the brain's temperature regulation center receives data from the sensors indicating that the body's temperature exceeds its normal range, it stimulates a cluster of brain cells referred to as the "heat-loss center." This stimulation has three major effects:

- Blood vessels in the skin begin to dilate allowing more blood from the body core to flow to the surface of the skin allowing the heat to radiate into the environment.
- As blood flow to the skin increases, sweat glands are activated to increase their output. As the sweat evaporates from the skin surface into the surrounding air, it takes heat with it.
- The depth of respiration increases, and a person may breathe through an open mouth instead of through the nasal passageways. This further increases heat loss from the lungs.

In contrast, activation of the brain's heat-gain center by exposure to cold reduces blood flow to the skin, and blood returning from the limbs is diverted into a network of deep veins. This arrangement traps heat closer to the body core and restricts heat loss. If heat loss is severe, the brain triggers an increase in random signals to skeletal muscles, causing them to contract and producing shivering. The muscle contractions of shivering release heat while using up ATP. The brain triggers the thyroid gland in the endocrine system to release thyroid hormone, which increases metabolic activity and heat production in cells throughout the body. The brain also signals the adrenal glands to release epinephrine (adrenaline), a hormone that causes the breakdown of glycogen into glucose, which can be used as an energy source. The breakdown of glycogen into glucose also results in increased metabolism and heat production.

Positive Feedback

Positive feedback intensifies a change in the body's physiological condition rather than reversing it. A deviation from the normal range results in more change, and the system moves farther away from the normal range. Positive feedback in the body is normal only when there is a definite end point. Childbirth and the body's response to blood loss are two examples of positive feedback loops that are normal but are activated only when needed.

Childbirth at full term is an example of a situation in which the maintenance of the existing body state is not desired. Enormous changes in the mother's body are required to expel the baby at the end of pregnancy. And the events of childbirth, once begun, must progress rapidly to a conclusion or the life of the mother and the baby are at risk. The extreme muscular work of labor and delivery are the result of a positive feedback system

Positive Feedback Loop

Normal childbirth is driven by a positive feedback loop. A positive feedback loop results in a change in the body's status, rather than a return to homeostasis.

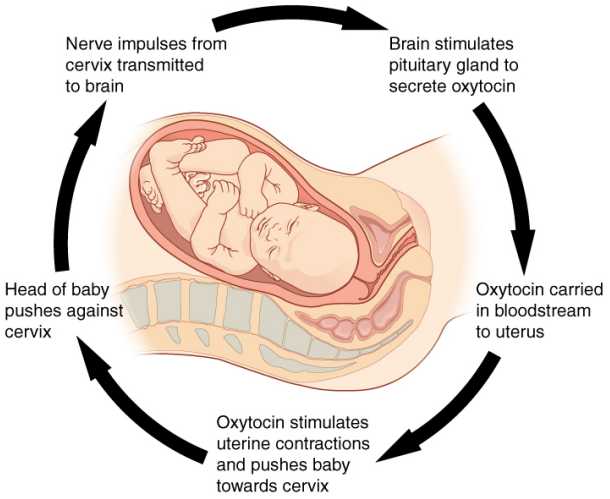

Figure 9 Positive Feedback Loop Normal childbirth is driven by a positive feedback loop. A positive feedback loop results in a change in the body's status, rather than a return to homeostasis.

The first contractions of labor push the baby toward the cervix (the lowest part of the uterus). The cervix contains stretch-sensitive nerve cells that monitor the degree of stretching. These nerve cells send messages to the brain, which in turn causes the pituitary gland at the base of the brain to release the hormone oxytocin into the bloodstream. Oxytocin causes stronger contractions of the smooth muscles in of the uterus, pushing the baby further down the birth canal. This causes even greater stretching of the cervix. The cycle of stretching, oxytocin release, and increasingly more forceful contractions stops only when the baby is born. At this point, the stretching of the cervix halts, stopping the release of oxytocin.

A second example of positive feedback centers on reversing extreme damage to the body. Following a penetrating wound, the most immediate threat is excessive blood loss. Less blood circulating means reduced blood pressure and reduced perfusion (penetration of blood) to the brain and other vital organs. If perfusion is severely reduced, vital organs will shut down and the person will die. The body responds to this potential catastrophe by releasing substances in the injured blood vessel wall that begin the process of blood clotting. As each step of clotting occurs, it stimulates the release of more clotting substances. This accelerates the processes of clotting and sealing off the damaged area. Clotting is contained in a local area based on the tightly controlled availability of clotting proteins. This is an adaptive, life-saving cascade of events.

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5. Levels of Organization of Living Things

Living things are highly organized and structured, following a hierarchy that can be examined on a scale from small to large. The **atom** is the smallest and most fundamental unit of matter. It consists of a nucleus surrounded by electrons. Atoms form **molecules.** A molecule is a chemical structure consisting of at least two atoms held together by one or more chemical bonds. Many molecules that are biologically important are **macromolecules,** large molecules that are typically formed by polymerization (a polymer is a large molecule that is made by combining smaller units called monomers, which are simpler than macromolecules). An example of a macromolecule is deoxyribonucleic acid (DNA) (Figure 1), which contains the instructions for the structure and functioning of all living organisms. See the section of your textbook about the chemistry of biological molecules for more information.

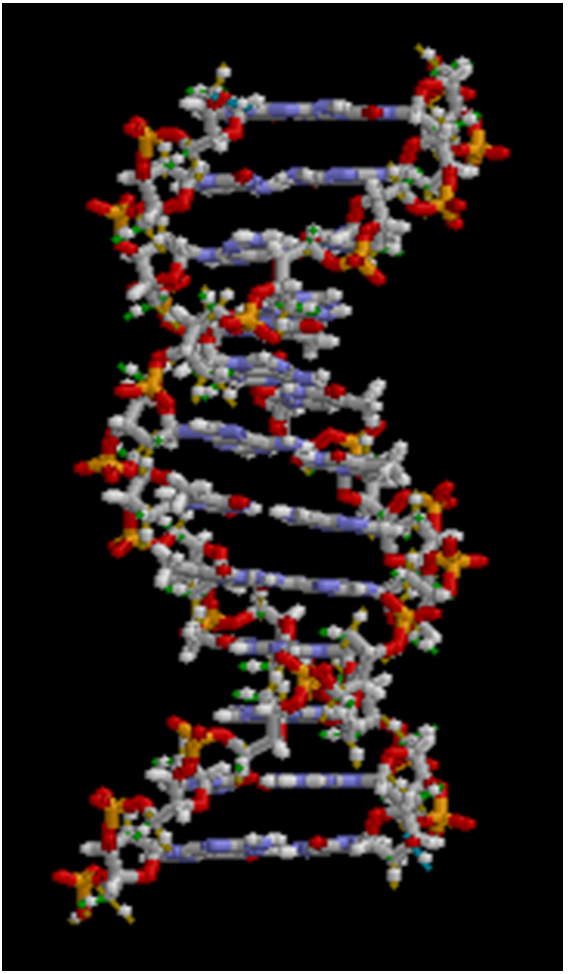

Figure 1 *All molecules, including this DNA molecule, are composed of atoms. (credit: "brian0918"/ Wikimedia Commons)*

Some cells contain aggregates of macromolecules surrounded by membranes; these are called **organelles.** Organelles are small structures that exist within cells. Examples of organelles include mitochondria and chloroplasts, which carry out indispensable functions: mitochondria produce energy to power the **cell,** while chloroplasts enable green plants to utilize the energy in sunlight

to make sugars. All living things are made of cells; the cell itself is the smallest fundamental unit of structure and function in living organisms. This requirement is one of the reasons why viruses are not considered living: they are not made of cells. To make new viruses, they have to invade and hijack the reproductive mechanism of a living cell; only then can they obtain the materials they need to reproduce. Some organisms consist of a single cell and others are multicellular. Cells are classified as prokaryotic or eukaryotic. Prokaryotes are single-celled or colonial organisms that do not have membrane-bound nuclei; in contrast, the cells of eukaryotes do have membrane-bound organelles and a membrane-bound nucleus.

In larger organisms, cells combine to make **tissues,** which are groups of similar cells carrying out similar or related functions. **Organs** are collections of tissues grouped together performing a common function. Organs are present not only in animals but also in plants. An organ system is a higher level of organization that consists of functionally related organs. Mammals have many **organ systems**. For instance, the circulatory system transports blood through the body and to and from the lungs; it includes organs such as the heart and blood vessels. **Organisms** are individual living entities. For example, each tree in a forest is an organism. Single-celled prokaryotes and single-celled eukaryotes are also considered organisms and are typically referred to as microorganisms.

All the individuals of a species living within a specific area are collectively called a **population.** For example, a forest may include many pine trees. All of these pine trees represent the population of pine trees in this forest. Different populations may live in the same specific area. For example, the forest with the pine trees includes populations of flowering plants and also insects and microbial populations. A **community** is the sum of populations inhabiting a particular area. For instance, all of the trees, flowers, insects, and other populations in a forest form the forest's community. The forest itself is an ecosystem. An **ecosystem** consists of all the living things in a particular area together with the abiotic, non-living parts of that environment such as nitrogen in the soil or rain water. At the

highest level of organization, the biosphere is the collection of all ecosystems, and it represents the zones of life on earth. It includes land, water, and even the atmosphere to a certain extent.

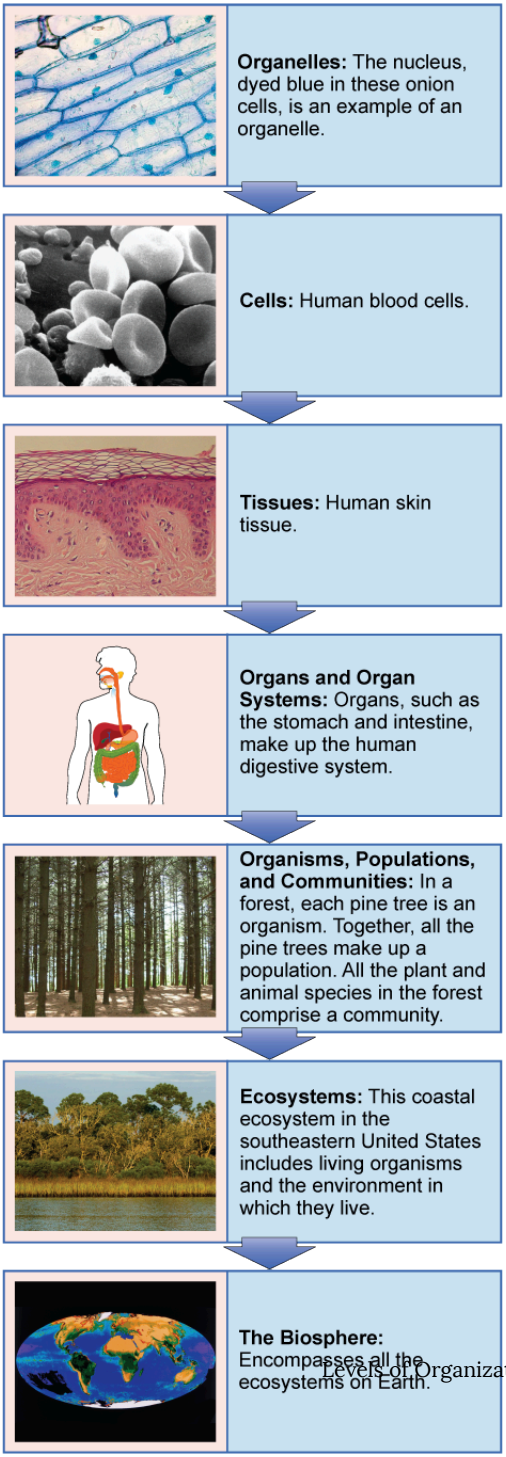

Figure 1*The biological levels of organization of living things are shown. From a single organelle to the entire biosphere, living organisms are parts of a highly structured hierarchy. (credit "organelles": modification of work by Umberto Salvagnin; credit "cells": modification of work by Bruce Wetzel, Harry Schaefer/ National Cancer Institute; credit "tissues": modification of work by Kilbad; Fama Clamosa; Mikael Häggström; credit "organs": modification of work by Mariana Ruiz Villareal; credit "organisms": modification*

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PART III

CHEMISTRY FOR BIOLOGY

Learning Outcomes

Course Outcomes for this section:

- Describe the structure of biologically-important molecules (carbohydrates, lipids, proteins, nucleic acids, water) and how their structure leads to their function.

Living things are highly organized and structured, following a hierarchy that can be examined on a scale from small to large. The examination of the smallest parts involves a knowledge of chemistry. We discussed the levels of organization of living things in the last chapter. In this chapter, we will learn some basic chemistry that is important in order to understand how molecules in cells function.

6. Atoms

An **atom** is the smallest component of an element that retains all of the chemical properties of that element. For example, one hydrogen atom has all of the properties of the element hydrogen, such as it exists as a gas at room temperature, and it bonds with oxygen to create a water molecule. Hydrogen atoms cannot be broken down into anything smaller while still retaining the properties of hydrogen. If a hydrogen atom were broken down into subatomic particles, it would no longer have the properties of hydrogen.

All atoms contain **protons, electrons,** and **neutrons** (Figure 1). The only exception is hydrogen (H), which is made of one proton and one electron. A proton is a positively charged particle that resides in the nucleus (the core of the atom) of an atom. An electron is a negatively charged particle that travels in the space around the nucleus. In other words, it resides outside of the nucleus. Neutrons, like protons, reside in the nucleus of an atom. The positive (protons) and negative (electrons) charges balance each other in a neutral atom, which has a net zero charge.

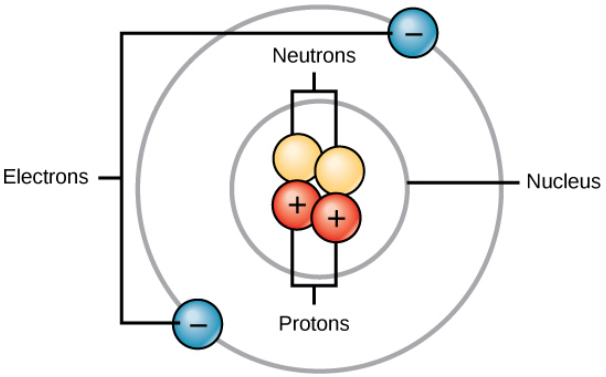

Figure 1*Atoms are made up of protons and neutrons located within the nucleus, and electrons surrounding the nucleus.*

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At the most basic level, all organisms are made of a combination of atoms. They contain atoms that combine together to form molecules. In multicellular organisms, such as animals, molecules can interact to form cells that combine to form tissues, which make up organs. These combinations continue until entire multicellular organisms are formed.

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Each element has its own unique properties. An element is a substance whose atoms all have the same number of protons. Different elements have different melting and boiling points, and are in different states (liquid, solid, or gas) at room temperature. They also combine in different ways. Some form specific types of bonds, whereas others do not. How they combine is based on the number of electrons present. Because of these characteristics, the elements are arranged into the periodic table of elements, a chart of the elements that includes the atomic number and relative atomic mass of each element. The periodic table also provides key information about the properties of elements (Figure 2) –often indicated by color-coding. The arrangement of the table also shows

how the electrons in each element are organized and provides important details about how atoms will react with each other to form molecules.

Isotopes are different forms of the same element that have the same number of protons, but a different number of neutrons. Some elements, such as carbon, potassium, and uranium, have naturally occurring isotopes. Carbon-12, the most common isotope of carbon, contains six protons and six neutrons. Carbon-14 contains six protons and eight neutrons. These two alternate forms of carbon are isotopes. Some isotopes are unstable and will lose protons, other subatomic particles, or energy to form more stable elements. These are called radioactive isotopes or radioisotopes.

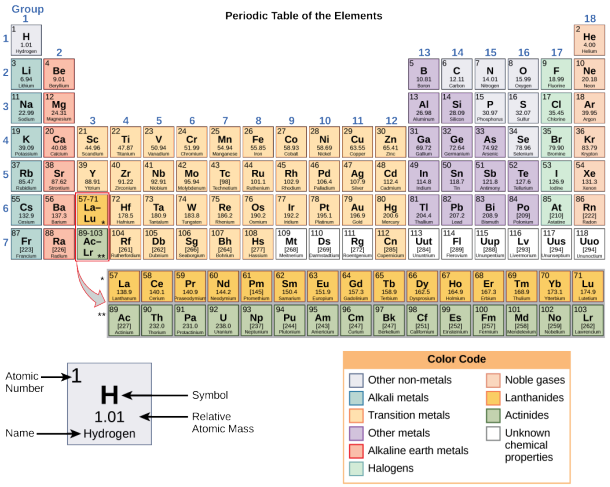

Figure 2*Arranged in columns and rows based on the characteristics of the elements, the periodic table provides key information about the elements and how they might interact with each other to form molecules. Most periodic tables provide a key or legend to the information they contain.*

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Evolution in Action

Carbon Dating: Carbon-14 (^{14}C) is a naturally occurring radioisotope that is created in the atmosphere by cosmic rays. This is a continuous process, so more ^{14}C is always being created. As a living organism develops, the relative level of ^{14}C in its body is equal to the concentration of ^{14}C in the atmosphere. When an organism dies, it is no longer ingesting ^{14}C, so the ratio will decline. ^{14}C decays to ^{14}N by a process called beta decay; it gives off energy in this slow process.

After approximately 5,730 years, only one-half of the starting concentration of ^{14}C will have been converted to ^{14}N. The time it takes for half of the original concentration of an isotope to decay to its more stable form is called its half-life. Because the half-life of ^{14}C is long, it is used to age formerly living objects, such as fossils. Using the ratio of the ^{14}C concentration found in an object to the amount of ^{14}C detected in the atmosphere, the amount of the isotope that has not yet decayed can be determined. Based on this amount, the age of the fossil can be calculated to about 50,000 years (Figure 3). Isotopes with longer half-lives,

such as potassium-40, are used to calculate the ages of older fossils. Through the use of carbon dating, scientists can reconstruct the ecology and biogeography of organisms living within the past 50,000 years.

Figure 3*The age of remains that contain carbon and are less than about 50,000 years old, such as this pygmy mammoth, can be determined using carbon dating. (credit: Bill Faulkner/ NPS)*

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7. Chemical Bonds

Atoms can form several types of chemical bonds. These bonds are interactions between two atoms that hold the atoms together. It is important to understand the various types of bonds because they help determine how different molecules function within an organism. There are four types of bonds or interactions: covalent, ionic, hydrogen bonds, and van der Waals interactions.

Covalent Bonds

Another type of strong chemical bond between two or more atoms is a **covalent bond**. These bonds form when an electron is shared between two elements. Covalent bonds are the strongest and most common form of chemical bond in living organisms.

The hydrogen and oxygen atoms that combine to form water molecules are bound together by strong covalent bonds. The electron from the hydrogen atom shares its time between the hydrogen atom and the oxygen atom. In order for the oxygen atom to be stable, two electrons from two hydrogen atoms are needed, hence the subscript "2" in H_2O. H_2O means that there are 2 hydrogen atoms bonded to 1 oxygen atom (the 1 is implied below the O in the chemical formula). This sharing makes both the hydrogen and oxygen atoms more chemically stable.

There are two types of covalent bonds: polar and nonpolar (Figure 3). **Nonpolar covalent bonds** form between two atoms that share the electrons equally so there is no overall charge on the molecule. For example, an oxygen atom can bond with another oxygen atom. This association is **nonpolar** because the electrons will be equally shared between each oxygen atom. Another example of a nonpolar covalent bond is found in the methane (CH_4) molecule. The carbon

atom shares electrons with four hydrogen atoms. The carbon and hydrogen atoms all share the electrons equally, creating four nonpolar covalent bonds (Figure 3).

In a **polar covalent bond**, the electrons shared by the atoms spend more time closer to one atom than to the other. Because of the unequal distribution of electrons between the atoms, a slightly positive (δ+) or slightly negative (δ−) charge develops. The covalent bonds between hydrogen and oxygen atoms in water are polar covalent bonds. The shared electrons spend more time near the oxygen than they spend near the hydrogen. This means that the oxygen has a small negative charge while the hydrogens have a small positive charge.

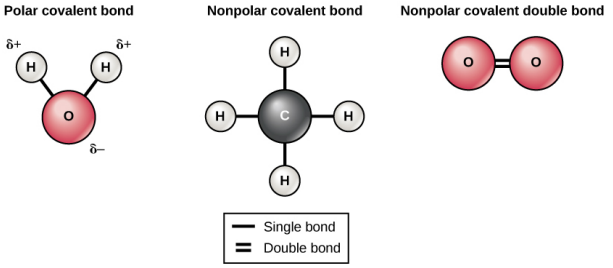


Figure 3 *The water molecule (left) depicts a polar bond with a slightly positive charge on the hydrogen atoms and a slightly negative charge on the oxygen. Examples of nonpolar bonds include methane (middle) and oxygen (right).*

Ionic Bonds

Atoms normally have an equal number of protons (positive charge)

and electrons (negative charge). This means that atoms are normally uncharged because the number of positively charged particles equals the number of negatively charged particles. When an atom does not contain equal numbers of protons and electrons, it will have a net charge. An atom with a net charge is called an **ion.** Positive ions are formed by losing electrons. Negative ions are formed by gaining electrons. Atoms can lose and donate electrons in order to become more stable.

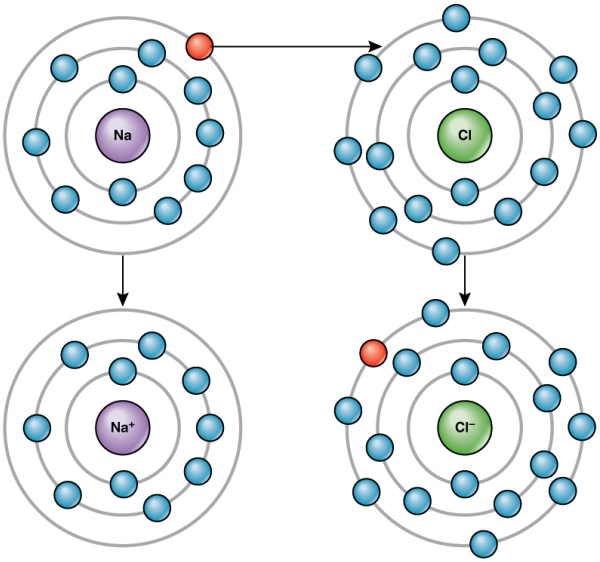


Figure 1 *If sodium (Na) gives an electron to chlorine (Cl), the sodium atom becomes positively charged (Na+) and the chlorine atom becomes negatively charged (Cl-).*

When an element donates an electron from its outer shell, as in the sodium atom example above, a positive ion is formed (Figure 2). The element accepting the electron is now negatively charged. Because positive and negative charges attract, these ions stay together and form an **ionic bond**, or a bond between ions. The elements bond together with the electron from one element staying predominantly with the other element. When Na and Cl combine to produce NaCl, an electron from a sodium atom goes to stay with the other seven electrons in the chlorine atom, forming a positively charged sodium

ion and a negatively charged chlorine ion. The sodium and chloride ions attract each other.

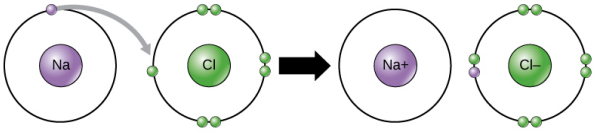


Figure 2 *The formation of the ionic compound NaCl.*

https://www.youtube.com/watch?v=OTgpN62ou24

Hydrogen Bonds

Ionic and covalent bonds are strong bonds that require considerable energy to break. However, not all bonds between elements are ionic or covalent bonds. Weaker bonds can also form. These are attractions that occur between positive and negative charges that do not require much energy to break. Two weak bonds that occur frequently are hydrogen bonds and van der Waals interactions. These bonds give rise to the unique properties of water and the unique structures of DNA and proteins.

When polar covalent bonds containing a hydrogen atom form, the hydrogen atom in that bond has a slightly positive charge. This is because the shared electron is pulled more strongly toward the other element and away from the hydrogen nucleus. Because the hydrogen atom is slightly positive (δ+), it will be attracted to neighboring negative partial charges (δ−). When this happens, a weak interaction occurs between the δ+ charge of the hydrogen atom of one molecule and the δ− charge of the other molecule. This interaction is called a hydrogen bond. This type of bond is common; for example, the liquid nature of water is caused by the hydrogen bonds between water molecules (Figure 4). Hydrogen bonds give water the unique properties that sustain life. If it were not for

hydrogen bonding, water would be a gas rather than a liquid at room temperature.

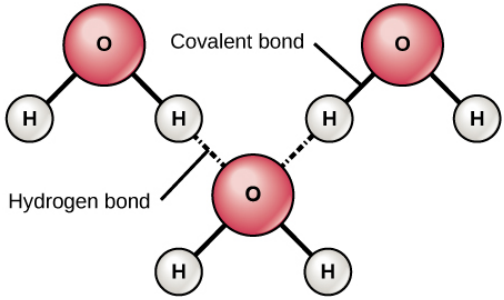
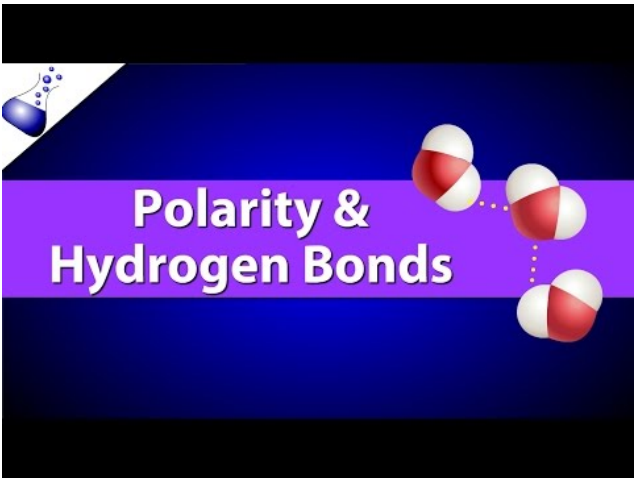


Figure 4 *Hydrogen bonds form between slightly positive (δ+) and slightly negative (δ–) charges of polar covalent molecules, such as water.*

Hydrogen bonds can form between different molecules and they do not always have to include a water molecule. Hydrogen atoms in polar bonds within any molecule can form bonds with other adjacent molecules. For example, hydrogen bonds hold together two long strands of DNA to give the DNA molecule its characteristic double-stranded structure. Hydrogen bonds are also responsible for some of the three-dimensional structure of proteins.



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van der Waals Interactions

Like hydrogen bonds, van der Waals interactions are weak attractions or interactions between molecules. They occur between polar, covalently bound, atoms in different molecules. Some of these weak attractions are caused by temporary partial charges formed when electrons move around a nucleus. These weak interactions between molecules are important in biological systems.

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8. Water

Figure 1 *Water: without it, life wouldn't exist. Photo credit ronymichaud; CC0 license; https://pixabay.com/en/users/ronymichaud-647623/*

Do you ever wonder why scientists spend time looking for water on other planets? It is because water is essential to life; even minute traces of it on another planet can indicate that life could or did exist on that planet. Water is one of the more abundant molecules in living cells and the one most critical to life as we know it. Approximately 60–70 percent of your body is made up of water. Without it, life simply would not exist.

Water Is Polar

The hydrogen and oxygen atoms within water molecules form **polar covalent bonds**. The shared electrons spend more time associated with the oxygen atom than they do with hydrogen atoms. There is no overall charge to a water molecule, but there is a slight positive charge on each hydrogen atom and a slight negative charge on

the oxygen atom. Because of these charges, the slightly positive hydrogen atoms repel each other and form the unique shape. Each water molecule attracts other water molecules because of the positive and negative charges in the different parts of the molecule.

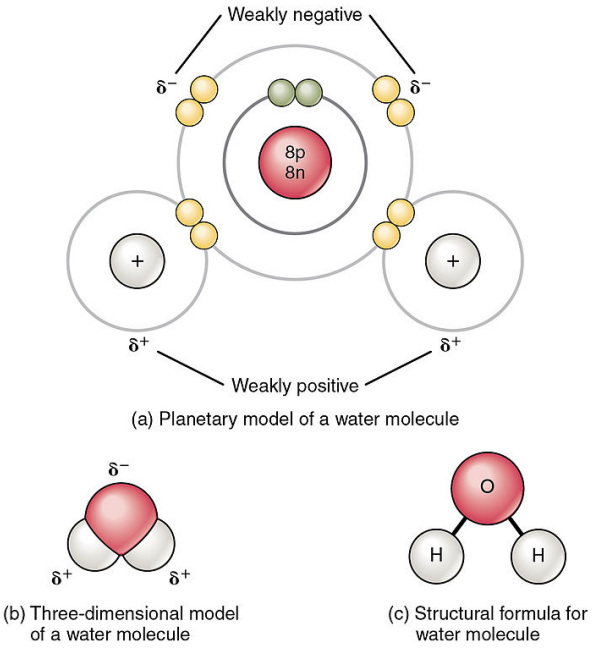

Figure 2*The electrons in the covalent bond connecting the two hydrogens to the atom of oxygen in a water molecule spend more time on the oxygen atom. This gives the oxygen atom a slightly negative charge (since electrons are negatively charged). Credit Anatomy & Physiology, Connexions Web site. http://cnx.org/content/col11496/1.6/, Jun 19, 2013.*

Water also attracts other polar molecules (such as sugars), forming hydrogen bonds. When a substance readily forms hydrogen bonds with water, it can dissolve in water and is referred to as **hydrophilic** ("water-loving"). Hydrogen bonds are not readily formed with nonpolar substances like oils and fats (Figure 3). These nonpolar

compounds are **hydrophobic** ("water-fearing") and will not dissolve in water.

Figure 3*As this macroscopic image of oil and water show, oil is a nonpolar compound and, hence, will not dissolve in water. Oil and water do not mix. (credit: Gautam Dogra)*

Water Stabilizes Temperature

The hydrogen bonds in water allow it to absorb and release heat energy more slowly than many other substances. Temperature is a measure of the motion (kinetic energy) of molecules. As the motion increases, energy is higher and thus temperature is higher. Water absorbs a great deal of energy before its temperature rises. Increased energy disrupts the hydrogen bonds between water molecules. Because these bonds can be created and disrupted rapidly, water absorbs an increase in energy and temperature changes only minimally. This means that water moderates temperature changes within organisms and in their environments. As energy input continues, the balance between hydrogen-bond formation and destruction swings toward the destruction side. More bonds are broken than are formed. This process results in the release of individual water molecules at the surface of the liquid

(such as a body of water, the leaves of a plant, or the skin of an organism) in a process called evaporation. Evaporation of sweat, which is 90 percent water, allows for cooling of an organism, because breaking hydrogen bonds requires an input of energy and takes heat away from the body.

Conversely, as molecular motion decreases and temperatures drop, less energy is present to break the hydrogen bonds between water molecules. These bonds remain intact and begin to form a rigid, lattice-like structure (e.g., ice) (Figure 4**a**). When frozen, ice is less dense than liquid water (the molecules are farther apart). This means that ice floats on the surface of a body of water (Figure4**b**). In lakes, ponds, and oceans, ice will form on the surface of the water, creating an insulating barrier to protect the animal and plant life beneath from freezing in the water. If this did not happen, plants and animals living in water would freeze in a block of ice and could not move freely, making life in cold temperatures difficult or impossible.

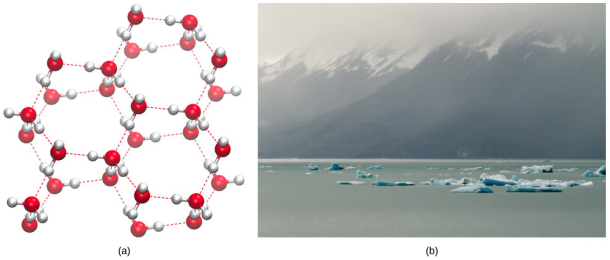

Figure 4*(a) The lattice structure of ice makes it less dense than the freely flowing molecules of liquid water. Ice's lower density enables it to (b) float on water. (credit a: modification of work by Jane Whitney; credit b: modification of work by Carlos Ponte)*

Water Is an Excellent Solvent

Because water is polar, with slight positive and negative charges, ionic compounds and polar molecules can readily dissolve in it. Water is, therefore, what is referred to as a solvent—a substance capable of dissolving another substance. The charged particles will form hydrogen bonds with a surrounding layer of water molecules. This is referred to as a sphere of hydration and serves to keep the particles separated or dispersed in the water. In the case of table salt (NaCl) mixed in water (Figure , the sodium and chloride ions separate, or dissociate, in the water, and spheres of hydration are formed around the ions. A positively charged sodium ion is surrounded by the partially negative charges of oxygen atoms in water molecules. A negatively charged chloride ion is surrounded by the partially positive charges of hydrogen atoms in water molecules. These spheres of hydration are also referred to as hydration shells. The polarity of the water molecule makes it an effective solvent and is important in its many roles in living systems.

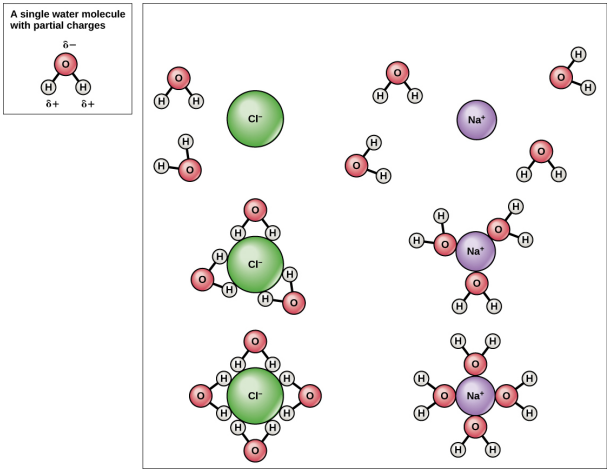

Figure 5*When table salt (NaCl) is mixed in water, spheres of hydration form around the ions.*

Water Is Cohesive

Have you ever filled up a glass of water to the very top and then slowly added a few more drops? Before it overflows, the water actually forms a dome-like shape above the rim of the glass. This water can stay above the glass because of the property of cohesion. In cohesion, water molecules are attracted to each other (because of hydrogen bonding), keeping the molecules together at the liquid-air (gas) interface, although there is no more room in the glass. Cohesion gives rise to surface tension, the capacity of a substance to withstand rupture when placed under tension or stress. When you drop a small scrap of paper onto a droplet of water, the paper floats on top of the water droplet, although the object is denser (heavier) than the water. This occurs because of the surface tension that is created by the water molecules. Cohesion and surface tension keep the water molecules intact and the item floating on the top. It is even possible to "float" a steel needle on top of a glass of water if you place it gently, without breaking the surface tension (Figure 6).

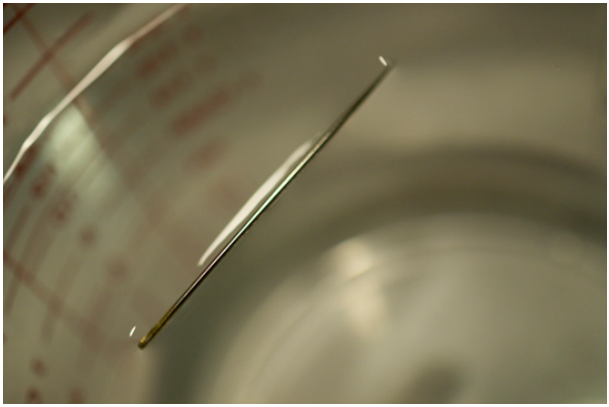

Figure 6*The weight of a needle on top of water pulls the surface tension downward; at the same time, the surface tension of the water is pulling it up, suspending the needle on the surface of the water and keeping it from sinking. Notice the indentation in the water around the needle. (credit: Cory Zanker)*

These cohesive forces are also related to the water's property of adhesion, or the attraction between water molecules and other molecules. This is observed when water "climbs" up a straw placed in a glass of water. You will notice that the water appears to be higher on the sides of the straw than in the middle. This is because the water molecules are attracted to the straw and therefore adhere to it.

Cohesive and adhesive forces are important for sustaining life. For example, because of these forces, water can flow up from the roots to the tops of plants to feed the plant.

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OpenStax, Concepts of Biology. OpenStax CNX. March 22, 2017 https://cnx.org/contents/s8Hh0oOc@9.21:t90BfSb7@4/Water

9. Buffers, pH, Acids, and Bases

The **pH** of a solution is a measure of its **acidity** or **alkalinity.** You may have used litmus paper or purple cabbage juice, which can both be used as a pH indicator – they change different colors in the presence of an acid or a base. You might have used a pH indicator to make sure the water in an outdoor swimming pool is properly treated. In both cases, this pH test measures the amount of hydrogen ions (H^+) that exists in a given solution. High concentrations of hydrogen ions yield a low pH, whereas low levels of hydrogen ions result in a high pH. The overall concentration of hydrogen ions is inversely related to its pH and can be measured on the pH scale (Figure 1). Therefore, the more hydrogen ions present, the lower the pH; conversely, the fewer hydrogen ions, the higher the pH.

The pH scale ranges from 0 to 14. A change of one unit on the pH scale represents a change in the concentration of hydrogen ions by a factor of 10, a change in two units represents a change in the concentration of hydrogen ions by a factor of 100. Thus, small changes in pH represent large changes in the concentrations of hydrogen ions. Pure water is **neutral.** It is neither acidic nor basic, and has a pH of 7.0. Anything below 7.0 (ranging from 0.0 to 6.9) is **acidic,** and anything above 7.0 (from 7.1 to 14.0) is **alkaline (basic).** The blood in your veins is slightly alkaline (pH = 7.4). The environment in your stomach is highly acidic (pH = 1 to 2). Orange juice is mildly acidic (pH = approximately 3.5), whereas baking soda is basic (pH = 9.0).

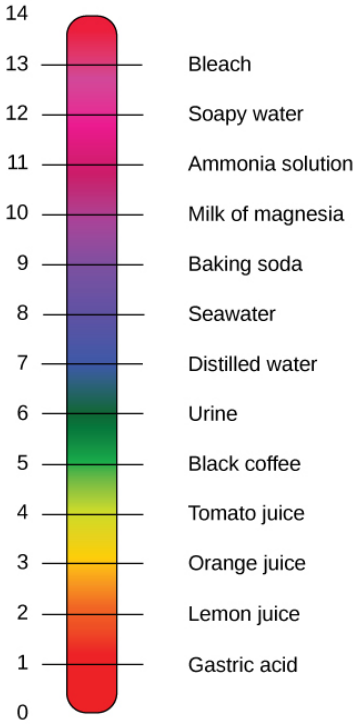

Figure 1 *The pH scale measures the amount of hydrogen ions (H+) in a substance. (credit: modification of work by Edward Stevens)*

Acids are substances that provide hydrogen ions (H^+) and lower pH, whereas bases provide hydroxide ions (OH^-) and raise pH. The stronger the acid, the more readily it donates H^+. For example, hydrochloric acid and lemon juice are very acidic and readily give up $H^+$when added to water. Conversely, bases are those substances that readily donate OH^-. The OH^- ions combine with $H^+$to produce water, which raises a substance's pH. Sodium hydroxide and many household cleaners are very alkaline and give up OH^-rapidly when placed in water, thereby raising the pH.

Most cells in our bodies operate within a very narrow window of the pH scale, typically ranging only from 7.2 to 7.6. If the pH of the body is outside of this range, the respiratory system malfunctions, as do other organs in the body. Cells no longer function properly,

and proteins will break down. Deviation outside of the pH range can induce coma or even cause death.

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So how is it that we can ingest or inhale acidic or basic substances and not die? Buffers are the key. **Buffers** readily absorb excess H^+or OH^-, keeping the pH of the body carefully maintained in the aforementioned narrow range (they help maintain homeostasis). Carbon dioxide is part of a prominent buffer system in the human body; it keeps the pH within the proper range. This buffer system involves carbonic acid (H_2CO_3) and bicarbonate (HCO_3^-) anion. If too much H^+enters the body, bicarbonate will combine with the $H^+$to create carbonic acid and limit the decrease in pH. Likewise, if too much $OH^-$is introduced into the system, carbonic acid will rapidly dissociate into bicarbonate and H^+ions. The H^+ions can combine with the OH^-ions, limiting the increase in pH. While carbonic acid is an important product in this reaction, its presence is fleeting because the carbonic acid is released from the body as carbon dioxide gas each time we breathe. Without this buffer system, the pH in our bodies would fluctuate too much and we would fail to survive.

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10. Absolutely Necessary Chemistry Summary

Matter

- Matter is anything that occupies space and has mass.
- Matter is made up of atoms of different elements.
- All of the 92 elements that occur naturally have unique qualities that allow them to combine in various ways to create compounds or molecules.
- Atoms consist of protons, neutrons, and electrons.
- Atoms are the smallest units of an element that retain all of the properties of that element.

Chemical Bonds

- Electrons can be donated or shared between atoms to create bonds.
    - Ionic bonds form between a positively and a negatively charged atom. They are fairly strong bonds.
    - Covalent bonds form when atoms share one or more electrons. They are very strong bonds.
    - Hydrogen bonds form between partially charged atoms. They are weak bonds.
    - van der Waals interactions form between polar, covalently bound atoms. They are weak attractions that are often temporary.

Water

- is POLAR, allowing for the formation of hydrogen bonds,
- is an excellent SOLVENT: because water is polar, it allows ions and other polar molecules to dissolve.
- STABILIZES TEMPERATURE: the hydrogen bonds between water molecules give water the ability to hold heat better than many other substances. As the temperature rises, the hydrogen bonds between water continually break and reform, allowing for the overall temperature to remain stable, although increased energy is added to the system.
- is COHESIVE: hydrogen bonds allow for the property of surface tension.

pH, Acids, Bases, and Buffers

- The pH of a solution is a measure of the concentration of hydrogen ions in the solution. The pH scale ranges from 0 to 14.
    - A solution with an equal number of hydrogen ions and hydroxide ions is neutral and has a pH of 7.
    - A solution with a high number of hydrogen ions is acidic and has a low pH value (below 7).
    - A solution with a high number of hydroxide ions is basic and has a high pH value (above 7).
- Buffers are solutions that moderate pH changes when an acid or base is added to the buffer system. Buffers are important in biological systems because of their ability to maintain constant pH conditions.

PART IV

BIOLOGICAL MOLECULES

Learning Outcomes

- Describe the structure of biologically-important molecules (carbohydrates, lipids, proteins, nucleic acids, water) and how their structure leads to their function.

Food provides an organism with nutrients–the matter it needs to survive. Many of these critical nutrients come in the form of **biological macromolecules**, or large molecules necessary for life. These macromolecules are built from different combinations of smaller organic molecules. What specific types of biological macromolecules do living things require? How are these molecules formed? What functions do they serve? In this chapter, we will explore these questions.

There are four major classes of biological macromolecules (carbohydrates, lipids, proteins, and nucleic acids), and each is an important component of the cell and performs a wide array of functions. Combined, these molecules make up the majority of a cell's mass. Biological macromolecules are organic, meaning that they contain carbon atoms. In addition, they may contain atoms of hydrogen, oxygen, nitrogen, phosphorus, sulfur, and additional minor elements.

These molecules are made up of subunits called monomers. Each type of biological molecule is made up of different monomers. The monomers are connected together into a chain by strong covalent

bonds. It is important that covalent bonds connect the monomers. If they were connected by hydrogen bonds the monomers would easily separate from each other and the biological molecule would come apart. If ionic bonds connected the monomers, the biological molecule would be likely to fall apart if it came into contact with water.

Figure 1 *The structure of a macromolecule can be compared to a necklace: both are larger structures that are built out of small pieces connected together into a chain. The "string" in a macromolecule would be strong covalent bonds connecting the individual subunits together. ("Beads on a string" by Daniel is licensed under CC BY-NC-ND 2.0)*

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OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:QhGQhr4x@6/Biological-Molecules

11. Carbohydrates

Carbohydrates are macromolecules with which most consumers are somewhat familiar. To lose weight, some individuals adhere to "low-carb" diets. Athletes, in contrast, often "carb-load" before important competitions to ensure that they have sufficient energy to compete at a high level. Carbohydrates are, in fact, an essential part of our diet; grains, fruits, and vegetables are all natural sources of carbohydrates. Carbohydrates provide energy to the body, particularly through glucose, a simple sugar. Carbohydrates also have other important functions in humans, animals, and plants.

Figure 1 *Bread, pasta, and sugar all contain high levels of carbohydrates. ("Wheat products" by US Department of Agriculture is in the Public Domain)*

Carbohydrates can be represented by the stoichiometric formula $(CH_2O)_n$, where n is the number of carbons in the molecule. In other words, the ratio of carbon to hydrogen to oxygen is 1:2:1

in carbohydrate molecules. This formula also explains the origin of the term "carbohydrate": the components are carbon ("carbo") and the components of water (hence, "hydrate"). Carbohydrates are classified into three subtypes: monosaccharides, disaccharides, and polysaccharides.

Monosaccharides

Monosaccharides (mono- = "one"; sacchar- = "sweet") are simple sugars, the most common of which is glucose. In monosaccharides, the number of carbons usually ranges from three to seven. Most monosaccharide names end with the suffix -ose.

The chemical formula for glucose is $C_6H_{12}O_6$. In humans, glucose is an important source of energy. During cellular respiration, energy is released from glucose, and that energy is used to help make adenosine triphosphate (ATP). Plants synthesize glucose using carbon dioxide and water, and glucose in turn is used for energy requirements for the plant. Excess glucose is often stored as starch that is catabolized (the breakdown of larger molecules by cells) by humans and other animals that feed on plants.

Galactose (part of lactose, or milk sugar) and fructose (found in sucrose, in fruit) are other common monosaccharides. Although glucose, galactose, and fructose all have the same chemical formula ($C_6H_{12}O_6$), they differ structurally and chemically (and are known as isomers) because of the different arrangement of functional groups around the asymmetric carbon; all of these monosaccharides have more than one asymmetric carbon. Within one monosaccharide, all of the atoms are connected to each other with strong covalent bonds.

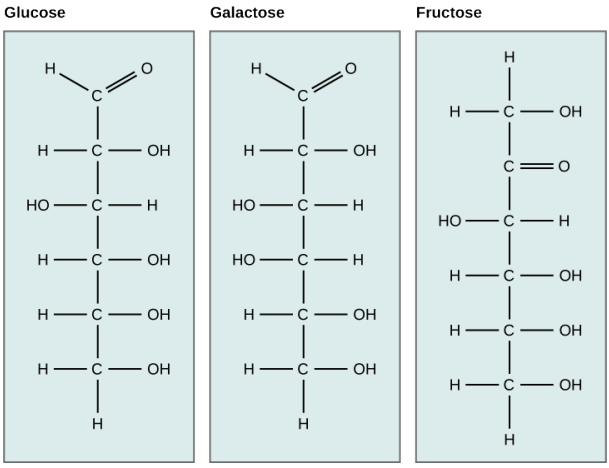


Figure 2*Glucose, galactose, and fructose are all hexoses. They are structural isomers, meaning they have the same chemical formula ($C_6H_{12}O_6$) but a different arrangement of atoms. The lines between atoms represent covalent bonds.*

Disaccharides

Disaccharides (di- = "two") form when two monosaccharides undergo a dehydration reaction (also known as a condensation reaction or dehydration synthesis). During this process, the hydroxyl (OH) group of one monosaccharide combines with the hydrogen of another monosaccharide, releasing a molecule of water and forming a covalent bond which joins the two monosaccharides together.

Common disaccharides include lactose, maltose, and sucrose (Figure 3). Lactose is a disaccharide consisting of the monomers glucose and galactose. It is formed by a dehydration reaction between the glucose and the galactose molecules, which removes a water molecule and forms a covalent bond. connected by a covalent

bond. It is found naturally in milk. Maltose, or malt sugar, is a disaccharide composed of two glucose molecules connected by a covalent bond. The most common disaccharide is sucrose, or table sugar, which is composed of the monomers glucose and fructose, also connected by a covalent bond.

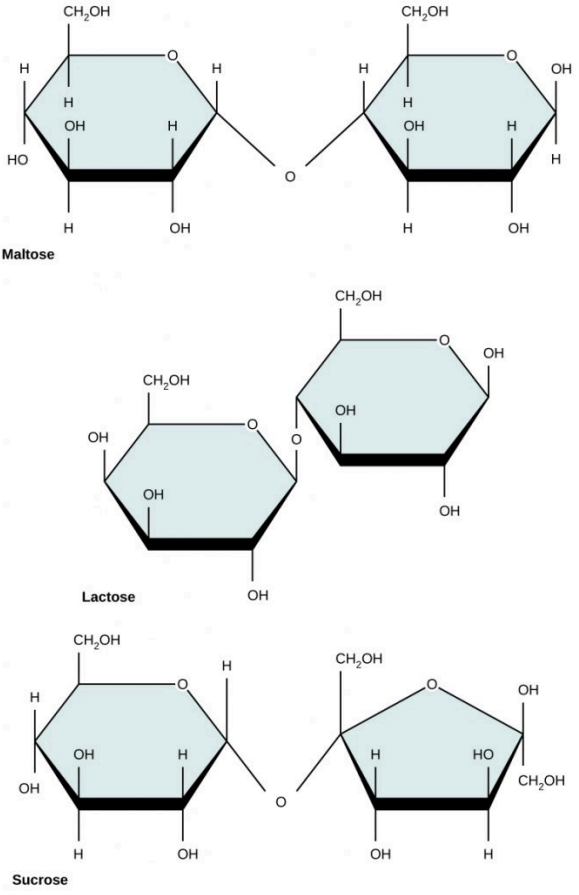


Figure 3*Common disaccharides include maltose (grain sugar), lactose (milk sugar), and sucrose (table sugar).*

Polysaccharides

A long chain of monosaccharides linked by glycosidic bonds is known as a polysaccharide (poly- = "many"). The chain may be branched or unbranched, and it may contain different types of monosaccharides. All of the monosaccharides are connected together by covalent bonds. The molecular weight may be 100,000 daltons or more depending on the number of monomers joined. Starch, glycogen, cellulose, and chitin are primary examples of polysaccharides.

Starch is the stored form of sugars in plants and is made up of a mixture of amylose and amylopectin (both polymers of glucose). Basically, starch is a long chain of glucose monomers. Plants are able to synthesize glucose, and the excess glucose, beyond the plant's immediate energy needs, is stored as starch in different plant parts, including roots and seeds. The starch in the seeds provides food for the embryo as it germinates and can also act as a source of food for humans and animals. The starch that is consumed by humans is broken down by enzymes, such as salivary amylases, into smaller molecules, such as maltose and glucose. The cells can then absorb the glucose.

Glycogen is the storage form of glucose in humans and other vertebrates and is made up of monomers of glucose. Glycogen is the animal equivalent of starch and is a highly branched molecule usually stored in liver and muscle cells. Whenever blood glucose levels decrease, glycogen is broken down to release glucose in a process known as glycogenolysis.

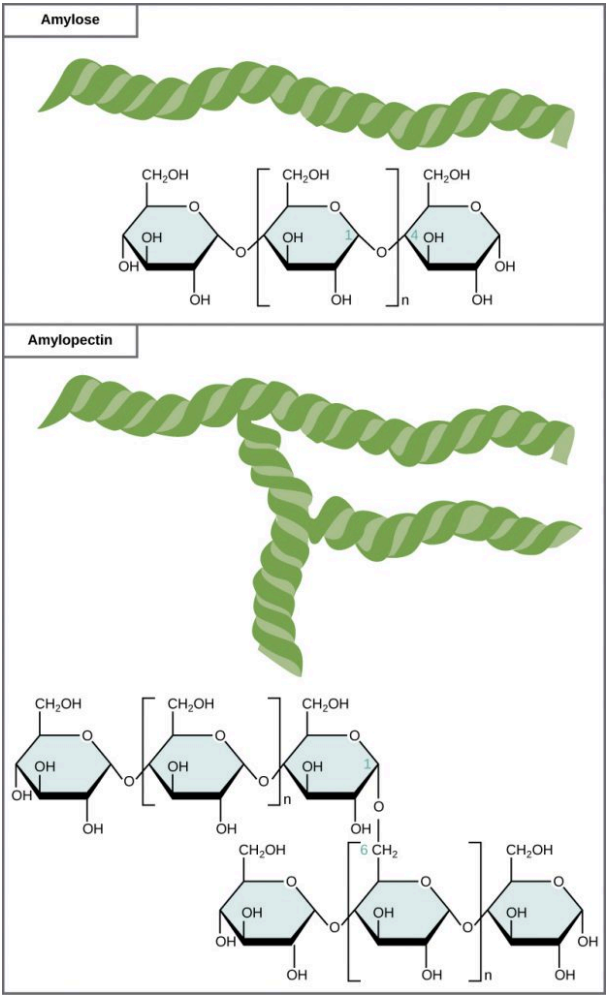


Figure 4*Amylose and amylopectin are two different forms of starch. Amylose is composed of unbranched chains of glucose monomers. Amylopectin is composed of branched chains of glucose monomers. Because of the way the subunits are joined, the glucose chains have a helical structure. Glycogen (not shown) is similar in structure to amylopectin but more highly branched.*

Cellulose is the most abundant natural biopolymer. The cell wall of plants is mostly made of cellulose; this provides structural support to the cell. Wood and paper are mostly cellulosic in nature. Cellulose is made up of glucose monomers (Figure 5).

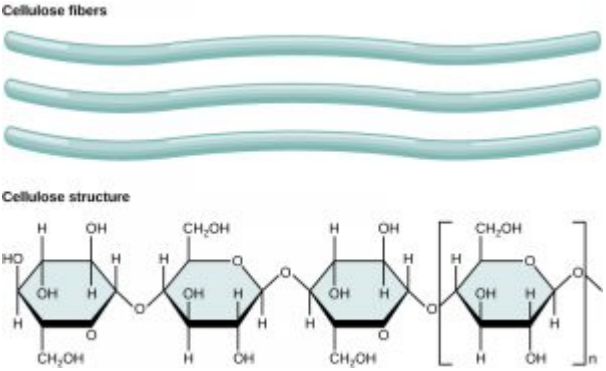


Figure 5*In cellulose, glucose monomers are linked in unbranched chains. Because of the way the glucose subunits are joined, every glucose monomer is flipped relative to the next one resulting in a linear, fibrous structure.*

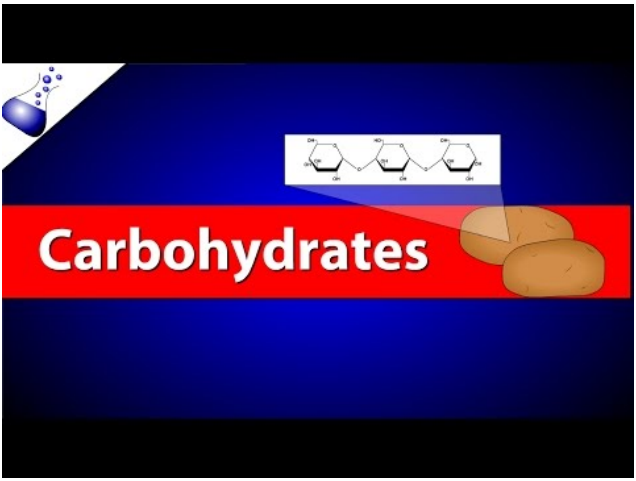
Carbohydrates serve various functions in different animals. Arthropods (insects, crustaceans, and others) have an outer skeleton, called the exoskeleton, which protects their internal body parts (as seen in the bee in Figure 6). This exoskeleton is made of the biological macromolecule chitin, which is a polysaccharide-containing nitrogen. It is made of repeating units of N-acetyl-β-d-glucosamine, a modified sugar. Chitin is also a major component of fungal cell walls; fungi are neither animals nor plants and form a kingdom of their own in the domain Eukarya.

Figure 6*Insects have a hard outer exoskeleton made of chitin, a type of polysaccharide. (credit: Louise Docker)*

How does carbohydrate structure relate to function?

Energy can be stored within the bonds of a molecule. Bonds connecting two carbon atoms or connecting a carbon atom to a hydrogen atom are high energy bonds. Breaking these bonds releases energy. This is why our cells can get energy from a molecule of glucose ($C_6H_{12}O_6$).

Polysaccharides form long, fibrous chains which are able to build strong structures such as cell walls.



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12. Lipids

Lipids are a diverse group of compounds that are united by a common feature. **Lipids** are hydrophobic ("water-fearing"), or insoluble in water. Lipids perform many different functions in a cell. Cells store energy for long-term use in the form of lipids called fats. Lipids also provide insulation from the environment for plants and animals. For example, they help keep aquatic birds and mammals dry because of their water-repelling nature. Lipids are also the building blocks of many hormones and are an important constituent of the plasma membrane. Lipids include fats, oils, waxes, phospholipids, and steroids.

Fats and Oils

A fat molecule consists of two main components—glycerol and fatty acids. Glycerol is an organic compound (an alcohol) that contains three carbons, five hydrogens, and three hydroxyl (OH) groups (Figure 1). Fatty acids have a long chain of hydrocarbons to which a carboxyl group is attached, hence the name "fatty acid." The number

of carbons in the fatty acid may range from 4 to 36; most common are those containing 12–18 carbons. In a fat molecule, the fatty acids are attached to each of the three carbons of the glycerol molecule with a covalent bond. This molecule is called a triglyceride.

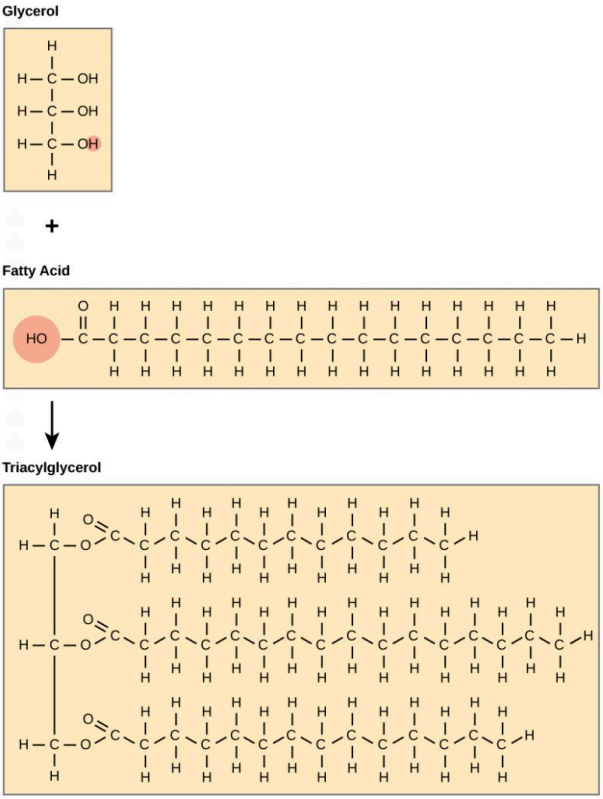


Figure 1 *Triacylglycerol is formed by the joining of three fatty acids to a glycerol backbone in a dehydration reaction (remember this removes a water molecule and forms a covalent bond). Three molecules of water are released in the process.*

Waxes

Wax covers the feathers of some aquatic birds and the leaf surfaces of some plants. Because of the hydrophobic nature of waxes, they prevent water from sticking on the surface (Figure 2). Waxes are

made up of long fatty acid chains covalently bonded to long-chain alcohols.

Figure 2 *Waxy coverings on some leaves are made of lipids. (credit: Roger Griffith)*

Phospholipids

Phospholipids are major constituents of the plasma membrane, the outermost layer of animal cells. Like fats, they are composed of fatty acid chains covalently bonded to a glycerol or sphingosine backbone. Instead of three fatty acids attached as in triglycerides, however, there are two fatty acids forming diacylglycerol, and the third carbon of the glycerol backbone is occupied by a modified phosphate group (Figure 3). Phosphatidylcholine and phosphatidylserine are two important phospholipids that are found in plasma membranes.

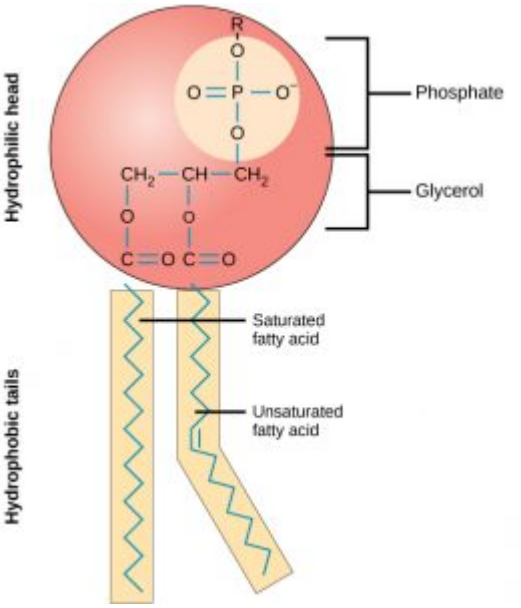


Figure 3 *A phospholipid is a molecule with two fatty acids and a modified phosphate group attached to a glycerol backbone. The phosphate may be modified by the addition of charged or polar chemical groups. Two chemical groups that may modify the phosphate, choline and serine, are shown here. Both choline and serine attach to the phosphate group at the position labeled R via the hydroxyl group indicated in green.*

A phospholipid is an **amphipathic**molecule, meaning it has a hydrophobic and a hydrophilic part. The fatty acid chains are hydrophobic and cannot interact with water, whereas the phosphate-containing group is hydrophilic and interacts with water (Figure 4). The head is the hydrophilic part, and the tail contains the

hydrophobic fatty acids. In a membrane, a bilayer of phospholipids forms the matrix of the structure, the fatty acid tails of phospholipids face inside, away from water, whereas the phosphate group faces the outside, aqueous side. This forms a hydrophobic layer on the inside of the bilayer, where the tails are located.

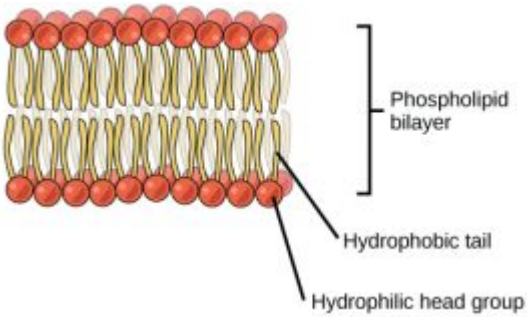


Figure 4 *The phospholipid bilayer is the major component of all cellular membranes. The hydrophilic head groups of the phospholipids face the aqueous solution. The hydrophobic tails are sequestered in the middle of the bilayer.*

Phospholipids are responsible for the dynamic nature of the plasma membrane. If a drop of phospholipids is placed in water, it spontaneously forms a structure known as a micelle, where the hydrophilic phosphate heads face the outside and the fatty acids face the interior of this structure (Figure 5).

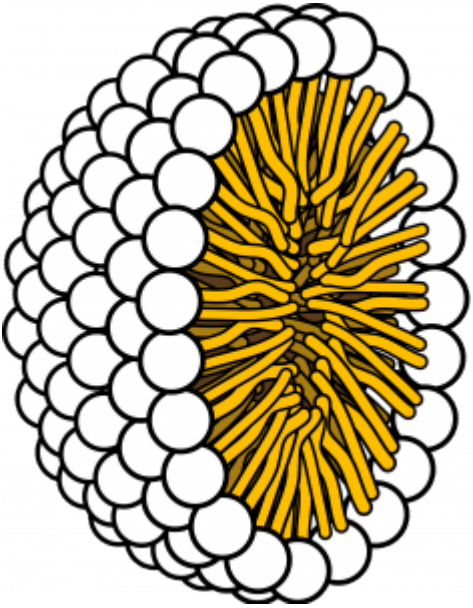
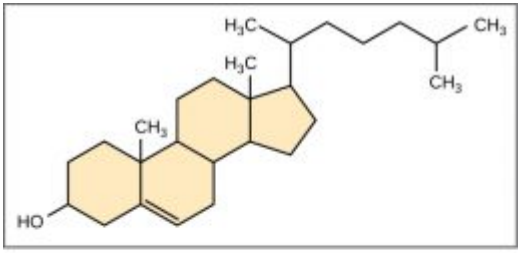


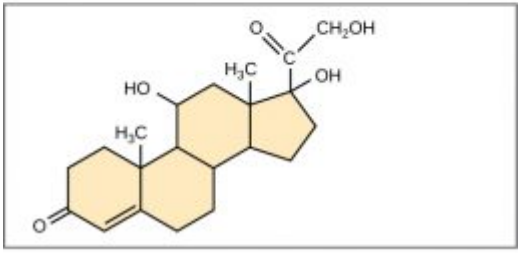
Figure 5 *A micelle may be the very early precursor of a cell. It is a single layer of phospholipids that form spontaneously. Credit AmitWo, Wikimedia; https://commons.wikimedia.org/wiki/File:Micelle.svg*

Steroids

Unlike the phospholipids and fats discussed earlier, steroids have a fused ring structure. Although they do not resemble the other lipids, they are grouped with them because they are also hydrophobic and insoluble in water. All steroids have four linked carbon rings and several of them, like cholesterol, have a short tail (Figure 6). Many steroids also have the –OH functional group, which puts them in the alcohol classification (sterols). Remember that each line in these diagrams of chemical structures represents a covalent bond. The points where the lines connect to each other show the location of carbon atoms – these carbon atoms are not labeled, but their existence is implied in the chemical structure.



Cholesterol



Cortisol

Figure 6 *Steroids such as cholesterol and cortisol are composed of four fused hydrocarbon rings.*

Cholesterol is the most common steroid. Cholesterol is mainly synthesized in the liver and is the precursor to many steroid hormones such as testosterone and estradiol, which are secreted by the gonads and endocrine glands. It is also the precursor to Vitamin D. Cholesterol is also the precursor of bile salts, which help in the emulsification of fats and their subsequent absorption by cells. Although cholesterol is often spoken of in negative terms by lay people, it is necessary for proper functioning of the body. It is a component of the plasma membrane of animal cells and is found within the phospholipid bilayer. Being the outermost structure in animal cells, the plasma membrane is responsible for the transport of materials and cellular recognition and it is involved in cell-to-cell communication.

How does lipid structure relate to function?

Fats (triglycerides) are made up of three fatty acid hydrocarbon chains connected to a glycerol. Fatty acid chains contain large numbers of carbon-carbon and carbon-hydrogen bonds – they are typically made up of between 4 and 28 carbons connected together in a chain. Just like the carbon-carbon and carbon-hydrogen bonds in glucose allow that molecule to store energy, the bonds in fatty acids allow triglycerides to store energy. In fact, triglycerides can store much more energy than carbohydrates because they contain so many more bonds! This is why fats contain more calories (a measure of energy) than sugars do.

Waxes function to provide a waterproof coating on a surface. Because they are hydrophobic, they can form a coating that repels water.

The structure of phospholipids is very important to their function. Because they are amphipathic (have a hydrophobic and a hydrophilic portion), they self-assemble into structures where the hydrophobic tails are hidden away from the watery environment. This gives the cell membrane a structure that prevents many molecules from moving through it.

Cholesterol is also amphipathic. It can insert into cell membranes in a manner similar to phospholipids. The presence of cholesterol within a membrane prevents the phospholipid tails from packing together tightly. This allows the membrane to remain fluid at lower temperatures.

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OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:QhGQhr4x@6/Biological-Molecules

13. Proteins

Proteins are one of the most abundant organic molecules in living systems and have the most diverse range of functions of all macromolecules. Proteins may be structural, regulatory, contractile, or protective; they may serve in transport, storage, or membranes; or they may be toxins or enzymes. Each cell in a living system may contain thousands of different proteins, each with a unique function. Their structures, like their functions, vary greatly. They are all, however, polymers of amino acids, arranged in a linear sequence and connected together by covalent bonds.

Amino acids are the monomers that make up proteins (Figure 1). Each amino acid has the same fundamental structure, which consists of a central carbon atom, also known as the alpha (α) carbon, bonded to an amino group (NH_2), a carboxyl group (COOH), and to a hydrogen atom. Every amino acid also has another atom or group of atoms bonded to the central atom known as the R group.

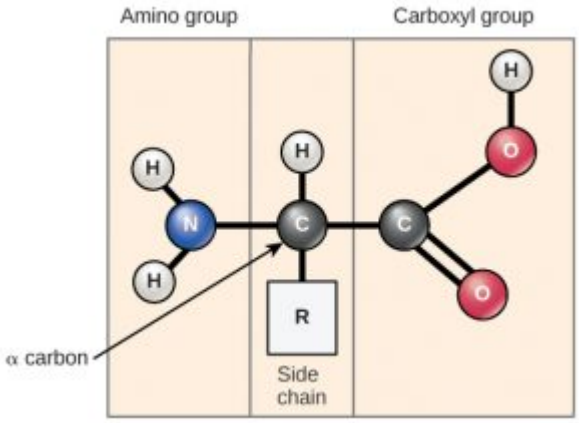


Figure 1 *Amino acids have a central asymmetric carbon to which an amino group, a carboxyl group, a hydrogen atom, and a side chain (R group) are attached.*

Function	Examples	Description
Defense	Immunoglobulins	Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.
Enzyme	Digestive enzymes such as amylase, lipase, pepsin, trypsin	Enzymes carry out almost all of the thousands of chemical reactions that take place in cells. They also assist with the formation of new molecules by reading the genetic information stored in DNA.
Messenger	Insulin, thyroxine	Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.
Structural component	Actin, tubulin, keratin	These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.
Transport/ storage	Hemoglobin, albumin, Legume storage proteins, egg white (albumin)	These proteins bind and carry atoms and small molecules within cells and throughout the body. Some provide nourishment in early development of the embryo and the seedling
Contractile	Actin, myosin	Affect muscle contraction.

You may have noticed that "source of energy" was not listed among the function of proteins. This is because proteins in our diet are typically broken back down into individual amino acids that our cells then assemble into our own proteins. Humans are actually unable to build some amino acids inside our own cells – we require them in our diet (these are the so-called "essential" amino acids). Our cells can digest proteins to release energy, but will usually only do so when carbohydrates or lipids are not available.

Figure 2 *Examples of foods that contain high levels of protein. ("Protein" by National Cancer Institute is in the Public Domain)*

The functions of proteins can be very diverse because they are made up of are 20 different chemically distinct amino acids that form long chains, and the amino acids can be in any order. The function of the protein is dependent on the protein's shape. The shape of a protein is determined by the order of the amino acids. Proteins are often hundreds of amino acids long and they can have very complex shapes because there are so many different possible orders for the 20 amino acids (Figure 3)!

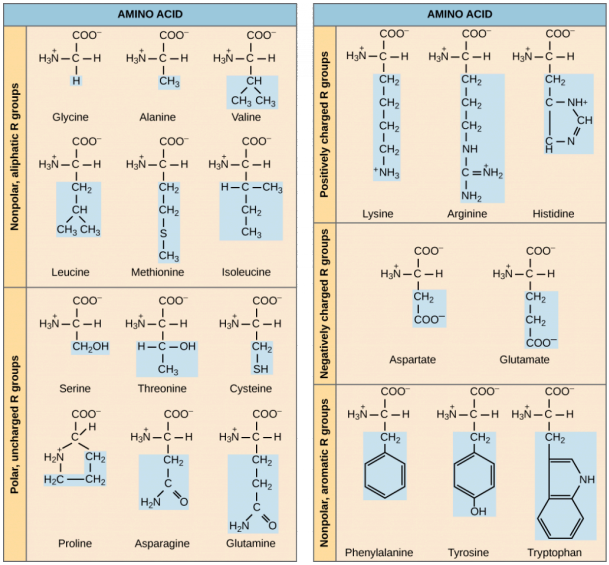


Figure 3 *There are 20 common amino acids commonly found in proteins, each with a different R group (variant group) that determines its chemical nature.*

The chemical nature of the side chain determines the nature of the amino acid (that is, whether it is acidic, basic, polar, or nonpolar). For example, the amino acid glycine has a hydrogen atom as the R group. Amino acids such as valine, methionine, and alanine are nonpolar or hydrophobic in nature, while amino acids such as serine, threonine, and cysteine are polar and have hydrophilic side chains. The side chains of lysine and arginine are positively charged, and therefore these amino acids are also known as basic amino acids. Proline has an R group that is linked to the amino group, forming a ring-like structure. Proline is an exception to the standard structure of an animo acid since its amino group is not separate from the side chain (Figure 3). Amino acids are represented by a single upper case letter as well as a three-letter abbreviation. For example, valine is known by the letter V or the three-letter symbol val.

Just as some fatty acids are essential to a diet, some amino acids are necessary as well. They are known as essential amino acids, and

in humans they include isoleucine, leucine, and cysteine. Essential amino acids refer to those necessary for construction of proteins in the body, although not produced by the body; which amino acids are essential varies from organism to organism.

The sequence and the number of amino acids ultimately determine the protein's shape, size, and function. Each amino acid is attached to another amino acid by a covalent bond, known as a peptide bond, which is formed by a dehydration reaction. The carboxyl group of one amino acid and the amino group of the incoming amino acid combine, releasing a molecule of water. The resulting bond is the peptide bond (Figure 4).

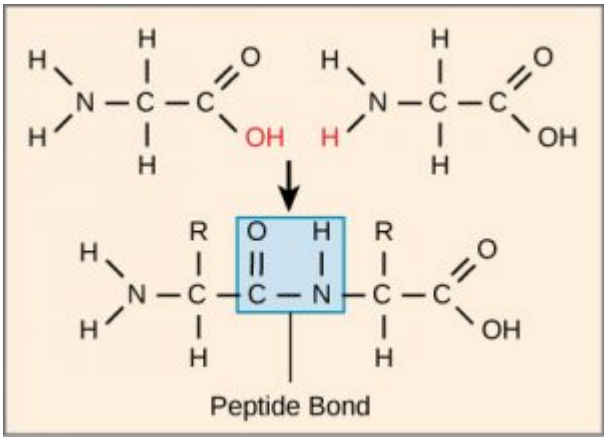


Figure 4 *Peptide bond formation is a dehydration synthesis reaction. The carboxyl group of one amino acid is linked to the amino group of the incoming amino acid. In the process, a molecule of water is released.*

Protein Structure

As discussed earlier, the shape of a protein is critical to its function. For example, an enzyme can bind to a specific substrate at a site known as the active site. If this active site is altered because of local

changes or changes in overall protein structure, the enzyme may be unable to bind to the substrate. To understand how the protein gets its final shape or conformation, we need to understand the four levels of protein structure: primary, secondary, tertiary, and quaternary (Figure 5).

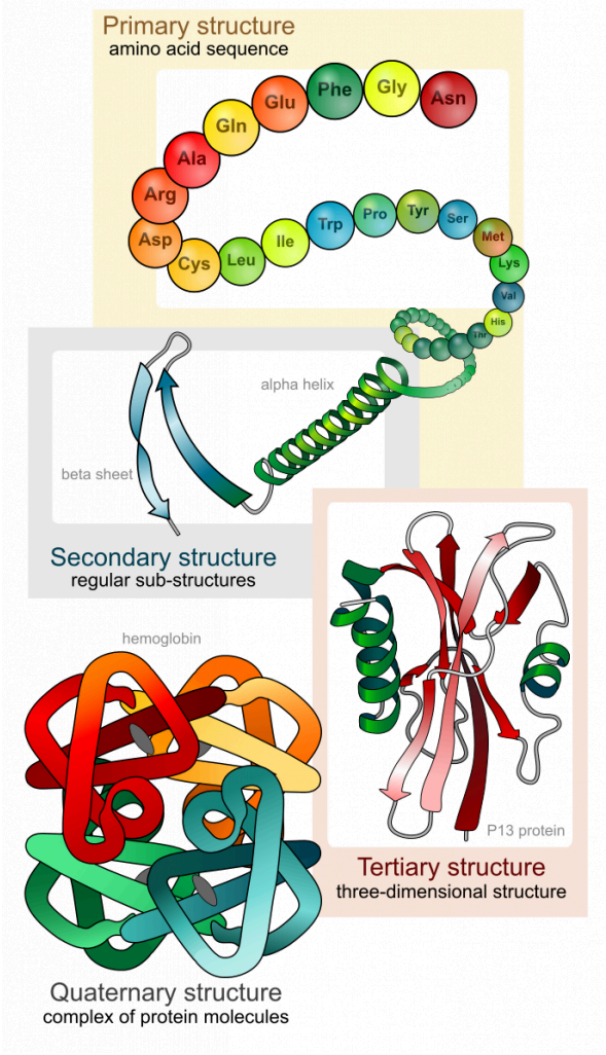


Figure 5 *Main levels of protein structure. ("Main protein structure levels en" by LadyofHats is in the Public Domain)*

Primary Structure

The unique sequence of amino acids in a polypeptide chain is its primary structure. For example, the pancreatic hormone insulin is made up of two polypeptide chains, A and B. The primary structure (sequences of amino acids) of the A and B chains are unique to insulin. Amino acids are linked together in polypeptide chains by strong covalent bonds.

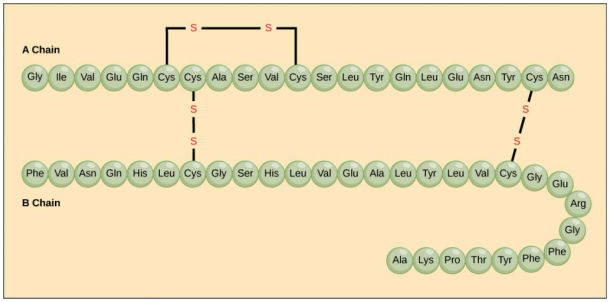


Figure 6 *Bovine serum insulin is a protein hormone made of two peptide chains, A (21 amino acids long) and B (30 amino acids long). In each chain, primary structure is indicated by three-letter abbreviations that represent the names of the amino acids in the order they are present. The amino acid cysteine (cys) has a sulfhydryl (SH) group as a side chain. Two sulfhydryl groups can react in the presence of oxygen to form a disulfide (S-S) bond. Two disulfide bonds connect the A and B chains together, and a third helps the A chain*

fold into the correct shape. Note that all disulfide bonds are the same length, but are drawn different sizes for clarity.

Secondary Structure

The local folding of the polypeptide in some regions gives rise to the secondary structure of the protein. The most common are the α-helix and β-pleated sheet structures (Figure 7). Both structures are held in shape by hydrogen bonds. The hydrogen bonds form between the oxygen atom in the carbonyl group in one amino acid and another amino acid that is four amino acids farther along the chain.

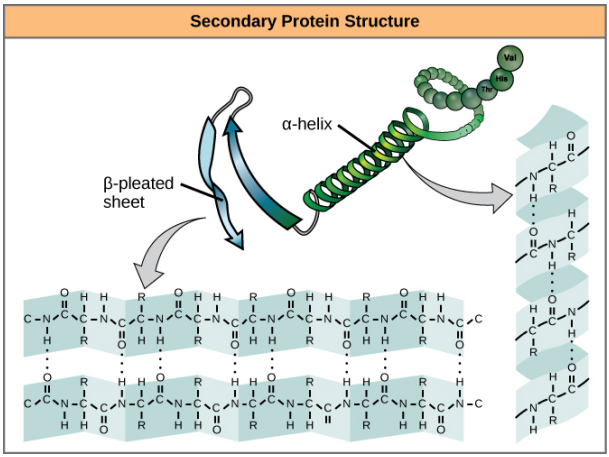


Figure 7 *The α-helix and β-pleated sheet are secondary structures of proteins that form because of hydrogen bonding between carbonyl and amino groups in the peptide backbone. Certain amino acids have a propensity to form an α-helix, while others have a propensity to form a β-pleated sheet.*

Tertiary Structure

The unique three-dimensional structure of a polypeptide is its tertiary structure (Figure 8). This structure is in part due to chemical interactions at work on the polypeptide chain. Primarily, the interactions among R groups (the variable part of the amino acid) creates the complex three-dimensional tertiary structure of a protein. For example, R groups with like charges are repelled by each other and those with unlike charges are attracted to each other (ionic bonds). Partially charged atoms within the R groups can form hydrogen bonds. When protein folding takes place, the hydrophobic R groups of non-polar amino acids lay in the interior of the protein, whereas the hydrophilic R groups lay on the outside. Interaction between cysteine side chains forms disulfide linkages in the presence of oxygen, which is the only covalent bond forming during protein folding and tertiary structure.

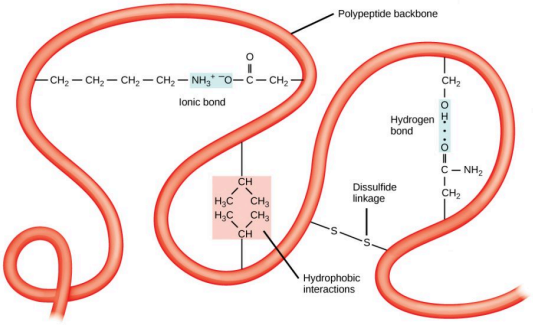


Figure 8 *The tertiary structure of proteins is determined by a variety of chemical interactions. These include hydrophobic interactions, ionic bonding, hydrogen bonding and disulfide linkages.*

Quaternary Structure

In nature, some proteins are formed from several polypeptides, also known as subunits, and the interaction of these subunits forms the quaternary structure. Weak interactions between the subunits help to stabilize the overall structure. For example, insulin (a globular protein) has a combination of hydrogen bonds and disulfide bonds that cause it to be mostly clumped into a ball shape. Insulin starts out as a single polypeptide and loses some internal sequences in the presence of post-translational modification after the formation of the disulfide linkages that hold the remaining chains together. Silk (a fibrous protein), however, has a β-pleated sheet structure that is the result of hydrogen bonding between different chains.

The four levels of protein structure (primary, secondary, tertiary, and quaternary) are illustrated in Figure 9.

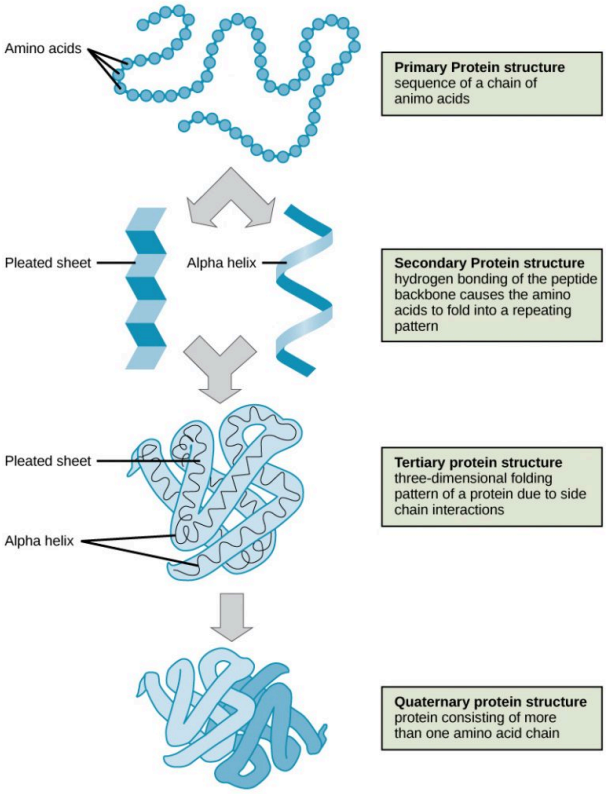


Figure 9 *The four levels of protein structure can be observed in these illustrations. (credit: modification of work by National Human Genome Research Institute)*

The unique shape for every protein is ultimately determined by the gene that encodes the protein. Any change in the gene sequence may lead to a different amino acid being added to the polypeptide chain, causing a change in protein structure and function. Individuals who are affected by sickle cell anemia can have a variety of serious health problems, such as breathlessness, dizziness, headaches, and abdominal pain. In this disease, the hemoglobin β chain has a single amino acid substitution, causing a change in both the structure (shape) and function (job) of the protein. What is most remarkable to consider is that a hemoglobin molecule is made up of about 600 amino acids. The structural difference between a normal

hemoglobin molecule and a sickle cell molecule is a single amino acid of the 600 (Figure 10).

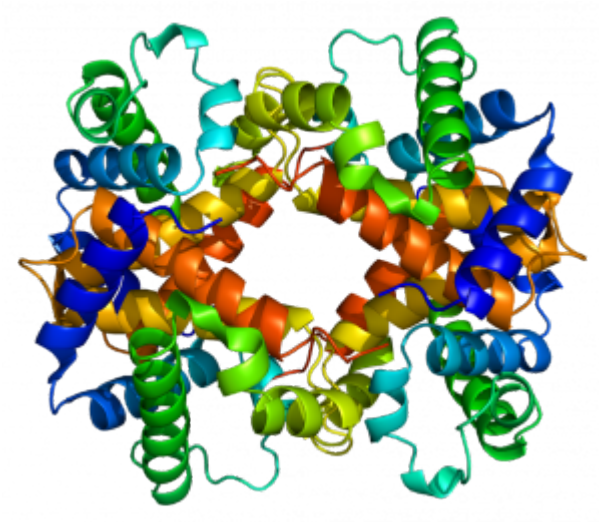


Figure 10 *The unique shape of the normal hemoglobin protein. ("Structure of hemoglobin Gower 2" by Emw is licensed under CC BY-SA 3.0)*

Denaturation and Protein Folding

Each protein has its own unique sequence and shape that are held together by chemical interactions. If the protein is subject to changes in temperature, pH, or exposure to chemicals, the protein structure may change, losing its shape without losing its primary sequence in what is known as denaturation. Denaturation is often reversible because the primary structure of the polypeptide is conserved in the process if the denaturing agent is removed, allowing the protein to resume its function. Sometimes denaturation is irreversible, leading to loss of function. One example of irreversible protein denaturation is when an egg is fried. The albumin protein in the liquid egg white is denatured when placed in a hot pan. Not all proteins are denatured at high temperatures; for instance, bacteria that survive in hot springs have proteins that

function at temperatures close to boiling. The stomach is also very acidic, has a low pH, and denatures proteins as part of the digestion process; however, the digestive enzymes of the stomach retain their activity under these conditions.

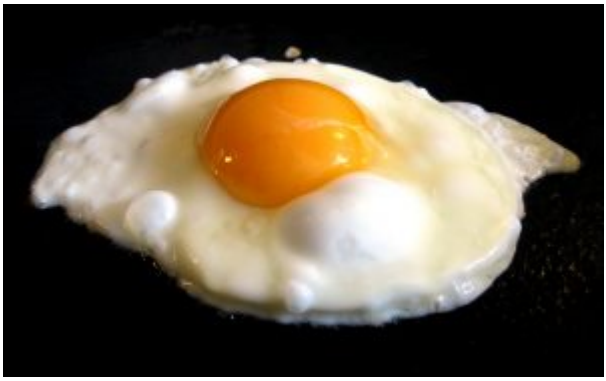


Figure 11 *The reason an egg white turns white as you cook it is because the albumin in the white denatures and then reconnects in an abnormal fashion. Credit Matthew Murdock; https://www.flickr.com/photos/54423233@N05/13916201522*

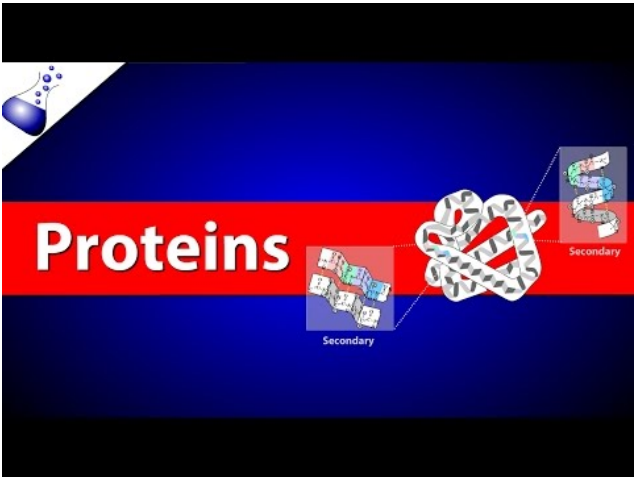
Protein folding is critical to its function. It was originally thought that the proteins themselves were responsible for the folding process. Only recently was it found that often they receive assistance in the folding process from protein helpers known as chaperones (or chaperonins) that associate with the target protein during the folding process. They act by preventing aggregation of polypeptides that make up the complete protein structure, and they disassociate from the protein once the target protein is folded.

How does protein structure relate to

function?

Recall that a protein is built from a long chain of amino acids connected together in a specific order. The specific order of amino acids determines how they will interact together to form the 3-D shape of the protein. The shape of a protein determines its function. Therefore, the order of the amino acids determines the protein's shape, which determines its function.

Because there are 20 different amino acids, they can be combined together in a practically infinite number of ways. This means that there is a huge number of different protein shapes that can be assumed based on the amino acid order. This is very important since proteins fulfill so many different functions within cells.



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14. Nucleic Acids

Nucleic acids are key macromolecules in the continuity of life. They carry the genetic blueprint of a cell and carry instructions for the functioning of the cell. The two main types of **nucleic acids** are **deoxyribonucleic acid (DNA)** and **ribonucleic acid (RNA)**. DNA is the genetic material found in all living organisms, ranging from single-celled bacteria to multicellular mammals. The other type of nucleic acid, RNA, is mostly involved in protein synthesis. The DNA molecules never leave the nucleus, but instead use an RNA intermediary to communicate with the rest of the cell. Other types of RNA are also involved in protein synthesis and its regulation. We will be going into more detail about nucleic acids in a later section.

DNA and RNA are made up of monomers known as **nucleotides** connected together in a chain with covalent bonds. Each nucleotide is made up of three components: a nitrogenous base, five-carbon sugar, and a phosphate group (**Figure 1**). The nitrogenous base in one nucleotide is attached to the sugar molecule, which is attached to the phosphate group.

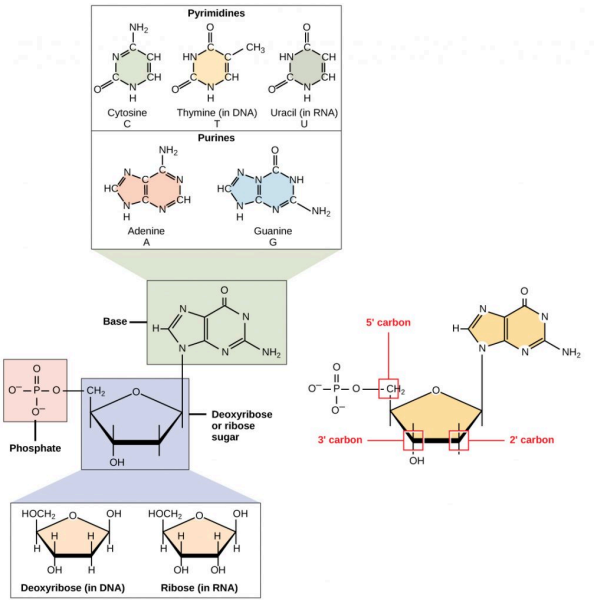


Figure 1 *A nucleotide is made up of three components: a nitrogenous base, a pentose sugar, and one or more phosphate groups.*

The nitrogenous bases, important components of nucleotides, are organic molecules and are so named because they contain carbon and nitrogen. They are bases because they contain an amino group that has the potential of binding an extra hydrogen, and thus, decreases the hydrogen ion concentration in its environment, making it more basic. Each nucleotide in DNA contains one of four possible nitrogenous bases: adenine (A), guanine (G) cytosine (C), and thymine (T). RNA contains the base uracil (U) instead of thymine. The order of the bases in a nucleic acid determines the information that the molecule of DNA or RNA carries. This is because the order of the bases in a DNA gene determines the order that amino acids will be assembled together to form a protein.

The pentose sugar in DNA is deoxyribose, and in RNA, the sugar is ribose (Figure 1). The difference between the sugars is the presence of the hydroxyl group on the second carbon of the ribose and hydrogen on the second carbon of the deoxyribose. The carbon

atoms of the sugar molecule are numbered as 1′, 2′, 3′, 4′, and 5′ (1′ is read as "one prime"). The phosphate residue is attached to the hydroxyl group of the 5′ carbon of one sugar and the hydroxyl group of the 3′ carbon of the sugar of the next nucleotide, which forms a 5′–3′ phosphodiester linkage (a specific type of covalent bond). A polynucleotide may have thousands of such phosphodiester linkages.

DNA Double-Helical Structure

DNA has a double-helical structure (**Figure 2**). It is composed of two strands, or chains, of nucleotides. The double helix of DNA is often compared to a twisted ladder. The strands (the outside parts of the ladder) are formed by linking the phosphates and sugars of adjacent nucleotides with strong chemical bonds, called **covalent bonds**. The rungs of the twisted ladder are made up of the two bases attached together with a weak chemical bond, called **a hydrogen bonds**. Two bases hydrogen bonded together is called a **base pair**. The ladder twists along its length, hence the "double helix" description, which means a double spiral.

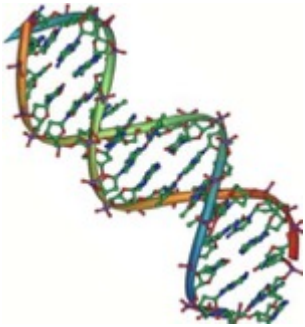


Figure 2 *The double-helix model shows DNA as two parallel strands of intertwining molecules. (credit: Jerome Walker, Dennis Myts).*

The alternating sugar and phosphate groups lie on the outside of each strand, forming the backbone of the DNA. The nitrogenous bases are stacked in the interior, like the steps of a staircase, and these bases pair; the pairs are bound to each other by hydrogen bonds. The bases pair in such a way that the distance between the backbones of the two strands is the same all along the molecule.

In a molecule of DNA, adenine (A) always pairs with thymine (T), and cytosine (C) always pairs with guanine (G). This means that the sequence of one strand of the DNA double helix can always be used to determine the other strand.

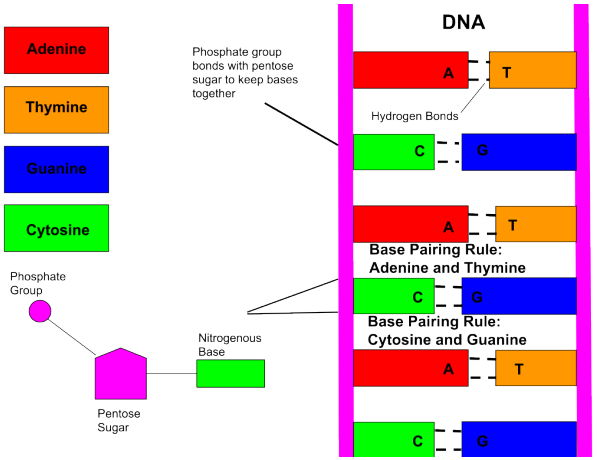
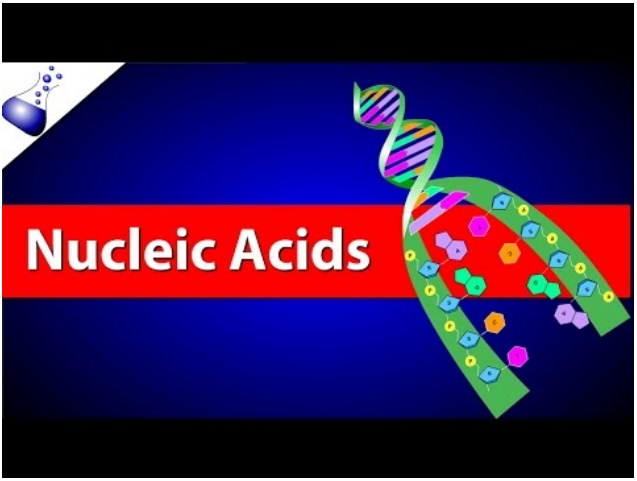


Figure 3 A diagram of the structure of a DNA molecule, showing the pairing of the nitrogenous bases, which are connected by hydrogen bonds. In DNA, A always pairs (hydrogen bonds) with T, C always pairs with G. Picture by Awedashsome; Wikimedia, CC SA 4.0.

How does nucleic acid structure determine function?

The major function of both DNA and RNA is to store and carry genetic information. The specific order of nucleotides in the molecule of DNA or RNA is what determines the genetic information it carries. You can think of it like letters in a book – if the order of the letters were changed, the book would no longer contain the same (or correct) information.



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15. Biological Macromolecule Practice Questions

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PART V

CELL STRUCTURE AND FUNCTION

Learning Objectives

Course Objective for this section: Explain how basic units of cellular structure define the function of all living things.

- Explain how various cell structures participate in the function of a cell and/or organism.

Close your eyes and picture a brick wall. What is the basic building block of that wall? It is a single brick, of course. Like a brick wall, your body is composed of basic building blocks, and the building blocks of your body are cells (**Figure 1**).

Your body has many kinds of cells, each specialized for a specific purpose. Just as a home is made from a variety of building materials, the human body is constructed from many cell types. For example, epithelial cells protect the surface of the body and cover the organs and body cavities within. Bone cells help to support and protect the body. Cells of the immune system fight invading bacteria. Additionally, red blood cells carry oxygen throughout the body. Each of these cell types plays a vital role during the growth, development, and day-to-day maintenance of the body. In spite of their enormous variety, however, all cells share certain fundamental characteristics.

Figure 1 various types of cells: animal, plant, and bacteria.

Microscopes

Cells vary in size. With few exceptions, individual cells are too small to be seen with the naked eye, so scientists use microscopes to study them. A **microscope** is an instrument that magnifies an object. Most images of cells are taken with a microscope and are called micrographs.

Light Microscopes

To give you a sense of the size of a cell, a typical human red blood cell is about eight millionths of a meter or eight micrometers (abbreviated as μm) in diameter; the head of a pin is about two thousandths of a meter (millimeters, or mm) in diameter. That means that approximately 250 red blood cells could fit on the head of a pin.

The optics of the lenses of a light microscope changes the orientation of the image. A specimen that is right-side up and facing right on the microscope slide will appear upside-down and facing left when viewed through a microscope, and vice versa. Similarly, if the slide is moved left while looking through the microscope, it will appear to move right, and if moved down, it will seem to move up. This occurs because microscopes use two sets of lenses to magnify the image. Due to the manner in which light travels through the

lenses, this system of lenses produces an inverted image (binoculars and a dissecting microscope work in a similar manner, but include an additional magnification system that makes the final image appear to be upright).

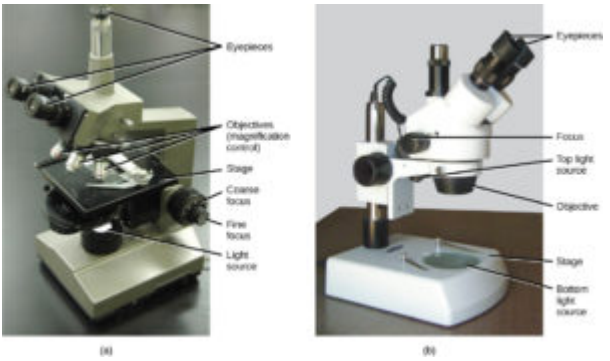

Figure 1 (a) Most light microscopes used in a college biology lab can magnify cells up to approximately 400 times. (b) Dissecting microscopes have a lower magnification than light microscopes and are used to examine larger objects, such as tissues.

Most student microscopes are classified as light microscopes (**Figure 1a**). Visible light both passes through and is bent by the lens system to enable the user to see the specimen. Light microscopes are advantageous for viewing living organisms, but since individual cells are generally transparent, their components are not distinguishable unless they are colored with special stains. Staining, however, usually kills the cells.

Light microscopes commonly used in the undergraduate college laboratory magnify up to approximately 400 times. Two parameters that are important in microscopy are magnification and resolving power. **Magnification** is the degree of enlargement of an object. **Resolving power** is the ability of a microscope to allow the eye to distinguish two adjacent structures as separate; the higher the

resolution, the closer those two objects can be, and the better the clarity and detail of the image. When oil immersion lenses are used, magnification is usually increased to 1,000 times for the study of smaller cells, like most prokaryotic cells. Because light entering a specimen from below is focused onto the eye of an observer, the specimen can be viewed using light microscopy. For this reason, for light to pass through a specimen, the sample must be thin or translucent.

A second type of microscope used in laboratories is the dissecting microscope (**Figure 1b**). These microscopes have a lower magnification (20 to 80 times the object size) than light microscopes and can provide a three-dimensional view of the specimen. Thick objects can be examined with many components in focus at the same time. These microscopes are designed to give a magnified and clear view of tissue structure as well as the anatomy of the whole organism.

Like light microscopes, most modern dissecting microscopes are also binocular, meaning that they have two separate lens systems, one for each eye. The lens systems are separated by a certain distance, and therefore provide a sense of depth in the view of their subject to make manipulations by hand easier. Dissecting microscopes also have optics that correct the image so that it appears as if being seen by the naked eye and not as an inverted image. The light illuminating a sample under a dissecting microscope typically comes from above the sample, but may also be directed from below.

Electron Microscopes

In contrast to light microscopes, electron microscopes use a beam of electrons instead of a beam of light (**Figure 2a,b**). Not only does this allow for higher magnification and, thus, more detail, it also provides higher resolving power. Preparation of a specimen for

viewing under an electron microscope will kill it; therefore, live cells cannot be viewed using this type of microscopy. In addition, the electron beam moves best in a vacuum, making it impossible to view living materials. There are two major types of electron microscopes which differ in the images they provide:

- In a scanning electron microscope (SEM) (**Figure 2b**), a beam of electrons moves back and forth across a cell's surface, rendering the details of cell surface characteristics by reflection. Cells and other structures are usually coated with a metal like gold.
- In a transmission electron microscope (TEM), the electron beam is transmitted through the cell and provides details of a cell's internal structures. As you might imagine, electron microscopes are significantly more bulky and expensive than are light microscopes.

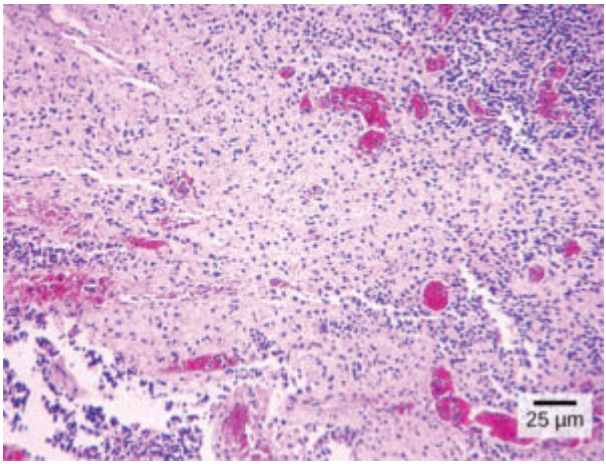

Figure 2 (a) Salmonella bacteria are viewed with a light microscope. (credit: credit a: modification of work by CDC, Armed Forces Institute of Pathology, Charles N. Farmer)

Figure 2 (b) This scanning electron micrograph (SEM) shows Salmonella bacteria (in red) invading human cells. (credit: modification of work by Rocky Mountain Laboratories, NIAID, NIH; scale-bar data from Matt Russell)

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16. Comparing Prokaryotic and Eukaryotic Cells

Cells fall into one of two broad categories: prokaryotic and eukaryotic. Bacteria are classified as prokaryotes (*pro–* = before; *–karyon–* = nucleus). Animal cells, plant cells, fungi, and protists are eukaryotes (*eu–* = true).

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https://openoregon.pressbooks.pub/mhccbiology112/?p=63

Components of Prokaryotic Cells

All cells share four common components: 1) a plasma membrane, an outer covering that separates the cell's interior from its surrounding environment; 2) cytoplasm, consisting of a gel-like region within the cell in which other cellular components are found; 3) DNA, the genetic material of the cell; and 4) ribosomes, the part of the cell that creates proteins.

Prokaryotes differ from eukaryotic cells in several important ways. A **prokaryotic cell** is a simple, single-celled (unicellular) organism that lacks a nucleus, or any other membrane-bound organelle. We will shortly come to see that this is significantly different in eukaryotes. Prokaryotic DNA is found in the central part of the cell: a darkened region called the nucleoid (**Figure 1**).

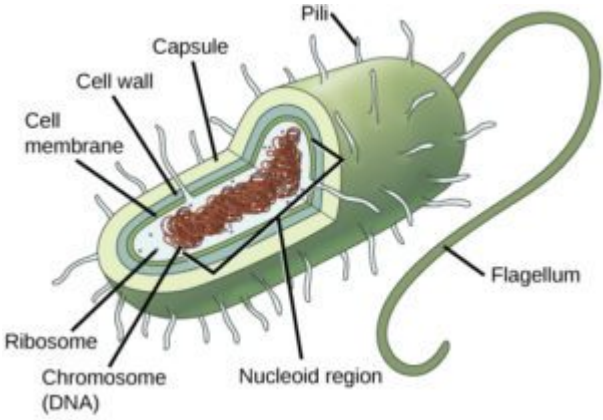


Figure 1 The generalized structure of a prokaryotic cell.

Unlike eukaryotes, bacteria have a cell wall made of peptidoglycan, comprised of sugars and amino acids, and many have a polysaccharide capsule (**Figure 1**). The cell wall acts as an extra layer of protection, helps the cell maintain its shape, and prevents dehydration. The capsule enables the cell to attach to surfaces in its environment. Some prokaryotes have flagella, pili, or fimbriae.

Flagella are used for locomotion, while most pili are used to exchange genetic material during a type of reproduction called conjugation.

Components of Eukaryotic Cells

In nature, the relationship between form and function is apparent at all levels, including the level of the cell, and this will become clear as we explore eukaryotic cells. The principle "form follows function" is found in many contexts. For example, birds and fish have streamlined bodies that allow them to move quickly through the medium in which they live, be it air or water. It means that, in general, one can deduce the function of a structure by looking at its form, because the two are matched.

A **eukaryotic cell** is a cell that has a membrane-bound nucleus and other membrane-bound compartments or sacs, called **organelles**, which have specialized functions (Figure 2 and 3). The word eukaryotic means "true kernel" or "true nucleus," pointing to the presence of the membrane-bound nucleus in these cells. The word "organelle" means "little organ," and, as already mentioned, organelles have specialized cellular functions, just as the organs of your body have specialized functions.

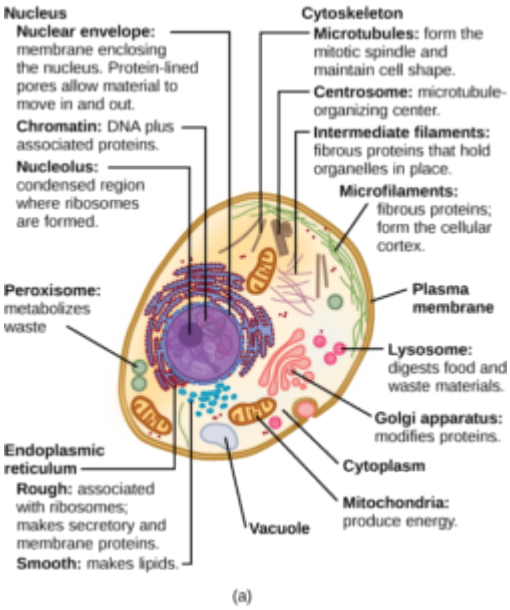


Figure 2 A *typical animal cell*

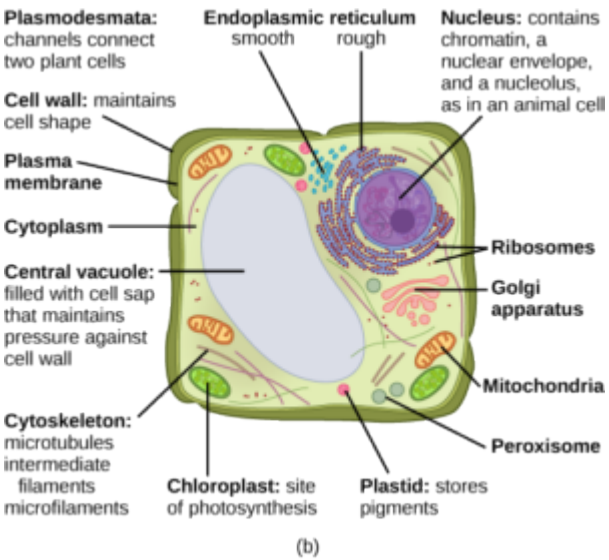
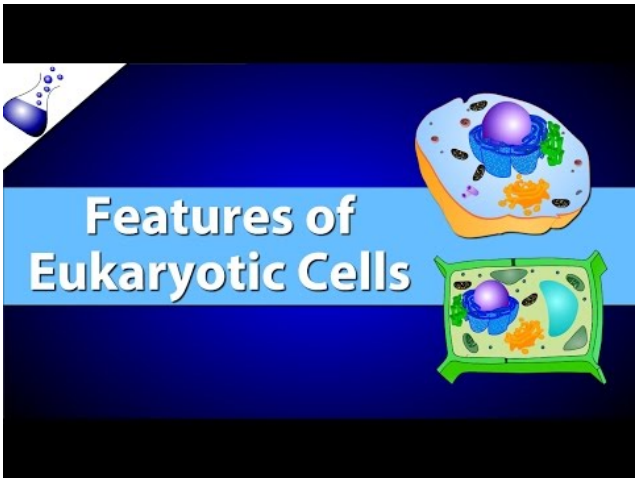


Figure 3 A *typical plant cell.*



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https://openoregon.pressbooks.pub/mhccbiology112/?p=63

Cell Size

At 0.1–5.0 μm in diameter, prokaryotic cells are significantly smaller than eukaryotic cells, which have diameters ranging from 10–100 μm (**Figure 4**). The small size of prokaryotes allows ions and organic molecules that enter them to quickly spread to other parts of the cell. Similarly, any wastes produced within a prokaryotic cell can quickly move out. However, larger eukaryotic cells have evolved different structural adaptations to enhance cellular transport. Indeed, the large size of these cells would not be possible without these adaptations. In general, cell size is limited because volume increases much more quickly than does cell surface area. As a cell

becomes larger, it becomes more and more difficult for the cell to acquire sufficient materials to support the processes inside the cell, because the relative size of the surface area across which materials must be transported declines.

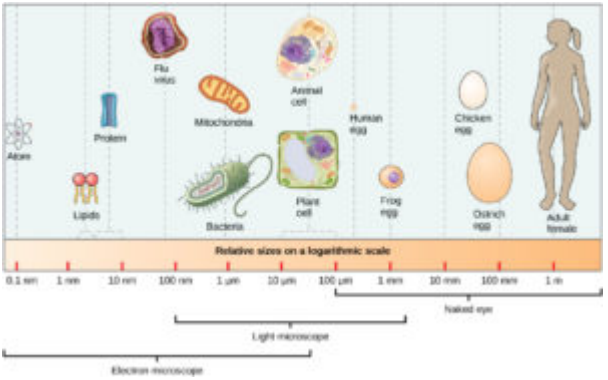


Figure 4 The relative sizes of different kinds of cells and cellular components. An adult human is shown for comparison.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

17. The Plasma Membrane and the Cytoplasm

At this point, it should be clear that eukaryotic cells have a more complex structure than do prokaryotic cells. Organelles allow for various functions to occur in the cell at the same time. Before discussing the functions of organelles within a eukaryotic cell, let us first examine two important components of all cells (prokaryotic and eukaryotic): the plasma membrane and the cytoplasm.

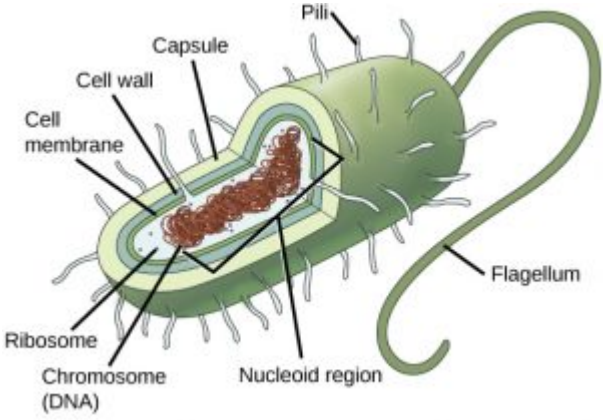


Figure 1 *A prokaryotic cell. The cytoplasm is not labeled, but is the light blue area inside the cell membrane. The ribosome label is pointing to one of the small brown dots representing the ribosome.*

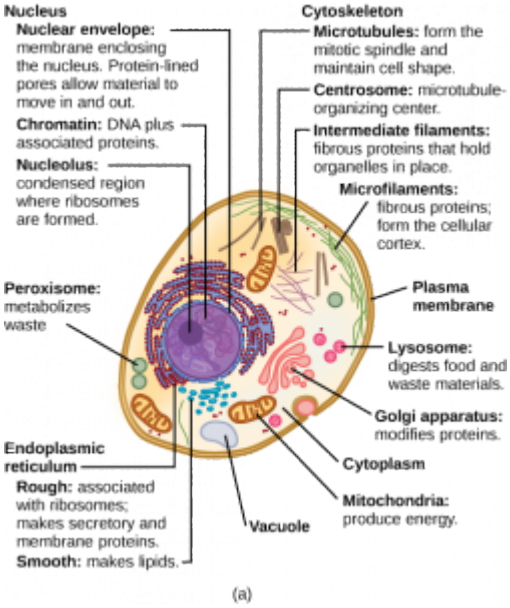


Figure 2 *This figure shows a typical animal cell*

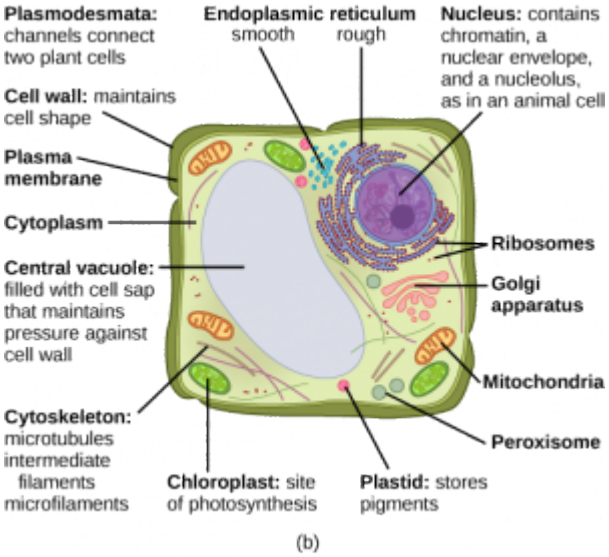


Figure 3 *This figure shows a typical plant cell.*

The Plasma Membrane

Like prokaryotes, eukaryotic cells have a **plasma membrane** (Find it in **Figures 1-3**, then look at the detailed structure in **Figure 4**) made up of a phospholipid bilayer with embedded proteins that separates the internal contents of the cell from its surrounding environment. A phospholipid is a lipid molecule composed of two fatty acid chains, a glycerol backbone, and a phosphate group. The plasma membrane regulates the passage of some substances, such as organic molecules, ions, and water, preventing the passage of some to maintain internal conditions, while actively bringing in or removing others. Other compounds move passively across the membrane.

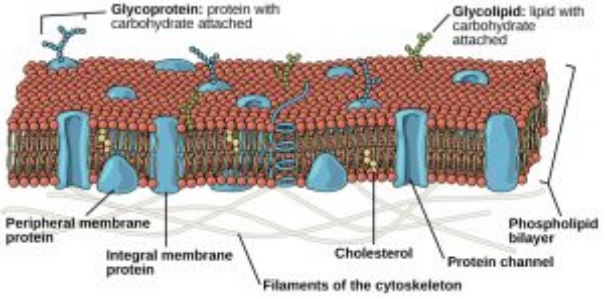


Figure 4 *The plasma membrane is a phospholipid bilayer with embedded proteins. There are other components, such as cholesterol and carbohydrates, which can be found in the membrane in addition to phospholipids and protein.*

The plasma membranes of cells that specialize in absorption are folded into fingerlike projections called microvilli(singular =

microvillus). This folding increases the surface area of the plasma membrane. Such cells are typically found lining the small intestine, the organ that absorbs nutrients from digested food (Figure 5). This is an excellent example of form matching the function of a structure.

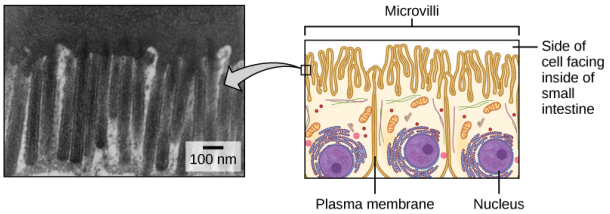


Figure 5 *Microvilli, shown here as they appear on cells lining the small intestine, increase the surface area available for absorption. These microvilli are only found on the area of the plasma membrane that faces the cavity from which substances will be absorbed. (credit "micrograph": modification of work by Louisa Howard)*

The Cytoplasm

The **cytoplasm** comprises the contents of a cell between the plasma membrane and the nuclear envelope (a structure to be discussed shortly). It is made up of organelles suspended in the gel-like

cytosol, the cytoskeleton, and various chemicals (Find it in **Figures 1-3**). Even though the cytoplasm consists of 70 to 80 percent water, it has a semi-solid consistency, which comes from the proteins within it. However, proteins are not the only organic molecules found in the cytoplasm. Glucose and other simple sugars, polysaccharides, amino acids, nucleic acids, fatty acids, and derivatives of glycerol are found there too. Ions of sodium, potassium, calcium, and many other elements are also dissolved in the cytoplasm. Many metabolic reactions, including protein synthesis, take place in the cytoplasm. Take note that the cytoplasm is not "empty" or "filler" – it is a vitally important component of cells that allows chemical reactions to take place!

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

18. Ribosomes

Ribosomes are the cellular structures responsible for protein synthesis. The word "synthesis" means "to combine things to produce something else." In this context, protein synthesis means combining different amino acids together to form a protein. Ribosomes join amino acids together in a chain to form a protein (**Figure 1**). This amino acid chain then folds into a complex 3-dimensional structure. The shape of a protein is what gives the protein its specific function.

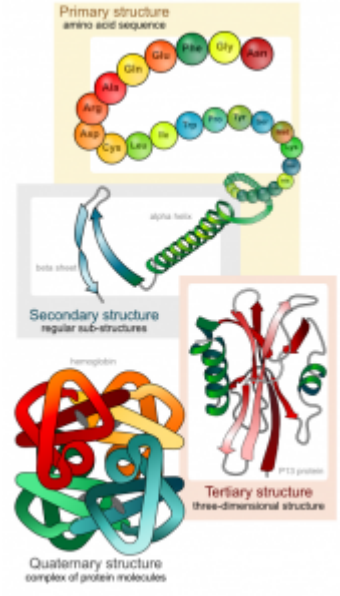


Figure 1 *Protein structure. The colored balls at the top of this diagram represent different amino acids. Amino acids are the subunits that are joined together by the ribosome to form a protein. This chain of amino acids then folds to form a complex 3D structure. (Credit: Lady of Hatsfrom Wikipedia; public domain)*

Helpful Hint: Proteins are not typically used as a source of energy for the body. Protein from your diet is broken down into individual amino acids which are reassembled by your ribosomes into proteins that your cells need. Ribosomes do not produce energy.

When viewed through an electron microscope, free ribosomes appear as either clusters or single tiny dots floating freely in the cytoplasm. Ribosomes may be attached to either the cytoplasmic side of the plasma membrane or the cytoplasmic side of the rough endoplasmic reticulum (Figure 2).

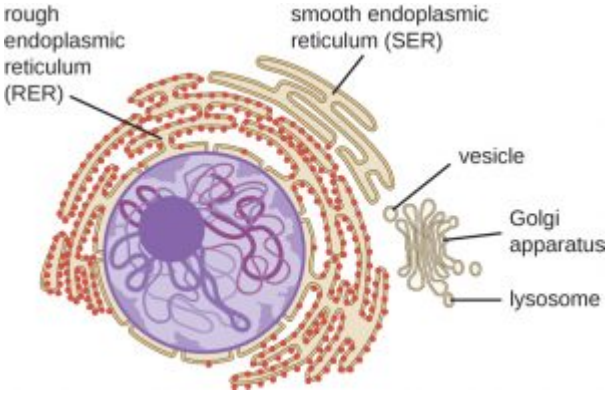


Figure 2*Ribosomes can be found free in the cytoplasm (not shown in this diagram), or attached to the outer membrane of the nucleus and the rough endoplasmic reticulum (RER). Credit CFCF; Wikimedia; CC license.*

Because protein synthesis is essential for all cells, ribosomes are found in practically every cell, although they are smaller in prokaryotic cells. They are particularly abundant in immature red blood cells for the synthesis of hemoglobin, which functions in the

transport of oxygen throughout the body. Electron microscopy has shown us that ribosomes, which are large complexes of protein and RNA, consist of two subunits, aptly called large and small (**Figure 3**). Ribosomes receive their "orders" for protein synthesis from the nucleus where the DNA is transcribed into messenger RNA (mRNA). The mRNA travels to the ribosomes, which translate the code provided by the sequence of the nitrogenous bases in the mRNA into a specific order of amino acids in a protein. Amino acids are the building blocks of proteins.

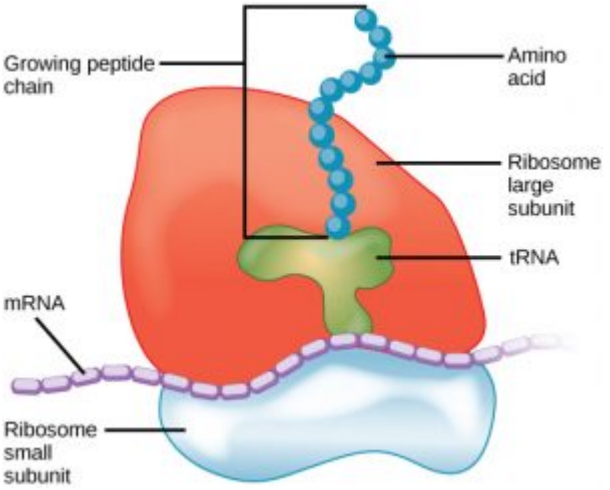


Figure 3 *Ribosomes are made up of a large subunit (top) and a small subunit (bottom). During protein synthesis, ribosomes assemble amino acids into proteins.*

Helpful Hint: Ribosomes are made up of protein and RNA molecules, they are not surrounded by membrane. This means they are not membrane-bound organelles, even when they are located on the rough endoplasmic reticulum.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

19. The Cytoskeleton

If you were to remove all the organelles from a cell, would the plasma membrane and the cytoplasm be the only components left? No. Within the cytoplasm, there would still be ions and organic molecules, plus a network of protein fibers known as the **cytoskeleton**.

Both prokaryotes and eukaryotes have a cytoskeleton. Both types of organisms use their cytoskeleton for cell division, protection, and shape determination.

In addition, in eukaryotes the cytoskeleton also functions to secure certain organelles in specific positions, and to allow cytoplasm and vesicles to move within the cell. It also enables unicellular organisms to move independently. There are three types of fibers within the cytoskeleton: microfilaments, also known as actin filaments, intermediate filaments, and microtubules (**Figure 1**).

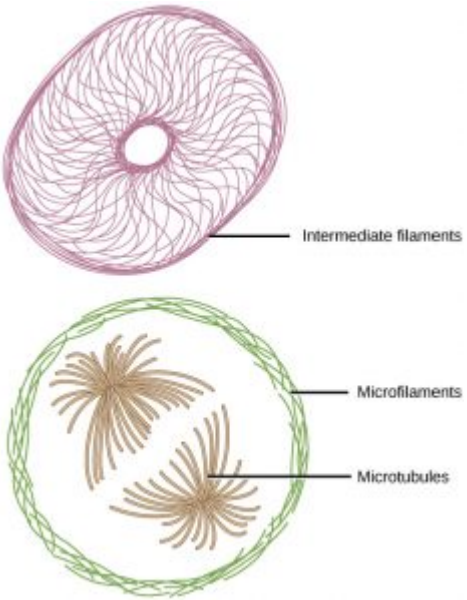


Figure 1*Microfilaments, intermediate filaments, and microtubules compose a cell's cytoskeleton.*

Microfilaments

Of the three types of protein fibers in the cytoskeleton, **microfilaments**are the narrowest. They function in cellular movement, have a diameter of about 7 nm, and are made of two intertwined strands of a globular protein called actin. For this reason, microfilaments are also known as actin filaments.

ATP is required for actin proteins to assemble into long filaments. These long actin filaments serve as a track for the movement of a motor protein called myosin. Actin and myosin are plentiful in muscle cells. When your actin and myosin filaments slide past each other, your muscles contract. Actin also enables your cells to engage in cellular events requiring motion, such as cell division in animal cells and cytoplasmic streaming, which is the circular movement of the cell cytoplasm in plant cells.

Microfilaments also provide some rigidity and shape to the cell. They can depolymerize (disassemble) and reform quickly, thus enabling a cell to change its shape and move. White blood cells (your body's infection-fighting cells) make good use of this ability. They can move to the site of an infection and phagocytize the pathogen.

Intermediate Filaments

Intermediate filaments are made of several strands of fibrous proteins that are wound together. These elements of the cytoskeleton get their name from the fact that their diameter, 8 to 10 nm, is between those of microfilaments and microtubules.

Intermediate filaments have no role in cell movement. Their function is purely structural. They bear tension, thus maintaining the shape of the cell, and anchor the nucleus and other organelles in place. Figure 1 shows how intermediate filaments create a supportive scaffolding inside the cell.

The intermediate filaments are the most diverse group of cytoskeletal elements. Several types of fibrous proteins are found in the intermediate filaments. You are probably most familiar with keratin, the fibrous protein that strengthens your hair, nails, and the epidermis of the skin.

Microtubules

As their name implies, microtubules are small hollow tubes. The walls of the microtubule are made of polymerized dimers of α-tubulin and β-tubulin, two globular proteins. With a diameter of about 25 nm, microtubules are the widest components of the cytoskeleton. They help the cell resist compression, provide a track along which vesicles move through the cell, and pull replicated chromosomes to opposite ends of a dividing cell. Like microfilaments, microtubules can dissolve and reform quickly.

Microtubules are also the structural elements of flagella, cilia, and centrioles (the latter are the two perpendicular bodies of the centrosome). In fact, in animal cells, the centrosome is the microtubule-organizing center. In eukaryotic cells, flagella and cilia are quite different structurally from their counterparts in prokaryotes, as discussed below.

The centrosome replicates itself before a cell divides, and the centrioles play a role in pulling the duplicated chromosomes to opposite ends of the dividing cell. However, the exact function of the centrioles in cell division is not clear, since cells that have the centrioles removed can still divide, and plant cells, which lack centrioles, are capable of cell division.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

20. Flagella and Cilia

Flagella (singular = flagellum) are long, hair-like structures that extend from the plasma membrane and are used to move an entire cell, (for example, sperm, *Euglena*). When present, the cell has just one flagellum or a few flagella. Prokaryotes sometimes have flagella, but they are structurally very different from eukaryotic flagella. Prokaryotes can have more than one flagella. They serve the same function in both prokaryotes and eukaryotes (to move an entire cell).

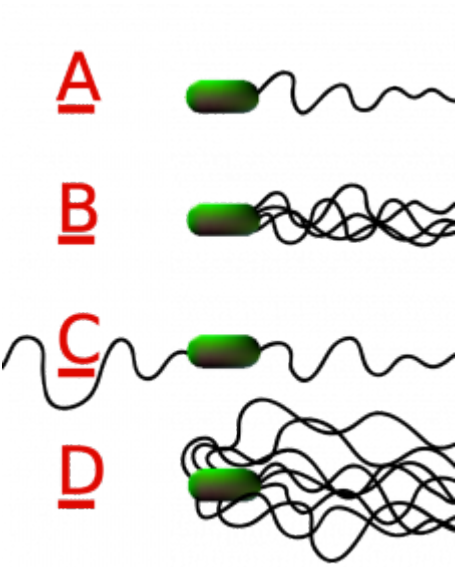


Figure 1*Examples of bacterial flagella arrangement schemes. Credit Adenosine; Wikimedia.*

When **cilia**(singular = cilium) are present, however, they are many in number and extend along the entire surface of the plasma membrane. They are short, hair-like structures that are used to move entire cells (such as paramecium) or move substances along

the outer surface of the cell (for example, the cilia of cells lining the fallopian tubes that move the ovum toward the uterus, or cilia lining the cells of the respiratory tract that move particulate matter toward the throat that mucus has trapped). Cilia are not found on prokaryotes.

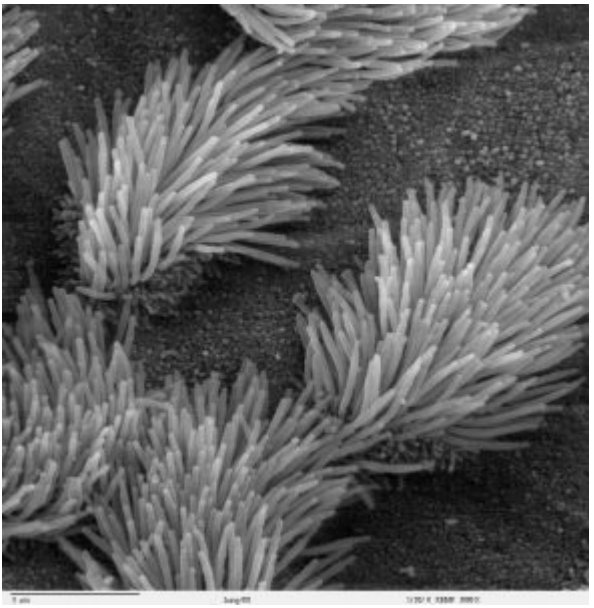


Figure 2*Scanning electron microscope image of lung trachea epithelium. There are both ciliated and non-ciliated cells in this epithelium. Note the difference in size between the cilia and the microvilli (on the non-ciliated cell surface). Photo credit Charles Daghlian; Wikimedia; public domain.*

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

21. The Endomembrane System

The **endomembrane system** (*endo* = within) is a group of membranes and organelles (see **Figure 1**) in eukaryotic cells that work together to modify, package, and transport lipids and proteins. It includes the nuclear envelope, lysosomes, and vesicles, the rough and smooth endoplasmic reticulum and Golgi apparatus, which we will cover shortly. Although not technically *within* the cell, the plasma membrane is included in the endomembrane system because, as you will see, it interacts with the other endomembranous organelles. None of the organelles that make up the endomembrane system are found in prokaryotes with the exception of the plasma membrane. Although ribosomes are found on the rough endoplasmic reticulum, they are not technically a member of the endomembrane system because they are not made of membrane. Also, remember that ribosomes can be found free in the cytoplasm, so are not always located on the rough ER.

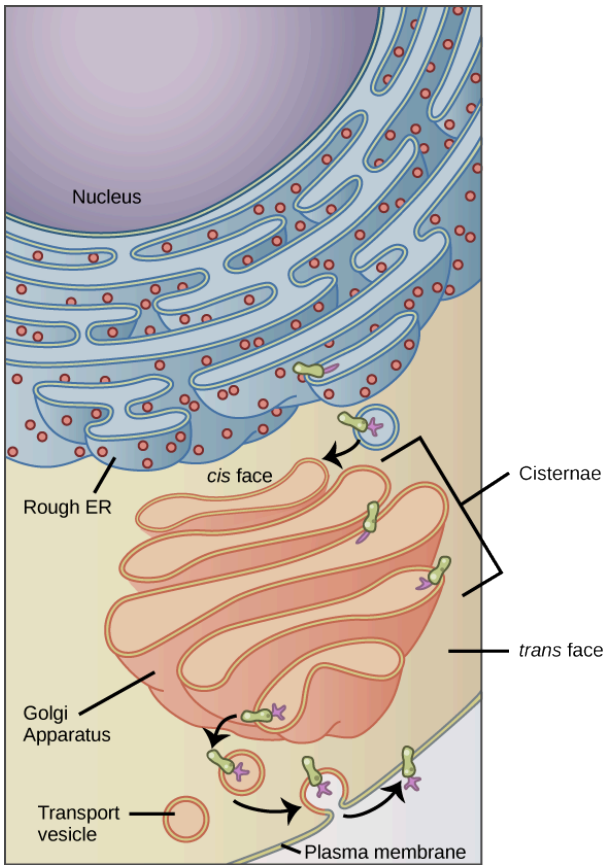
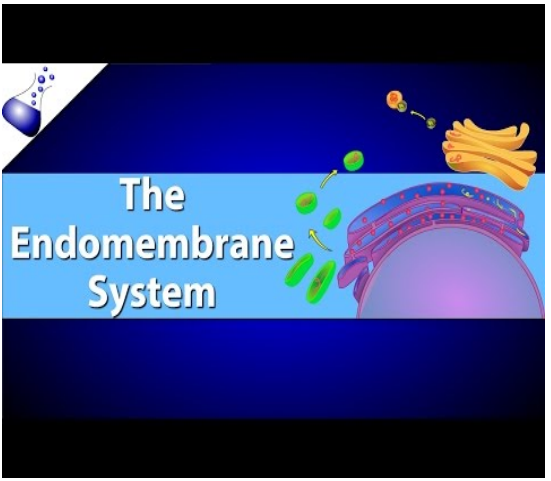


Figure 1 *Membrane and secretory proteins are synthesized in the rough endoplasmic reticulum (RER). The RER also sometimes modifies proteins. In this illustration, a (green) integral membrane protein in the ER is modified by attachment of a (purple) carbohydrate. Vesicles with the integral protein bud from the ER and fuse with the cis face of the Golgi apparatus. As the protein passes along the Golgi's cisternae, it is further modified by the addition of more carbohydrates. After its synthesis is complete, it exits as integral membrane*



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protein of the vesicle that bud from the Golgi's trans face and when the vesicle fuses with the cell membrane the protein becomes integral portion of that cell membrane. The smooth ER is also a part of the endomembrane system, but is not involved in protein synthesis and is not shown in this figure. (credit: modification of work by Magnus Manske)

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

22. Nucleus

Typically, the nucleus is the most prominent organelle in a cell. The **nucleus** (plural = nuclei) houses the cell's DNA in the form of chromatin and directs the synthesis of ribosomes and proteins. Let us look at it in more detail (**Figure1**).

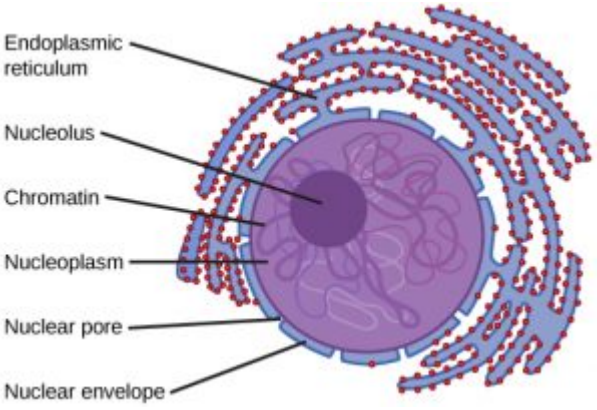

Figure 1*The outermost boundary of the nucleus is the nuclear envelope. Notice that the nuclear envelope consists of two phospholipid bilayers (membranes) —an outer membrane and an inner membrane—i n contrast to the plasma membrane, which consists of only one phospholipid bilayer. (credit: modification of work by* NIGMS, NIH)

The **nuclear envelope** is a double-membrane structure that constitutes the outermost portion of the nucleus (**Figure 2**). Both

the inner and outer membranes of the nuclear envelope are phospholipid bilayers.

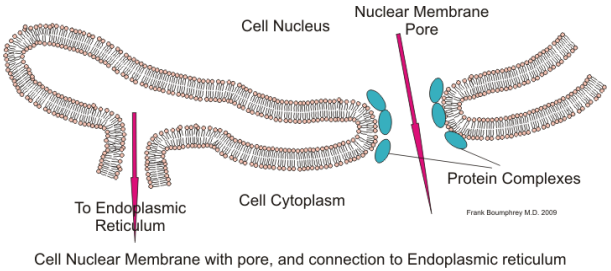

Figure 2*This illustration shows the double membrane structure surrounding the nucleus. Notice that both membranes are composed of a phospholipid bilayer. Credit Boumphreyfr ; Wikimedia*

Chromatin

The nuclear envelope is punctuated with pores that control the passage of ions, molecules, and RNA between the nucleoplasm and the cytoplasm (**Figure 2**). The nucleoplasm is the semi-solid fluid inside the nucleus, where we find the chromatin and the nucleolus.

You may remember that in prokaryotes, DNA is organized into a single circular chromosome. In eukaryotes, chromosomes are linear structures. In eukaryotes, chromosomes are structures within the nucleus that are made up of DNA, the hereditary material, and proteins. This combination of DNA and proteins is called chromatin. Every species has a specific number of chromosomes in the nucleus of its body cells. For example, in humans, the chromosome number is 46, whereas in fruit flies, the chromosome number is eight.

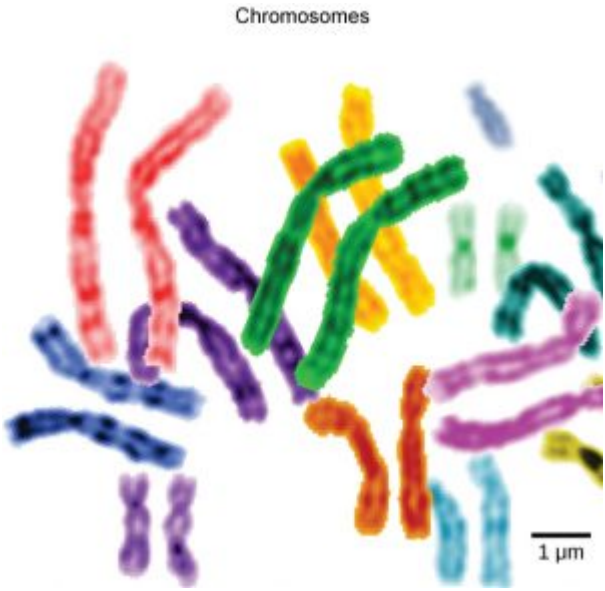

Figure 3*This image shows paired chromosomes. Each pair of chromosomes is shown in a different color. In reality, chromosomes are not colorful and typically look grayish. (Credit: modification of work by NIH; scale-bar data from Matt Russell)*

Chromosomes are only visible and distinguishable from one another when the cell is getting ready to divide. When the cell is in the growth and maintenance phases of its life cycle, the chromosomes resemble an unwound, jumbled bunch of threads. These unwound protein-chromosome complexes are called chromatin (Figure 4); chromatin describes the material that makes up the chromosomes both when condensed and decondensed.

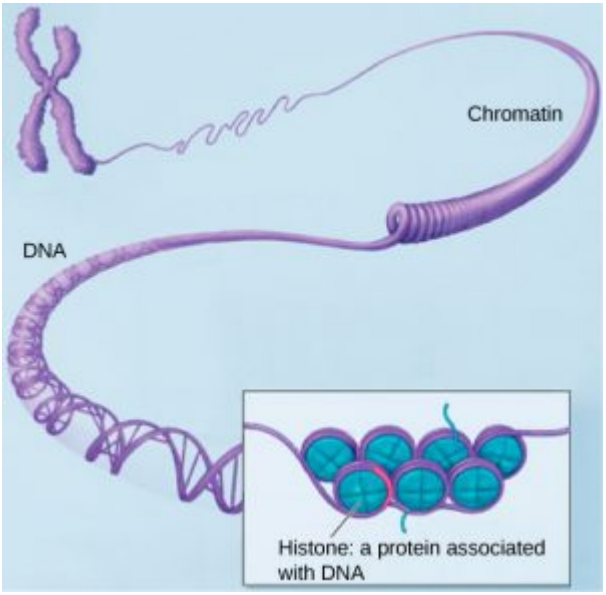

Figure 4*This image shows various levels of the organization of chromatin (DNA and protein).*

Nucleolus

We already know that the nucleus directs the synthesis of ribosomes, but how does it do this? Some chromosomes have sections of DNA that encode ribosomal RNA. A darkly staining area within the nucleus, called the **nucleolus** (plural = nucleoli) (See Figure 1), aggregates the ribosomal RNA with associated proteins to assemble the ribosomal subunits that are then transported through the nuclear pores into the cytoplasm.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

23. The Endoplasmic Reticulum

The **endoplasmic reticulum (ER)** is a series of interconnected membranous tubules that collectively modify proteins and synthesize lipids. However, these two functions are performed in separate areas of the endoplasmic reticulum: the **rough endoplasmic reticulum**and the **smooth endoplasmic reticulum**, respectively.

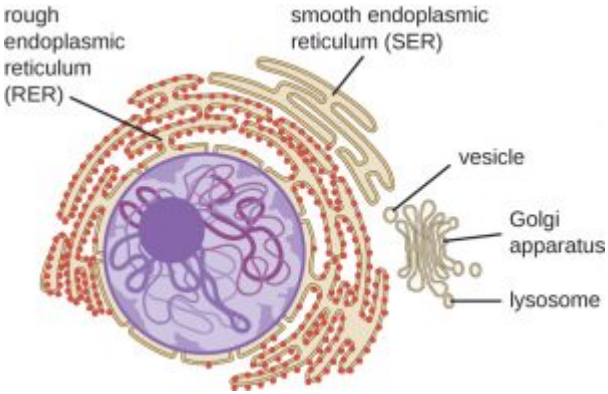

Figure 1*The rough and smooth endoplasmic reticulum are part of the endomembrane system.*

The hollow portion of the ER tubules is called the lumen or cisternal space. The membrane of the ER, which is a phospholipid bilayer embedded with proteins, is continuous with the nuclear envelope (**Figure 1**).

The **rough endoplasmic reticulum (RER)** is so named because the ribosomes attached to its cytoplasmic surface give it a studded appearance when viewed through an electron microscope (**Figure 2**). The ribosomes synthesize proteins while attached to the ER, resulting in transfer of their newly synthesized proteins into the lumen of the RER where they undergo modifications such as folding

or addition of sugars. The RER also makes phospholipids for cell membranes.

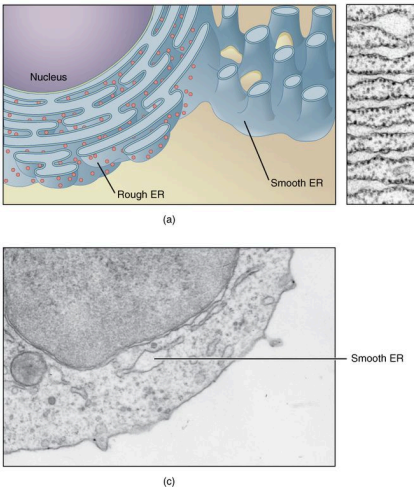

Figure 2
(a)*The ER is a winding network of thin membranous sacs found in close association with the cell nucleus. The smooth and rough endoplasmic reticula are very different in appearance and function (source: mouse tissue).* ***(b)****Rough ER is studded with numerous ribosomes, which are sites of protein synthesis (source: mouse tissue). EM × 110,000.* ***(c)****Smooth ER synthesizes phospholipids, steroid hormones, regulates the concentration of cellular Ca++, metabolizes some carbohydrates, and breaks down certain toxins (source:*

mouse tissue). EM × 110,510. (Micrographs provided by the Regents of University of Michigan Medical School © 2012). Figure from The Cytoplasm and Cellular Organelles; OpenStax.

If the phospholipids or modified proteins are not destined to stay in the RER, they will be packaged within vesicles and transported from the RER by budding from the membrane (**Figure 3**). Since the RER is engaged in modifying proteins that will be secreted from the cell, it is abundant in cells that secrete proteins, such as the liver.

The **smooth endoplasmic reticulum (SER)** is continuous with the RER but has few or no ribosomes on its cytoplasmic surface (see **Figures 1-3**). The SER's functions include synthesis of carbohydrates, lipids, and steroid hormones; detoxification of medications and poisons; alcohol metabolism; and storage of calcium ions.

In muscle cells, a specialized SER called the sarcoplasmic reticulum is responsible for storage of the calcium ions that are needed to trigger the coordinated contractions of the muscle cells.

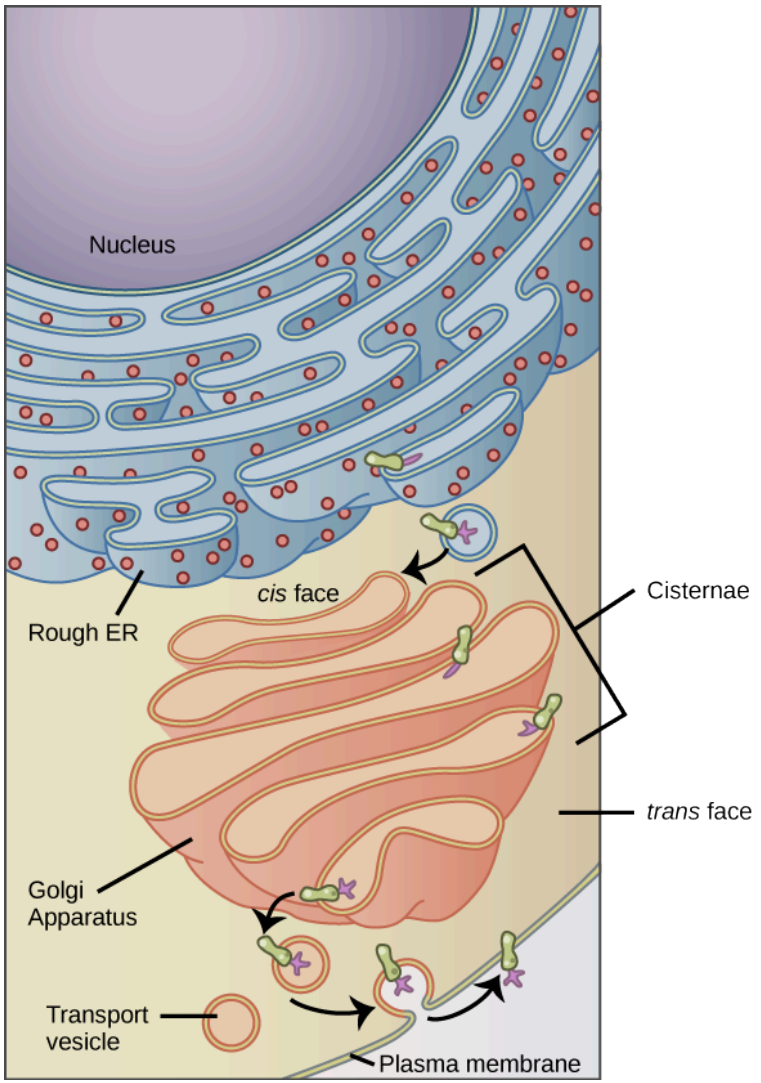

Figure 3 The endomembrane system works to modify, package, and transport lipids and proteins. (credit: modification of work by Magnus Manske)

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

24. The Golgi Apparatus

We have already mentioned that vesicles can bud from the ER, but where do the vesicles go? Before reaching their final destination, the lipids or proteins within the transport vesicles need to be sorted, packaged, and tagged so that they wind up in the right place. The sorting, tagging, packaging, and distribution of lipids and proteins take place in the **Golgi apparatus**(also called the Golgi body), a series of flattened membranous sacs (**Figure 1**).

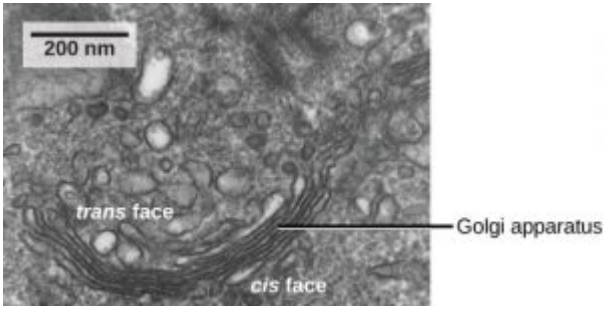

Figure 1*The Golgi apparatus in this transmission electron micrograph of a white blood cell is visible as a stack of semicircular flattened rings in the lower portion of this image. Several vesicles can be seen near the Golgi apparatus.(credit: modification of work by Louisa Howard; scale-bar data from Matt Russell)*

The Golgi apparatus has a receiving face near the endoplasmic reticulum (the *cis* face) and a releasing face on the side away from the ER, toward the cell membrane (the *trans* face) (**Figure 2**). The transport vesicles that form from the ER travel to the receiving face, fuse with it, and empty their contents into the lumen (empty space inside) of the Golgi apparatus. As the proteins and lipids travel through the Golgi, they undergo further modifications. The most frequent modification is the addition of short chains of sugar molecules. The newly modified proteins and lipids are then tagged with small molecular groups to enable them to be routed to their proper destinations.

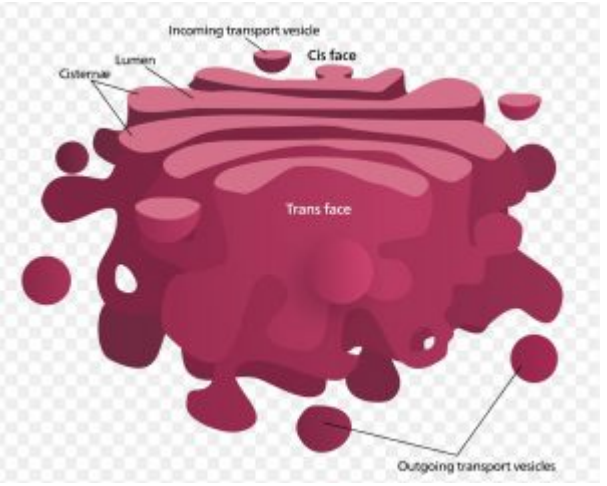

***Figure 2** Diagram of the Golgi apparatus showing the cisand transfaces. The cisface would be near the nucleus while the transface would be facing the cell membrane. Credit [Kelvinsong; Wikimedia]*

Finally, the modified and tagged proteins are packaged into vesicles that bud from the opposite face of the Golgi. While some of these vesicles, transport vesicles, deposit their contents into other parts of the cell where they will be used, others, secretory vesicles, fuse with the plasma membrane and release their contents outside the cell.

The amount of Golgi in different cell types again illustrates that

form follows function within cells. Cells that engage in a great deal of secretory activity (such as cells of the salivary glands that secrete digestive enzymes or cells of the immune system that secrete antibodies) have an abundant number of Golgi.

In plant cells, the Golgi has an additional role of synthesizing polysaccharides, some of which are incorporated into the cell wall and some of which are used in other parts of the cell.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

25. Vesicles and Vacuoles, Lysosomes, and Peroxisomes

Vesicles and Vacuoles

Vesicles and **vacuoles** are membrane-bound sacs that function in storage and transport. Vacuoles are somewhat larger than vesicles, and the membrane of a vacuole does not fuse with the membranes of other cellular components. Vesicles can fuse with other membranes within the cell system (**Figure 1**). Additionally, enzymes within plant vacuoles can break down macromolecules.

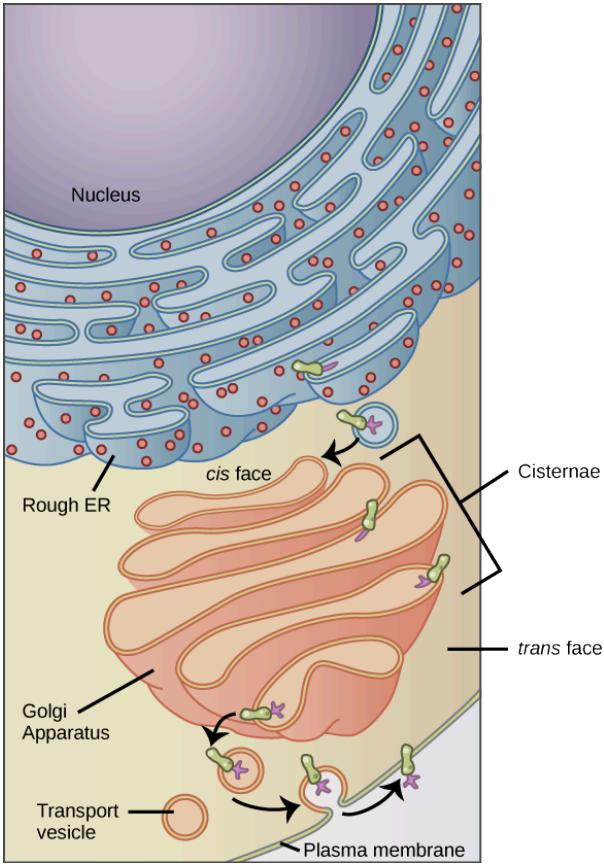

Figure 1*The endomembrane system works to modify, package, and transport lipids and proteins. (credit: modification of work by Magnus Manske)*

The Central Vacuole (plants)

Previously, we mentioned vacuoles as essential components of plant cells. If you look at **Figure 2**, you will see that plant cells each have a large, central vacuole that occupies most of the cell.

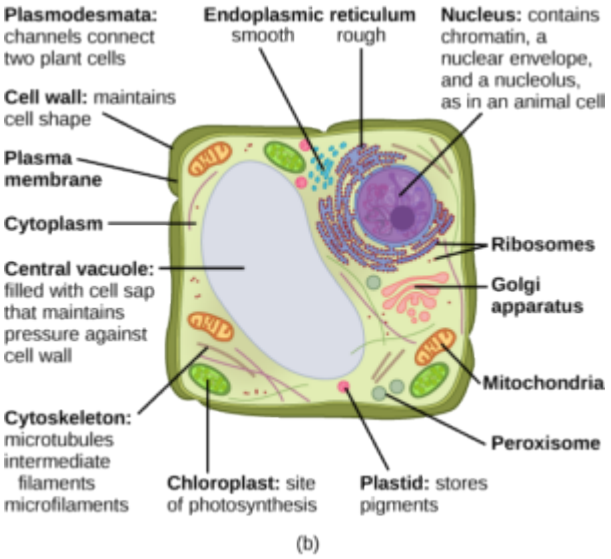

Figure 2*Diagram of a plant cell.*

The **central vacuole** plays a key role in regulating the cell's concentration of water in changing environmental conditions. In plant cells, the liquid inside the central vacuole provides turgor pressure, which is the outward pressure caused by the fluid inside the cell. Have you ever noticed that if you forget to water a plant for a few days, it wilts? That is because as the water concentration in the soil becomes lower than the water concentration in the plant, water moves out of the central vacuoles and cytoplasm and into the soil. As the central vacuole shrinks, it leaves the cell wall unsupported. This loss of support to the cell walls of a plant results in the wilted appearance. Additionally, this fluid has a very bitter taste, which discourages consumption by insects and animals. The central vacuole also functions to store proteins in developing seed cells.

Lysosome

In animal cells, the **lysosomes** are the cell's "garbage disposal." Digestive enzymes within the lysosomes aid the breakdown of proteins, polysaccharides, lipids, nucleic acids, and even worn-out organelles. In single-celled eukaryotes, lysosomes are important for digestion of the food they ingest and the recycling of organelles. These enzymes are active at a much lower pH (more acidic) than those located in the cytoplasm. Many reactions that take place in the cytoplasm could not occur at a low pH, thus the advantage of compartmentalizing the eukaryotic cell into organelles is apparent.

Lysosomes also use their hydrolytic enzymes to destroy disease-causing organisms that might enter the cell. A good example of this occurs in a group of white blood cells called macrophages, which are part of your body's immune system. In a process known as phagocytosis, a section of the plasma membrane of the macrophage invaginates (folds in) and engulfs a pathogen. The invaginated section, with the pathogen inside, then pinches itself off from the plasma membrane and becomes a vesicle. The vesicle fuses with a lysosome. The lysosome's hydrolytic enzymes then destroy the pathogen (**Figure 3**).

Lysosomes are basically small bags of membrane containing enzymes, so they look structurally similar to a small vacuole.

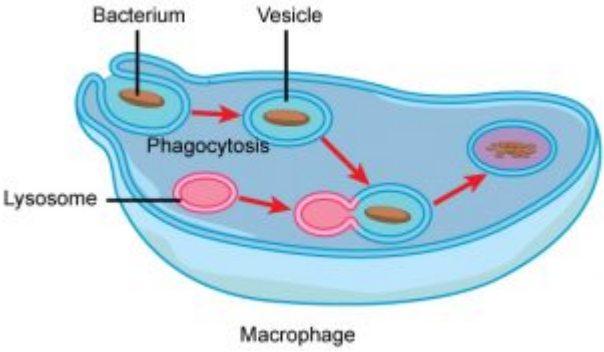

Figure 3*A macrophage has phagocytized a potentially pathogenic bacterium into a vesicle, which then fuses with a lysosome within the cell so that the pathogen can be destroyed. Other organelles are present in the cell, but for simplicity, are not shown.*

Peroxisomes

Peroxisomes are small, round organelles enclosed by single membranes (so again, they look similar to small vacuoles). They carry out oxidation reactions that break down fatty acids and amino acids. They also detoxify many poisons that may enter the body. Alcohol is detoxified by peroxisomes in liver cells. A byproduct of these oxidation reactions is hydrogen peroxide, H_2O_2, which is contained within the peroxisomes to prevent the chemical from causing damage to cellular components outside of the organelle. Hydrogen peroxide is safely broken down by peroxisomal enzymes into water and oxygen.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

26. Mitochondria and Chloroplasts

Mitochondria

Mitochondria (singular = mitochondrion) are often called the "powerhouses" or "energy factories" of a cell because they are responsible for making adenosine triphosphate (ATP), the cell's main energy-carrying molecule. The formation of ATP from the breakdown of glucose is known as cellular respiration. Mitochondria are oval-shaped, double-membrane organelles (**Figure 1**) that have their own ribosomes and DNA. Each membrane is a phospholipid bilayer embedded with proteins. The inner layer has folds called cristae, which increase the surface area of the inner membrane. The area surrounded by the folds is called the mitochondrial matrix. The cristae and the matrix have different roles in cellular respiration.

In keeping with our theme of form following function, it is important to point out that muscle cells have a very high concentration of mitochondria because muscle cells need a lot of energy to contract.

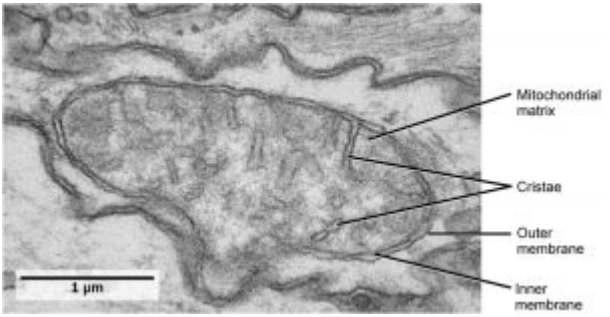

Figure 1*This transmission electron micrograph shows a mitochondrion as viewed with an electron microscope. Notice the inner and outer membranes, the cristae, and the mitochondrial matrix. (credit: modification of work by Matthew Britton; scale-bar data from Matt Russell)*

Like mitochondria, chloroplasts also have their own DNA and ribosomes. **Chloroplasts** function in photosynthesis and can be found in eukaryotic cells such as plants and algae. Carbon dioxide (CO_2), water, and light energy are used to make glucose and oxygen in photosynthesis. This is the major difference between plants and animals: Plants (autotrophs) are able to make their own food, like glucose, whereas animals (heterotrophs) must rely on other organisms for their organic compounds or food source.

Like mitochondria, chloroplasts have outer and inner membranes, but within the space enclosed by a chloroplast's inner membrane is a set of interconnected and stacked, fluid-filled membrane sacs called thylakoids (**Figure 2**). Each stack of thylakoids is called a granum (plural = grana). The fluid enclosed by the inner membrane and surrounding the grana is called the stroma.

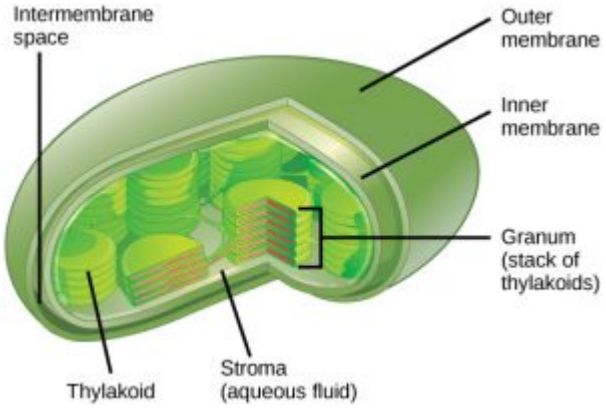

Figure 2*This simplified diagram of a chloroplast shows the outer membrane, inner membrane, thylakoids, grana, and stroma.*

The chloroplasts contain a green pigment called **chlorophyll**, which captures the energy of sunlight for photosynthesis. Like plant cells, photosynthetic protists also have chloroplasts. Some bacteria also perform photosynthesis, but they do not have chloroplasts. Their photosynthetic pigments are located in the thylakoid membrane within the cell itself.

Theory of Endosymbiosis

We have mentioned that both mitochondria and chloroplasts contain DNA and ribosomes. Have you wondered why? Strong evidence points to endosymbiosis as the explanation.

Symbiosis is a relationship in which organisms from two separate species live in close association and

typically exhibit specific adaptations to each other. Endosymbiosis (endo-= within) is a relationship in which one organism lives inside the other. Endosymbiotic relationships abound in nature. Microbes that produce vitamin K live inside the human gut. This relationship is beneficial for us because we are unable to synthesize vitamin K. It is also beneficial for the microbes because they are protected from other organisms and are provided a stable habitat and abundant food by living within the large intestine.

Scientists have long noticed that bacteria, mitochondria, and chloroplasts are similar in size. We also know that mitochondria and chloroplasts have DNA and ribosomes, just as bacteria do. Scientists believe that host cells and bacteria formed a mutually beneficial endosymbiotic relationship when the host cells ingested aerobic bacteria and cyanobacteria but did not destroy them. Through evolution, these ingested bacteria became more specialized in their functions, with the aerobic bacteria becoming mitochondria and the photosynthetic bacteria becoming chloroplasts.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

27. Extracellular matrix and intercellular junctions

Extracellular Matrix of Animal Cells

Most animal cells release materials into the extracellular space. The primary components of these materials are glycoproteins and the protein collagen. Collectively, these materials are called the **extracellular matrix** (**Figure 1**). Not only does the extracellular matrix hold the cells together to form a tissue, but it also allows the cells within the tissue to communicate with each other.

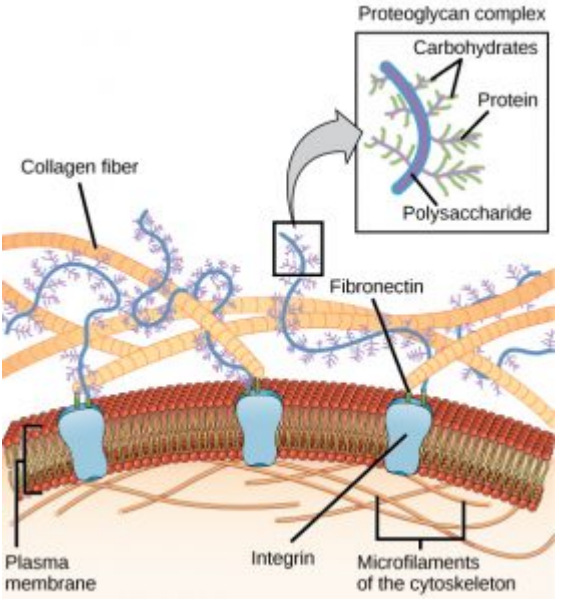

Figure 1*The extracellular matrix consists of a network of substances secreted by cells.*

Blood clotting provides an example of the role of the extracellular matrix in cell communication.

When the cells lining a blood vessel are damaged, they display a protein receptor called tissue factor. When tissue factor binds with another factor in the extracellular matrix, it causes platelets to adhere to the wall of the damaged blood vessel, stimulates adjacent smooth muscle cells in the blood vessel to contract (thus constricting the blood vessel), and initiates a series of steps that stimulate the platelets to produce clotting factors.

Intercellular Junctions

Cells can also communicate with each other by direct contact, referred to as intercellular junctions. There are some differences in the ways that plant and animal cells do this. **Plasmodesmata** (singular = plasmodesma) are junctions between plant cells, whereas animal cell contacts include tight and gap junctions, and desmosomes.

In general, long stretches of the plasma membranes of neighboring plant cells cannot touch one another because they are separated by the cell walls surrounding each cell. Plasmodesmata are numerous channels that pass between the cell walls of adjacent plant cells, connecting their cytoplasm and enabling signal molecules and nutrients to be transported from cell to cell (**Figure 2a**).

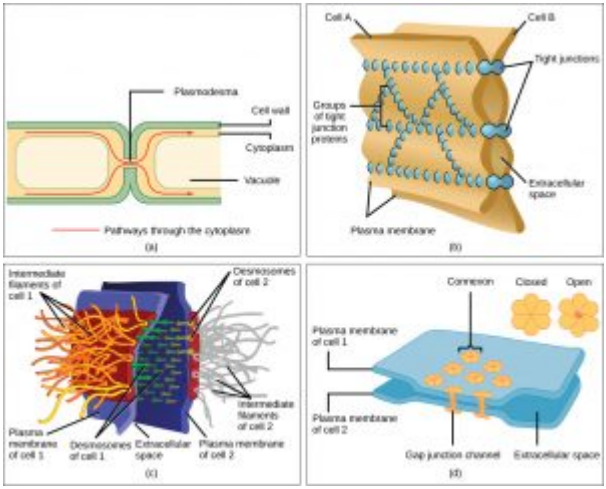

Figure 2*There are four kinds of connections between cells. (a) A plasmodesma is a channel between the cell walls of two adjacent plant cells. (b) Tight junctions join adjacent animal cells. (c) Desmosomes join two animal cells together. (d) Gap junctions act as channels between animal cells. (credit b, c, d: modification of work by Mariana Ruiz Villareal)*

A **tight junction** is a watertight seal between two adjacent animal cells (**Figure 2b**). Proteins hold the cells tightly against each other. This tight adhesion prevents materials from leaking between the cells. Tight junctions are typically found in the epithelial tissue that lines internal organs and cavities, and composes most of the skin. For example, the tight junctions of the epithelial cells lining the urinary bladder prevent urine from leaking into the extracellular space.

Also found only in animal cells are **desmosomes**, which act like

spot welds between adjacent epithelial cells (**Figure 2c**). They keep cells together in a sheet-like formation in organs and tissues that stretch, like the skin, heart, and muscles.

Gap junctions in animal cells are like plasmodesmata in plant cells in that they are channels between adjacent cells that allow for the transport of ions, nutrients, and other substances that enable cells to communicate (**Figure 2d**). Structurally, however, gap junctions and plasmodesmata differ.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

28. Summary Table of Prokaryotic and Eukaryotic Cells and Functions

Components of Prokaryotic and Eukaryotic Cells and Functions

Cell Component	Function	Present in Prokaryotes	Present in Animal Cells	Present in Plant Cells
Plasma Membrane	Separates cell from external environment; controls passage of organic molecules, ions, water, oxygen, and wastes into and out of the cell	Yes	Yes	Yes
Cytoplasm	Provides structure to cell; site of many metabolic reactions; medium in which organelles are found	Yes	Yes	Yes
Nucleoid	Location of DNA	Yes	No	No
Nucleus	Cell organelle that houses DNA and directs synthesis of ribosomes and proteins	No	Yes	Yes
Ribosomes	Protein synthesis	Yes	Yes	Yes
Mitochondria	ATP production/ cellular respiration	No	Yes	Yes
Peroxisomes	Oxidizes and breaks down fatty acids and amino acids, and detoxifies poisons	No	Yes	Yes
Vesicles and vacuoles	Storage and transport; digestive function in plant cells	No	Yes	Yes

Cell Component	Function	Present in Prokaryotes	Present in Animal Cells	Present in Plant Cells
Centrosome	Unspecified role in cell division in animal cells; organizing center of microtubules in animal cells	No	Yes	No
Lysosomes	Digestion of macromolecules; recycling of worn-out organelles	No	Yes	No
Cell wall	Protection, structural support and maintenance of cell shape	Yes, primarily peptidoglycan in bacteria but not Archaea	No	Yes, primarily cellulose
Chloroplasts	Photosynthesis	No	No	Yes
Endoplasmic reticulum	Modifies proteins and synthesizes lipids	No	Yes	Yes
Golgi apparatus	Modifies, sorts, tags, packages, and distributes lipids and proteins	No	Yes	Yes
Cytoskeleton	Maintains cell's shape, secures organelles in specific positions, allows cytoplasm and vesicles to move within the cell, and enables unicellular organisms to move independently	Yes	Yes	Yes

Cell Component	Function	Present in Prokaryotes	Present in Animal Cells	Present in Plant Cells
Flagella	Cellular locomotion	Some	Some	No, except for some plant sperm.
Cilia	Cellular locomotion, movement of particles along extracellular surface of plasma membrane, and filtration	No	Some	No

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

29. The Production of a Protein

Proteins are one of the most abundant organic molecules in living systems and have an incredibly diverse range of functions. Proteins are used to:

- Build structures within the cell (such as the cytoskeleton)
- Regulate the production of other proteins by controlling protein synthesis
- Slide along the cytoskeleton to cause muscle contraction
- Transport molecules across the cell membrane
- Speed up chemical reactions (enzymes)
- Act as toxins

Each cell in a living system may contain thousands of different proteins, each with a unique function. Their structures, like their functions, vary greatly. They are all, however, polymers of amino acids, arranged in a linear sequence (**Figure 1**).

The functions of proteins are very diverse because they are made up of are 20 different chemically distinct amino acids that form long chains, and the amino acids can be in any order. The function of the protein is dependent on the protein's shape. The shape of a protein is determined by the order of the amino acids. Proteins are often hundreds of amino acids long and they can have very complex shapes because there are so many different possible orders for the 20 amino acids!

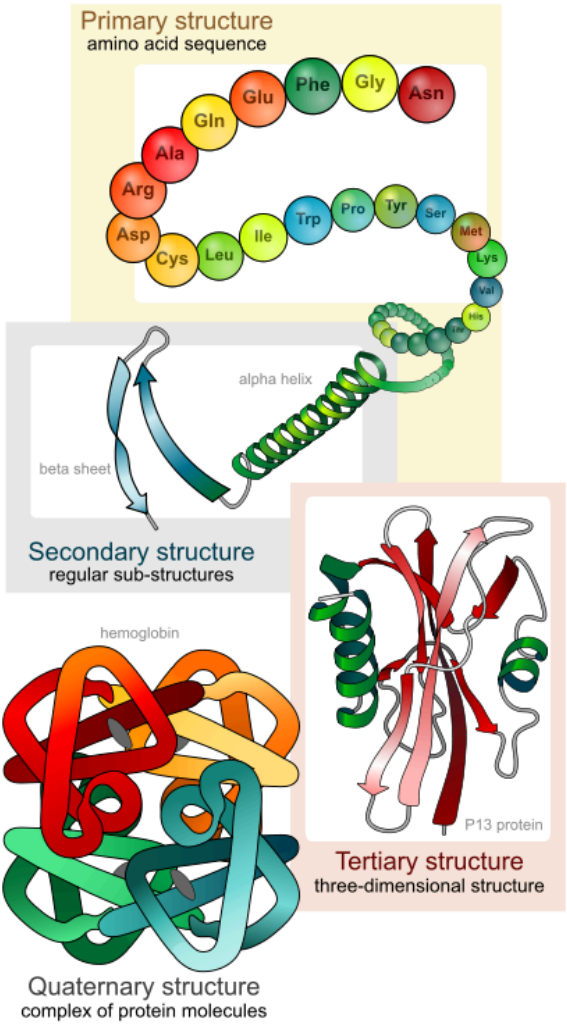

Figure 1 *Protein structure. The colored balls at the top of this diagram represent different amino acids. Amino acids are the subunits that are joined together by the ribosome to form a protein. This chain of amino acids then folds to form a complex 3D structure. (Credit: Lady of Hats from Wikipedia; public domain)*

Contrary to what you may believe, proteins are not typically used as a source of energy by cells. Protein from your diet is broken down into individual amino acids which are reassembled by your

ribosomes into proteins that your cells need. Ribosomes do not produce energy.

Figure 2 *Examples of foods that contain high levels of protein. ("Protein" by National Cancer Institute is in the Public Domain)*

The information to produce a protein is encoded in the cell's DNA. When a protein is produced, a copy of the DNA is made (called mRNA) and this copy is transported to a ribosome. Ribosomes read the information in the mRNA and use that information to assemble amino acids into a protein. If the protein is going to be used within the cytoplasm of the cell, the ribosome creating the protein will be free-floating in the cytoplasm. If the protein is going to be targeted to the lysosome, become a component of the plasma membrane, or be secreted outside of the cell, the protein will be synthesized by a ribosome located on the rough endoplasmic reticulum (RER). After being synthesized, the protein will be carried in a vesicle from the RER to the *cis*face of the Golgi (the side facing the inside of the cell). As the protein moves through the Golgi, it can be modified. Once the final modified protein has been completed, it exits the Golgi in a vesicle that buds from the *trans*face. From there, the vesicle can be targeted to a lysosome or targeted to the plasma membrane. If the vesicle fuses with the plasma membrane, the protein will become part of the membrane or be ejected from the cell.

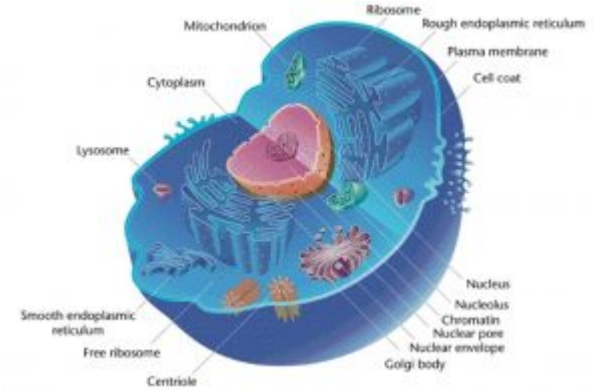

Figure 3*Diagram of a eukaryotic cell. (Photo credit: Medir an, Wikimedia. 14 Aug 2002)*

Insulin

Insulin is a protein hormone that is made by specific cells inside the pancreas called beta cells. When the beta cells sense that glucose (sugar) levels in the bloodstream are high, they produce insulin protein and secrete it outside of the cells into the bloodstream. Insulin signals cells to absorb sugar from the bloodstream. Cells can't absorb sugar without insulin. Insulin protein is first produced as an immature, inactive chain of amino acids (preproinsulin – See Figure 4). It contains a signal sequence that targets the immature protein to the rough endoplasmic reticulum, where it folds into the correct shape. The targeting sequence is then cut off of the amino acid chain to form proinsulin. This trimmed, folded protein is then shipped to the Golgi inside a vesicle. In the Golgi, more amino acids (chain C) are trimmed off of the protein to produce the final mature insulin. Mature insulin is stored inside special

vesicles until a signal is received for it to be released into the bloodstream.

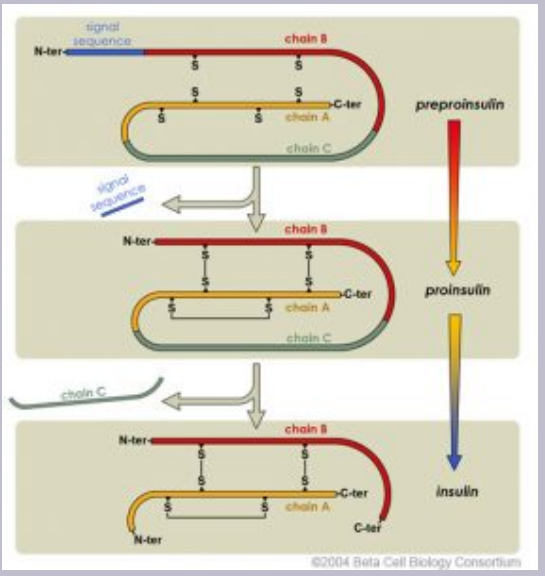

Figure 4*Insulin maturation. (Photo credit: Beta Cell Biology Consortium, Wikimedia. 2004. This picture is in the public domain.*

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

PART VI

CELL DIVISION: MITOSIS

Learning Objectives

Compare the process and consequences of mitosis, and meiosis and how they are important in the lifecycle of an animal (such as a human).

Since all living things are made up of one or more cells, all living things have to undergo some type of cell division. Cell division serves several basic purposes: reproduction, repair, and growth. Typically during cell division, the DNA of the organism is copied, then divided into the new cells using one or more divisions. We will therefore start our discussion of cell division with a brief overview of the process of DNA replication (copying DNA), followed by the process by which various types of cells divide that DNA into new cells.

30. DNA Replication

Cells divide for a number of different reasons:

- Growth – as a baby grows into an adult, new cells must be created so the organism can increase in size.
- Repair – if you cut yourself, new cells must be creased to heal the wound.
- Replacement – you are constantly shedding skin cells, so new cells must be created to replace the ones that are lost.
- Reproduction – egg cells and sperm cells need to be produced in order for sexual reproduction to take place.

When a cell divides, it is important that each daughter cell receives a copy of the DNA. This is accomplished by the process of **DNA replication**. The replication of DNA occurs before the cell begins to divide into two separate cells.

The discovery and characterization of the structure of the double helix provided a hint as to how DNA is copied. Recall that adenine nucleotides pair with thymine nucleotides, and cytosine with guanine. This means that the two strands are complementary to each other. For example, a strand of DNA with a nucleotide sequence of AGTCATGA will have a complementary strand with the sequence TCAGTACT (**Figure 1**).

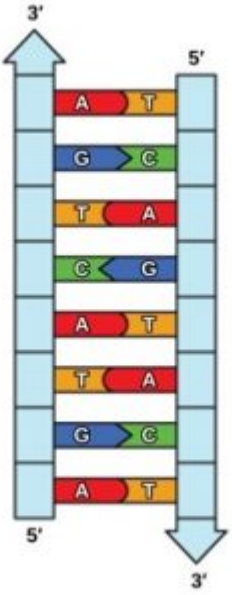

Figure 1: The two strands of DNA are complementary, meaning the sequence of bases in one strand can be used to create the correct sequence of bases in the other strand.

Because of the complementarity of the two strands, having one strand means that it is possible to recreate the other strand. This model for replication suggests that the two strands of the double helix separate during replication, and each strand serves as a template from which the new complementary strand is copied (**Figure 2**).

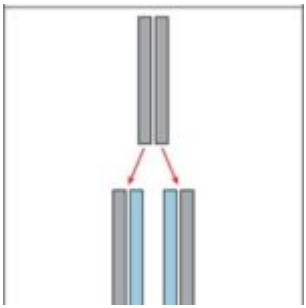

Figure 2: The semiconservative model of DNA replication is shown. Gray indicates the original DNA strands, and blue indicates newly synthesized DNA.

During DNA replication, each of the two strands that make up the double helix serves as a template from which new strands are copied. The new strand will be complementary to the parental or "old" strand. Each new double strand consists of one parental strand and one new daughter strand. This is known as semiconservative replication. When two DNA copies are formed, they have an identical sequence of nucleotide bases.

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OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016

http://cnx.org/contents/s8Hh0oOc@9.10:2ousESf0@5/DNA-Replication

31. DNA Repair

DNA replication is a highly accurate process, but mistakes can occasionally occur. If these mistakes are not corrected, this can lead to a **mutation:** a change in the sequence of DNA. Uncorrected mutations may sometimes lead to serious consequences, such as cancer. One way that a mutation can occur is through DNA polymerase inserting a wrong base. Repair mechanisms typically correct these mistakes, but they occasionally fail to correct the error.

Most of the mistakes during DNA replication are promptly corrected by DNA polymerase (the enzyme that builds new DNA during replication) by proofreading the base that has been just added (Figure 1). In proofreading, the DNA polymerase reads the newly added base before adding the next one, so a correction can be made. The polymerase checks whether the newly added base has paired correctly with the base in the template strand. If it is the right base, the next nucleotide is added. If an incorrect base has been added, the enzyme makes a cut at the covalent bond and releases the wrong nucleotide. Once the incorrect nucleotide has been removed, a new one will be added again (**Figure 1**).

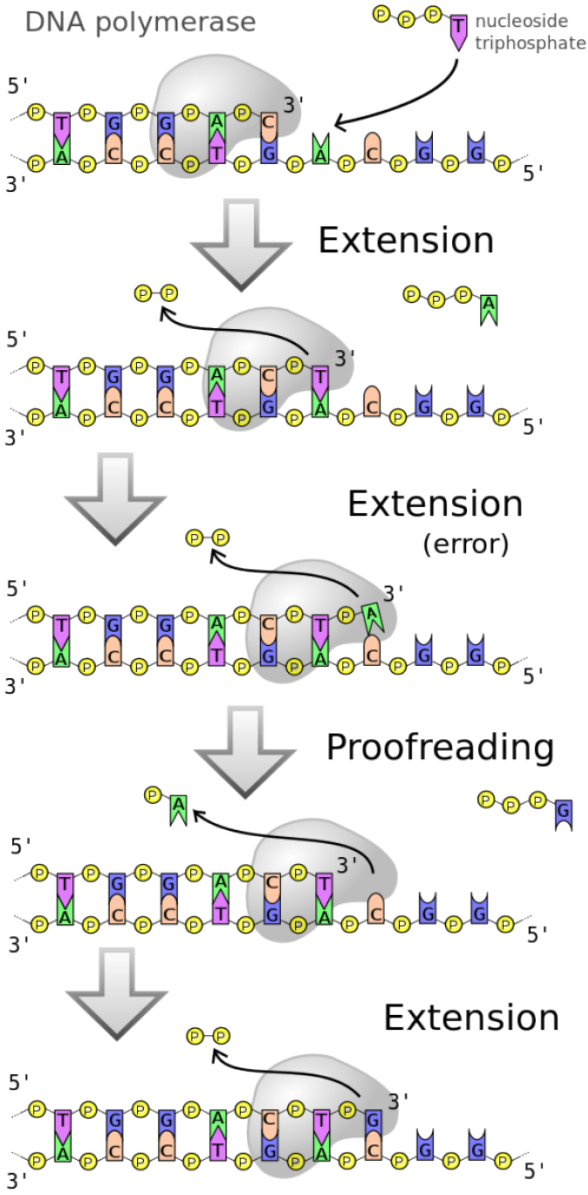


Figure 1 Proofreading by DNA polymerase corrects errors during replication. Photo credit Madeline Price Ball; Wikimedia.

Some errors are not corrected during replication, but are instead corrected after replication is completed (**Figure 2**). The enzymes recognize the incorrectly added nucleotide and excise it; this is then replaced by the correct base. If this remains uncorrected, it may lead to more permanent damage.

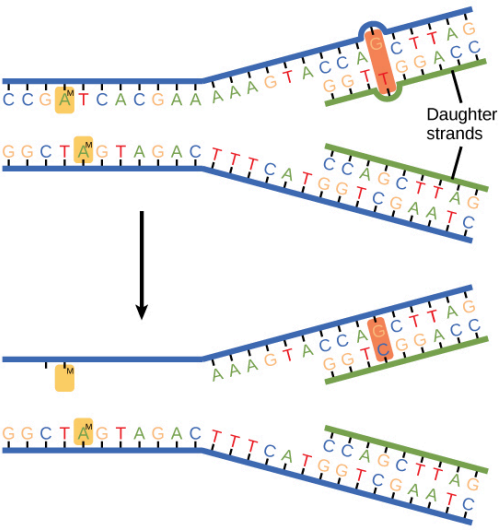


Figure 2 The incorrectly added base is detected after replication. The repair proteins detect this base and remove it from the newly synthesized strand by nuclease action. The gap is now filled with the correctly paired base.

In another type of repair mechanism, enzymes replace incorrect bases by making a cut on both sides of the incorrect base (**Figure 3**). The segment of DNA is removed and replaced with the correctly paired nucleotides by the action of DNA polymerase. Once the bases are filled in, the remaining gap is sealed by an enzyme called DNA ligase. This repair mechanism is often used when UV exposure causes two thymines to become connected to each other into a thymine–thymine dimer (the small – connecting the two Ts in Figure 3).

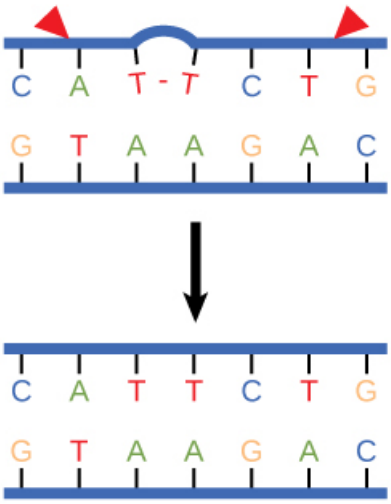


Figure 3 Repair of thymine dimers. When exposed to UV, thymines lying adjacent to each other can form thymine dimers. In normal cells, they are excised and replaced.

A well-studied example of mistakes not being corrected is seen in people suffering from xeroderma pigmentosa (**Figure 4**). Affected individuals have skin that is highly sensitive to UV rays from the sun. When individuals are exposed to UV, thymine-thymine dimers are formed. Normally, these dimers could be are cut out and repaired, but people with xeroderma pigmentosa are not able to repair the damage because of a defect in the repair enzymes. The thymine dimers distort the structure of the DNA double helix, and this causes problems during DNA replication. People with xeroderma pigmentosa have a higher risk of developing skin cancer than those who don't have the condition.

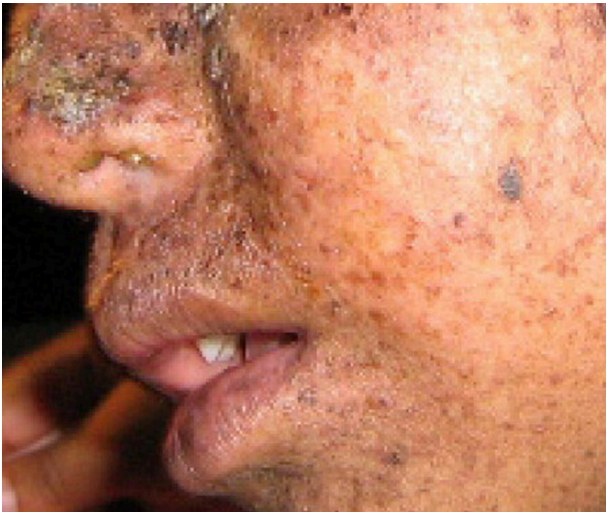


Figure 4 Xeroderma pigmentosa is a condition in which thymine dimerization from exposure to UV is not repaired. Exposure to sunlight results in skin lesions. (credit: James Halpern et al.)

Errors during DNA replication are not the only reason why mutations arise in DNA. Mutations can also occur because of damage to DNA. Mutations can result from an exposure to a **mutagen:** chemicals, UV rays, x-rays, or some other environmental agent. Mutations can also occur without any exposure to any environmental agent; they are a result of natural reactions taking place within the body.

Mutations may have a wide range of effects. Some mutations have no effect on the protein produced by the organism; these are known as silent mutations. Other mutations can have serious effects on the organism (such as the mutation that causes xeroderma pigmentosa).

Mutations in repair genes have been known to cause cancer. Many mutated repair genes have been implicated in certain forms of pancreatic cancer, colon cancer, and colorectal cancer. Mutations can affect either somatic cells or gametes. If many mutations accumulate in a cell, they may lead to problems such as the uncontrolled cell division observed in cancer. If a mutation takes

place in a sex cell, the mutation can be passed on to the next generation.

References

OpenStax, Concepts of Biology. OpenStax CNX. December 21, 2017. https://cnx.org/contents/GFy_h8cu@10.120:MPy5UMKm@7/DNA-Repair

32. Binary Fission: Prokaryotic Cell Division

The cell division process of prokaryotes (such as E. coli bacteria) is called **binary fission**. For unicellular organisms, cell division is the only method to produce new individuals. The outcome of this type of cell reproduction is a pair of daughter cells that are genetically identical to the parent cell. In unicellular organisms, daughter cells are whole individual organisms. This is a less complicated and much quicker process than cell division in eukaryotes. Because of the speed of bacterial cell division, populations of bacteria can grow very rapidly.

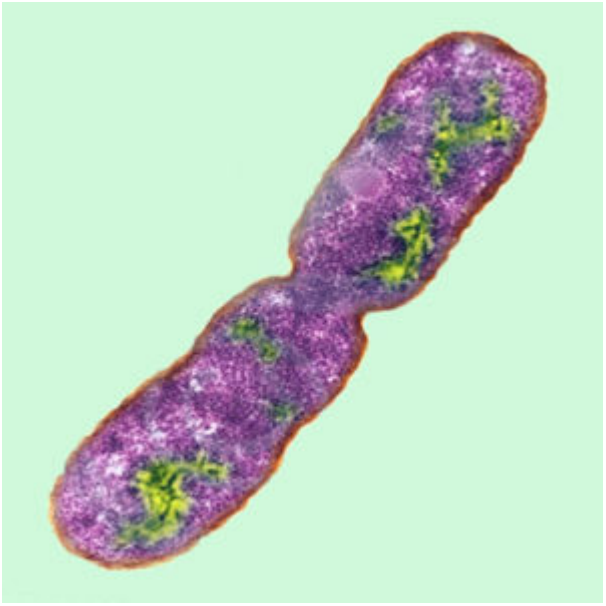


Figure 1: An E. coli bacteria dividing into two identical daughter cells

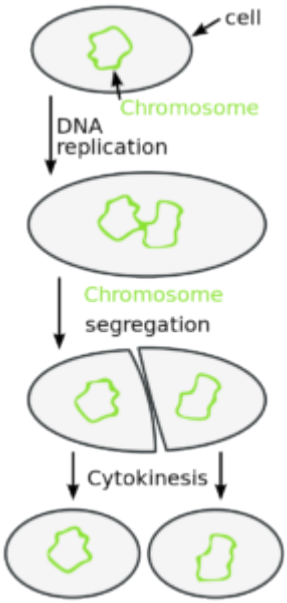
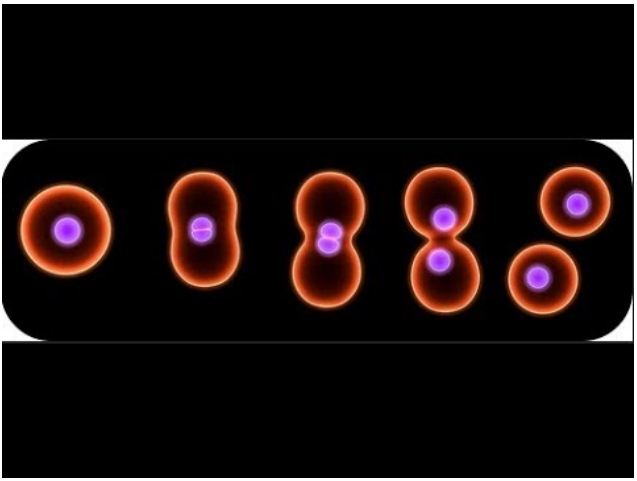


Figure 2: Prokaryotic cell division occurs via a process called binary fission.

To achieve the outcome of identical daughter cells, there are some essential steps. The genomic DNA must be replicated (using DNA replication) and then one copy must be moved into each of the daughter cells. The cytoplasmic contents must also be divided to give both new cells the machinery to sustain life. In bacterial cells, the genome consists of a single, circular DNA chromosome; therefore, the process of cell division is very simple.



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33. Mitosis: Eukaryotic Cell Division

Eukaryotes use two major types of cell division: mitosis and meiosis. Mitosis is used to produce new identical **somatic (body) cells** for growth and healing, while meiosis is used to produce sex cells (eggs and sperm). Meiosis will be discussed in a later chapter.

The **cell cycle** is an ordered series of events involving cell growth and cell division that produces two new daughter cells via mitosis. The length of the cell cycle is highly variable even within the cells of an individual organism. In humans, the frequency of cell turnover ranges from a few hours in early embryonic development to an average of two to five days for epithelial cells, or to an entire human lifetime spent without dividing in specialized cells such as cortical neurons or cardiac muscle cells. There is also variation in the time that a cell spends in each phase of the cell cycle. When fast-dividing mammalian cells are grown in culture (outside the body under optimal growing conditions), the length of the cycle is approximately 24 hours. The timing of events in the cell cycle is controlled by mechanisms that are both internal and external to the cell.

Cells on the path to cell division proceed through a series of precisely timed and carefully regulated stages of growth, DNA replication, and division that produce two genetically identical cells. The cell cycle has two major phases: interphase and the mitotic phase (**Figure 1**). During **interphase**, the cell grows and DNA is replicated. During the **mitotic phase**, the replicated DNA and cytoplasmic contents are separated and the cell divides.

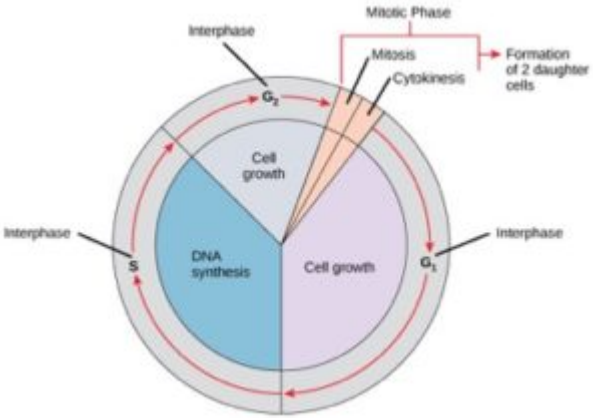


Figure 1:A *cell moves through a series of phases in an orderly manner. During interphase, G1 involves cell growth and protein synthesis, the S phase involves* DNA *replication and the replication of the centrosome, and G2 involves further growth and protein synthesis. The mitotic phase follows interphase. Mitosis is nuclear division during which duplicated chromosome s are segregated and distributed into daughter nuclei. Usually the cell will divide after mitosis in a process called cytokinesis in which the*

cytoplasm is divided and two daughter cells are formed.

Interphase

During interphase, the cell undergoes normal cellular processes while also preparing for cell division. For a cell to move from interphase to the mitotic phase, many internal and external conditions must be met. During interphase, the cell is very active biochemically. It is getting ready to divide by accumulating the required molecules and sufficient energy reserves. One very important process that happens during interphase is DNA replication. By the end of interphase, there are two identical copies of the DNA. Each chromosome is replicated and the two identical copies remain attached to each other at the centromere (**Figure 2**).

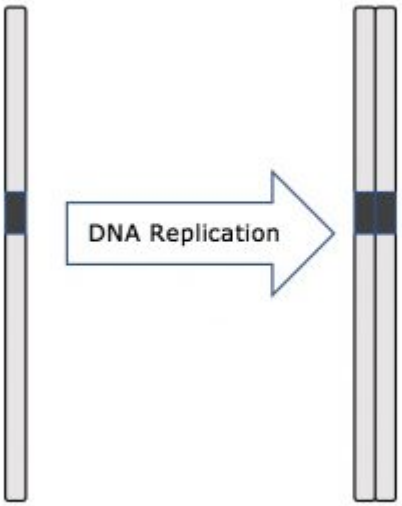


Figure 2DNA *replication during S phase copies each linear chromosome. The chromosomes remain attached together at a region called the centromere. Photo credit: Lisa Bartee*

The **centrosome** is also duplicated during interphase. Each centrosome is made up of rod-like objects called centrioles. Centrioles help organize cell division. Centrioles are not

present in the centrosomes of other eukaryotic species, such as plants and most fungi. Spindle fibers connect the centrosomes to the centromere of each chromosome. The spindle fibers will direct movement of the chromosomes during the rest of the process.

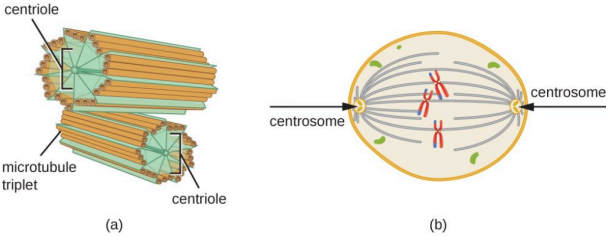


Figure 3*(a) Structure of the centrioles making up the centrosome. (b) Centrioles give rise to the mitotic spindle (grey threadlike structures). Photo credit: CNX OpenStax Microbiology .*

The Mitotic Phase

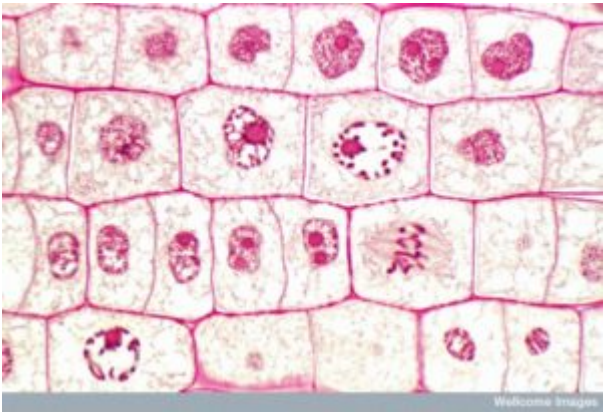


Figure 4:*Mitosis in onion root cells. The cells in this image are in various stages of mitosis. (Credit: Spike Walker. Wellcome Imagesimages@wellcome.ac.uk)*

To make two daughter cells, the contents of the nucleus and the cytoplasm must be divided. The mitotic phase is a multistep process during which the copied chromosomes are lined up in the center of the cell, then pulled apart to opposite ends of the cell. The cell is then divided into two new identical daughter cells. The first portion of the mitotic phase, **mitosis**, is composed of five phases, which accomplish nuclear division (**Figure 5**). The second portion of the mitotic phase, called **cytokinesis,** is the physical separation of the cytoplasmic components into two daughter cells. Although the stages of mitosis are similar for most eukaryotes, the process of cytokinesis is quite different for eukaryotes that have cell walls, such as plant cells.

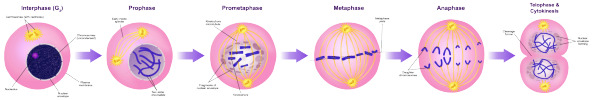
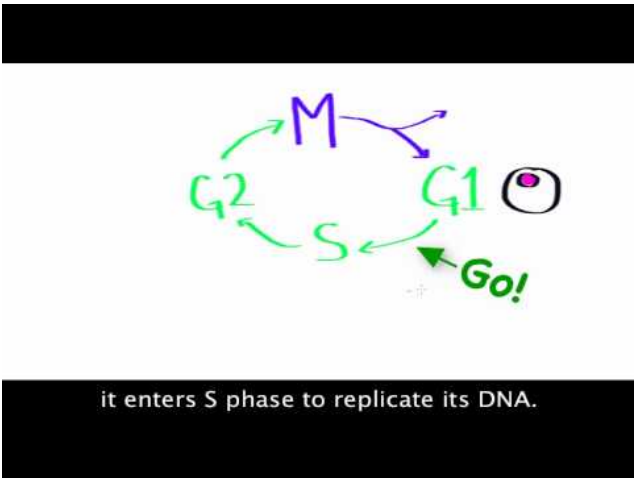


***Figure 5** Summary of the process of mitosis. Photo credit Oganesson007, Wikimedia.*

To summarize the process of mitosis:

1. Somatic (body) cell receives a signal that it is time to divide. This might be to heal a wound or to allow the organism to grow larger.
2. DNA replication takes place during interphase. The end result is two identical copies of each chromosome connected at the centromere. These identical copies are called sister chromatids.
3. During mitosis (division of the nucleus), the replicated chromosomes condense (wind up tightly), then spindle fibers attach to the centromere of each chromosome. The spindle fibers pull on the chromosomes, which causes them to line up

in the center of the cell.
4. The centromeres separate and the spindle fibers shorten, pulling one sister chromatid to either end of the cell.
5. During cytokinesis, the cytoplasm of the cell is divided into two new cells by the formation of a new cell membrane between the daughter cells.
6. The result of mitosis is two identical somatic cells.



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Phases of Mitosis

The mitotic phase is divided into a number of different phases. YOU DO NOT NEED TO MEMORIZE WHAT HAPPENS DURING EACH

PHASE OF MITOSIS. If you would like to read about what occurs, you can find this information below.

Prophase

The nuclear envelope starts to break down, and the organelles (such as the Golgi apparatus and endoplasmic reticulum), fragment and move toward the edges of the cell. The nucleolus disappears. The centrosomes begin to move to opposite poles of the cell. Microtubules that will form the mitotic spindle extend between the centrosomes, pushing them farther apart as the microtubule fibers lengthen. The sister chromatids begin to coil more tightly with the aid of condensin proteins and become visible under a light microscope.

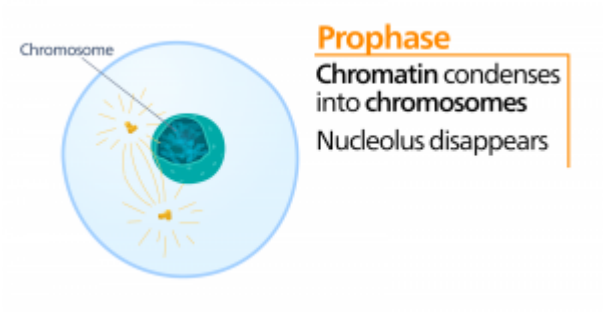

Figure 6 *Prophase. Photo credit Kelvin13; Wikimedia.*

Prometaphase

During **prometaphase,**the "first change phase," many processes that were begun in prophase continue to advance. The remnants of the nuclear envelope fragment. The mitotic spindle continues to develop as more microtubules assemble and stretch across the length of the former nuclear area. Chromosomes become more

condensed and discrete. Each sister chromatid develops a protein structure called a **kinetochore**in the centromeric region.

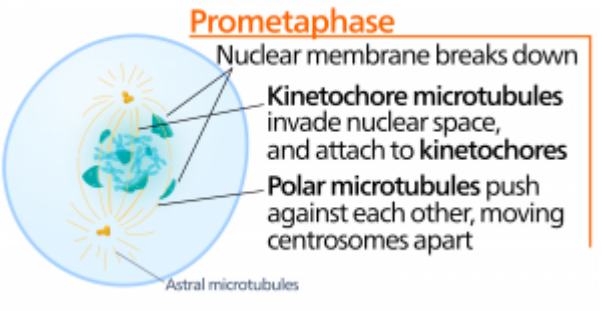

Figure 7 *Prometaphase. Photo credit Kelvin13; Wikimedia.*

The proteins of the kinetochore attract and bind mitotic spindle microtubules. As the spindle microtubules extend from the centrosomes, some of these microtubules come into contact with and firmly bind to the kinetochores. Once a mitotic fiber attaches to a chromosome, the chromosome will be oriented until the kinetochores of sister chromatids face the opposite poles. Eventually, all the sister chromatids will be attached via their kinetochores to microtubules from opposing poles. Spindle microtubules that do not engage the chromosomes are called polar microtubules. These microtubules overlap each other midway between the two poles and contribute to cell elongation. Astral microtubules are located near the poles, aid in spindle orientation, and are required for the regulation of mitosis.

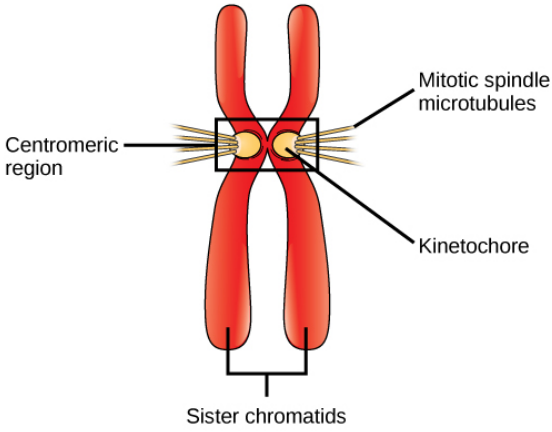

Figure 8 *During prometaphase, mitotic spindle microtubules from opposite poles attach to each sister chromatid at the kinetochore. In anaphase, the connection between the sister chromatids breaks down, and the microtubules pull the chromosomes toward opposite poles.*

Metaphase

During **metaphase,**the "change phase," all the chromosomes are aligned in a plane called the metaphase plate, or the equatorial plane, midway between the two poles of the cell. The sister chromatids are still tightly attached to each other by cohesin proteins. At this time, the chromosomes are maximally condensed.

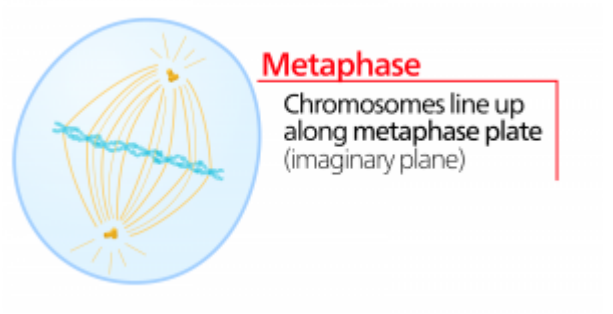

Figure 9 *Metaphase. Photo credit Kelvin13; Wikimedia.*

Anaphase

During anaphase, the "upward phase," the cohesin proteins degrade, and the sister chromatids separate at the centromere. Each chromatid, now called a chromosome, is pulled rapidly toward the centrosome to which its microtubule is attached. The cell becomes visibly elongated (oval shaped) as the polar microtubules slide against each other at the metaphase plate where they overlap.

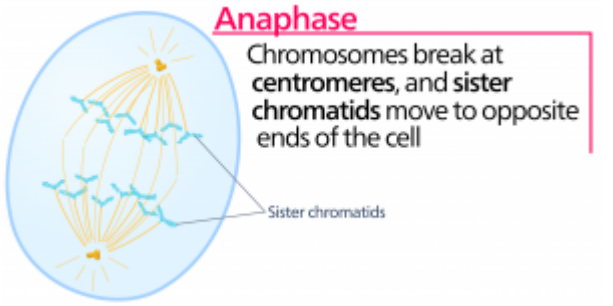

Figure 10 *Anaphase. Photo credit Kelvin13; Wikimedia.*

Telophase

During telophase, the "distance phase," the chromosomes reach the

opposite poles and begin to decondense (unravel), relaxing into a chromatin configuration. The mitotic spindles are depolymerized into tubulin monomers that will be used to assemble cytoskeletal components for each daughter cell. Nuclear envelopes form around the chromosomes, and nucleosomes appear within the nuclear area.

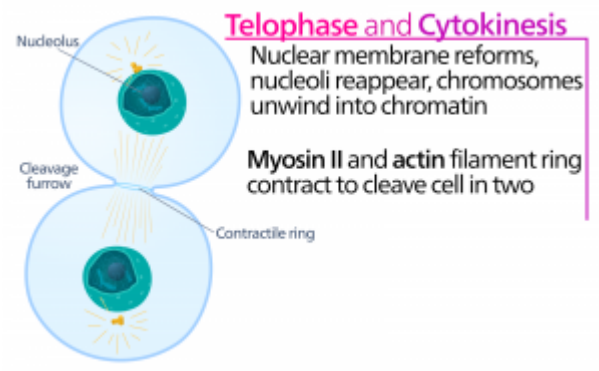

Figure 11 *Telophase. Photo credit Kelvin13; Wikimedia.*

Cytokinesis

Cytokinesis,or "cell motion," is the second main stage of the mitotic phase during which cell division is completed via the physical separation of the cytoplasmic components into two daughter cells. Division is not complete until the cell components have been divided and completely separated into the two daughter cells. Although the stages of mitosis are similar for most eukaryotes, the process of cytokinesis is quite different for eukaryotes that have cell walls, such as plant cells.

In cells such as animal cells that lack cell walls, cytokinesis follows the onset of anaphase. A contractile ring composed of actin filaments forms just inside the plasma membrane at the former metaphase plate (**Figure 12**). The actin filaments pull the equator of the cell inward, forming a fissure. This fissure, or "crack," is called

the cleavage furrow. The furrow deepens as the actin ring contracts, and eventually the membrane is cleaved in two.

In plant cells, a new cell wall must form between the daughter cells. During interphase, the Golgi apparatus accumulates enzymes, structural proteins, and glucose molecules prior to breaking into vesicles and dispersing throughout the dividing cell (**Figure 12**). During telophase, these Golgi vesicles are transported on microtubules to form a phragmoplast (a vesicular structure) at the metaphase plate. There, the vesicles fuse and coalesce from the center toward the cell walls; this structure is called a cell plate. As more vesicles fuse, the cell plate enlarges until it merges with the cell walls at the periphery of the cell. Enzymes use the glucose that has accumulated between the membrane layers to build a new cell wall. The Golgi membranes become parts of the plasma membrane on either side of the new cell wall.

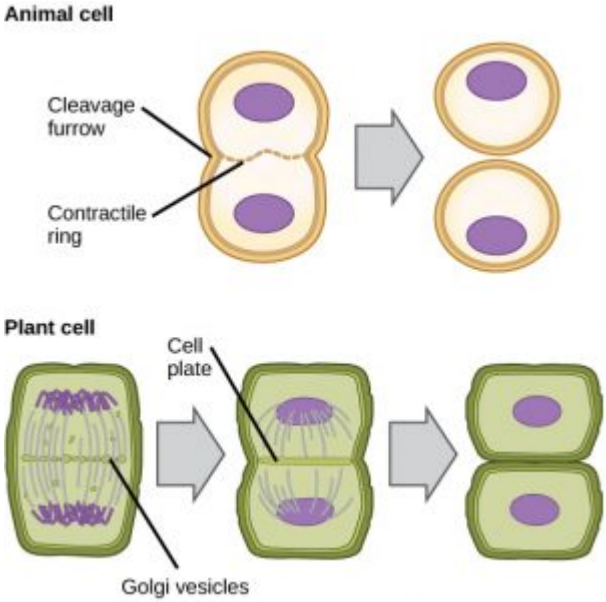

Figure 12 *During cytokinesis in animal cells, a ring of actin filaments forms at the metaphase plate. The ring contracts, forming a cleavage furrow, which divides the cell in two. In plant cells, Golgi vesicles coalesce at the former metaphase plate, forming a phragmoplast. A cell plate formed by the fusion of the vesicles of the phragmoplast grows from the center toward the cell walls, and the membranes of the vesicles fuse to form a plasma membrane that divides the cell in two.*

Summary of Mitosis and Cytokinesis

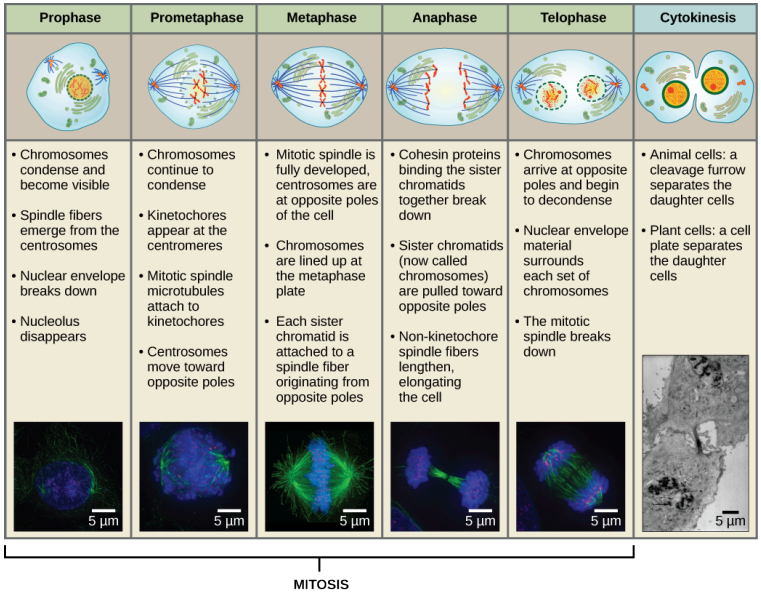

Figure 13 Mitosis is divided into five stages—prophase, prometaphase, metaphase, anaphase, and telophase. The pictures at the bottom were taken by fluorescence microscopy of cells artificially stained by fluorescent dyes: blue fluorescence indicates DNA (chromosomes) and green fluorescence indicates microtubules (spindle apparatus). (credit "mitosis drawings": modification of work by Mariana Ruiz Villareal; credit "micrographs": modification of work by Roy van Heesbeen; credit "cytokinesis micrograph": Wadsworth Center/New York State Department of Health; scale-bar data from Matt Russell)

Go Phase

Not all cells adhere to the classic cell-cycle pattern in which a newly formed daughter cell immediately enters interphase, closely followed by the mitotic phase. Cells in the **G0 phase** are not actively preparing to divide. The cell is in a quiescent (inactive) stage, having exited the cell cycle. Some cells enter G0 temporarily until an external signal triggers the onset of G1. Other cells that never or rarely divide, such as mature cardiac muscle and nerve cells, remain in G0 permanently).

References

OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:Vbi92lHB@9/The-Cell-Cycle

34. Control of the Cell Cycle

It is essential that daughter cells be exact duplicates of the parent cell. Mistakes in the duplication or distribution of the chromosomes lead to mutations that may be passed forward to every new cell produced from the abnormal cell. To prevent a compromised cell from continuing to divide, there are internal control mechanisms that operate at three main **cell cycle checkpoints** at which the cell cycle can be stopped until conditions are favorable.

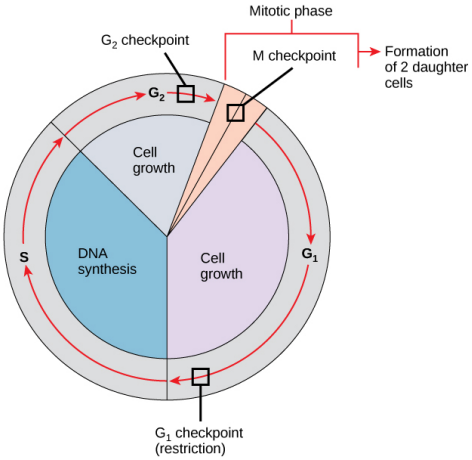

Figure 1 *The cell cycle is controlled at three checkpoints. Integrity of the DNA is assessed at the G1 checkpoint. Proper chromosome duplication is assessed at the G2 checkpoint. Attachment of each kinetochore to a spindle fiber is assessed at the M checkpoint.*

The first checkpoint (G_1) determines whether all conditions are favorable for cell division to proceed. This checkpoint is the point at which the cell irreversibly commits to the cell-division process. In addition to adequate reserves and cell size, there is a check for

damage to the genomic DNA. A cell that does not meet all the requirements will not be released into the S phase.

The second checkpoint (G_2) bars the entry to the mitotic phase if certain conditions are not met. The most important role of this checkpoint is to ensure that all of the chromosomes have been replicated and that the replicated DNA is not damaged.

The final checkpoint (M) occurs in the middle of mitosis. This checkpoint determines if all of the copied chromosomes are arranged appropriately to be separated to opposite sides of the cell. If this doesn't happen correctly, incorrect numbers of chromosomes can be partitioned into each of the daughter cells, which would likely cause them to die.

Regulator Molecules of the Cell Cycle

In addition to the internally controlled checkpoints, there are two groups of intracellular molecules that regulate the cell cycle. These regulatory molecules either promote progress of the cell to the next phase (positive regulation) or halt the cycle (negative regulation). Regulator molecules may act individually, or they can influence the activity or production of other regulatory proteins. Therefore, it is possible that the failure of a single regulator may have almost no effect on the cell cycle, especially if more than one mechanism controls the same event. It is also possible that the effect of a deficient or non-functioning regulator can be wide-ranging and possibly fatal to the cell if multiple processes are affected.

Positive Regulation of the Cell Cycle

Two groups of proteins, called **cyclins** and **cyclin-dependent kinases (CDKs)**, are responsible for the progress of the cell through

the various checkpoints. The levels of the four cyclin proteins fluctuate throughout the cell cycle in a predictable pattern. Increases in the concentration of cyclin proteins are triggered by both external and internal signals. After the cell moves to the next stage of the cell cycle, the cyclins that were active in the previous stage are degraded.

Cyclins are active only when they are tightly bound to CDKs. When a cyclin is tightly bound to its CDK, it will phosphorylate other proteins. Phosphorylation (addition of a phosphate group) activates the protein by changing its shape. The proteins phosphorylated by cyclin/CDK complexes are involved in advancing the cell to the next phase. Because there are different cyclins present at different points during the cell cycle, different cyclin/CDK complexes regulate different checkpoints. Without a specific concentration of fully activated cyclin/CDK complexes, the cell cycle cannot proceed through the checkpoints.

Negative Regulation of the Cell Cycle

The second group of cell cycle regulatory molecules are negative regulators. In positive regulation, active molecules such as CDK/cyclin complexes cause the cell cycle to progress. In negative regulation, active molecules halt the cell cycle.

The best understood negative regulatory molecules are retinoblastoma protein (Rb), p53, and p21. All three of these regulatory proteins were discovered to be damaged or non-functional in cells that had begun to replicate uncontrollably (became cancerous). In each case, the main cause of the unchecked progress through the cell cycle was a faulty copy of one of these regulatory proteins. For this reason, Rb and other proteins that negatively regulate the cell cycle are sometimes called **tumor suppressors**.

Rb, p53, and p21 act primarily at the G_1 checkpoint, where the cell determines whether it has adequate energy reserves, is large enough, and whether there is damage to the genomic DNA. The**p53** protein has a major impact on the commitment of a cell to divide. If damaged DNA is detected at the G_1 checkpoint, p53 halts the cell cycle and recruits enzymes to repair the DNA. If the DNA cannot be repaired, p53 can trigger apoptosis, or cell suicide, to prevent the duplication of damaged chromosomes. As p53 levels rise, the production of **p21** is triggered. p21 enforces the halt in the cycle dictated by p53 by binding to and inhibiting the activity of the cyclin/CDK complexes. If cyclin/CDK complexes are inhibited, the cell cycle can't move forward. As a cell is exposed to more stress, higher levels of p53 and p21 accumulate, making it less likely that the cell will move into the S phase.

Rb exerts its regulatory influence on other positive regulator proteins. Chiefly, Rb monitors cell size. In the active state, Rb binds to proteins called transcription factors. Transcription factors "turn on" transcription of specific genes, allowing the production of proteins encoded by that gene. When Rb is bound to transcription factors, production of proteins necessary for the G_1/S transition is blocked. As the cell increases in size, Rb is slowly inactivated. Rb releases the transcription factors, which can now turn on the gene that produces the transition protein, and this particular block is removed. For the cell to move past each of the checkpoints, all positive regulators must be "turned on," and all negative regulators must be "turned off."

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OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:Vbi92lHB@9/The-Cell-Cycle

OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:LlKfCy5H@4/Prokaryotic-Cell-Division

35. Cancer and the Cell Cycle

Cancer comprises many different diseases caused by a common mechanism: uncontrolled cell growth. Despite the redundancy and overlapping levels of cell cycle control, errors do occur. One of the critical processes monitored by the cell cycle checkpoint surveillance mechanism is the proper replication of DNA during the S phase. Even when all of the cell cycle controls are fully functional, a small percentage of replication errors (mutations) will be passed on to the daughter cells. If changes to the DNA nucleotide sequence of a gene are not corrected, a mutation results. All cancers start when a mutation causes a change in the order of the amino acids that make up a protein that plays a key role in cell reproduction. Changes in the amino acid sequence can change the shape of the protein. Since the shape of the protein is changed, its function may be changed as well. The change in the cell that results from the misshaped protein may be minor: perhaps a slight delay in the binding of CDK to cyclin or an Rb protein that detaches from its target DNA while still active. Even minor mistakes, however, may allow subsequent mistakes to occur more readily. Over and over, small uncorrected errors are passed from the parent cell to the daughter cells and amplified as each generation produces more non-functional proteins from uncorrected DNA damage. Eventually, the pace of the cell cycle speeds up as the effectiveness of the control and repair mechanisms decreases. Uncontrolled growth of the mutated cells outpaces the growth of normal cells in the area, and a tumor ("-oma") can result.

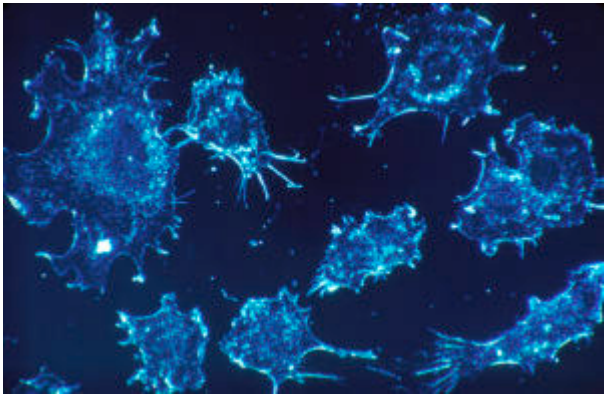

Figure 1*Cancer cells in culture from human connective tissue, illuminated by darkfield amplified contrast, at a magnificatio n of 500x.*

Proto-oncogenes

When the genes that code for the positive cell cycle regulators are mutated in certain ways, they become **oncogenes:** genes that cause a cell to become cancerous. We all contain these genes because when they are not mutated, they perform important functions in cells. These genes are called **proto-oncogenes**. It is only when mutations occur in porto-oncogenes that they can become dangerous oncogenes.

In most instances, a mutation in the DNA sequence of a porto-oncogene will result in a less functional or non-functional protein. This result is harmful to the cell and will likely prevent the cell from completing the cell cycle, which means that this cell cannot divide and create daughter cells. In this case, the organism is not harmed because the mutation will not be carried forward to new cells, so the damage is minimal.

Occasionally, however, a gene mutation causes a change that increases the activity of a positive regulator. For example, a mutation that allows CDK to be activated without being partnered with cyclin could push the cell cycle past a checkpoint before all of the required conditions are met. If the resulting daughter cells

are too damaged to undergo further cell divisions, the mutation would not be propagated and no harm would come to the organism. However, if the mutated daughter cells are able to undergo further cell divisions, subsequent generations of cells will probably accumulate even more mutations, possibly in additional genes that regulate the cell cycle.

The CDK gene in the above example is only one of many genes that can become an oncogene if it is mutated. In addition to the cell cycle regulatory proteins, any protein that influences the cycle can be altered in such a way as to override cell cycle checkpoints. An oncogene is any gene that, when altered, leads to an increase in the rate of cell cycle progression. Mutated oncogenes are similar to the gas pedal in a vehicle: a gas pedal that is stuck down (mutated) will cause a car to speed out of control (uncontrolled cell division) and potentially crash (cancer)

Tumor Suppressor Genes

Tumor suppressor genes are segments of DNA that code for negative regulator proteins. Activated negative regulator proteins prevent the cell from undergoing uncontrolled division. The collective function of the best-understood tumor suppressor gene proteins, Rb, p53, and p21, is to put up a roadblock to cell cycle progression until certain events are completed. A cell that carries a mutated form of a negative regulator might not be able to halt the cell cycle if there is a problem. Tumor suppressors are similar to brakes in a vehicle: brakes that aren't working correctly (mutated) can also cause a car to speed out of control (uncontrolled cell division) and contribute to a car crash (cancer).

Mutated p53 genes have been identified in more than one-half of all human tumor cells. This discovery is not surprising in light of the multiple roles that the p53 protein plays at the G_1checkpoint. A cell with a faulty p53 may fail to detect errors present in the genomic

DNA (**Figure 2**). Even if a partially functional p53 does identify the mutations, it may no longer be able to signal the necessary DNA repair enzymes. Either way, damaged DNA will remain uncorrected. At this point, a functional p53 will deem the cell unsalvageable and trigger programmed cell death (apoptosis). The damaged version of p53 found in cancer cells, however, cannot trigger apoptosis.

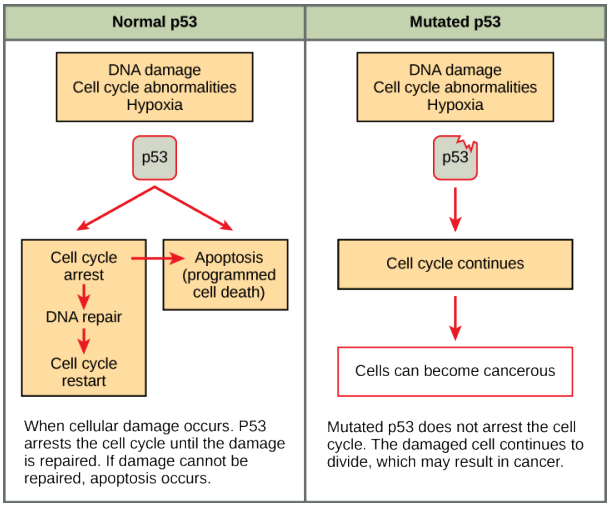

Figure 2 *The role of normal p53 is to monitor DNA and the supply of oxygen (hypoxia is a condition of reduced oxygen supply). If damage is detected, p53 triggers repair mechanisms. If repairs are unsuccessful, p53 signals apoptosis. A cell with an abnormal p53 protein cannot repair damaged DNA and thus cannot signal apoptosis. Cells with abnormal p53 can become cancerous. (credit: modification of work by Thierry Soussi)*

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OpenStax, Biology. OpenStax CNX. November 11, 2017 https://cnx.org/contents/GFy_h8cu@10.118:CYZpmedR@7/Cancer-and-the-Cell-Cycle

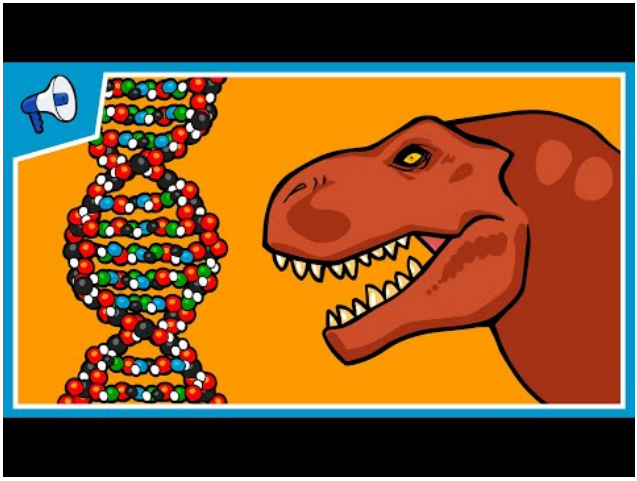
PART VII

PROTEIN SYNTHESIS

Learning Objectives

By the end of this section, you will be able to:

- Describe how DNA is used for the process of protein synthesis.
- Describe processes through which gene expression can be regulated.



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In both prokaryotes and eukaryotes, the function of DNA is to provide the information needed to construct the proteins necessary so that the cell can perform all of its functions. Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.

Recall that proteins are made up of hundreds or thousands of smaller units called amino acids, which are attached to one another in long chains. There are 20 different types of amino acids that can be combined to make a protein. The sequence of amino acids determines each protein's unique 3-dimensional structure and its specific function.

Proteins can be described according to their large range of functions in the body, listed in alphabetical order in the table below. This chapter of the book will describe how proteins are produced by cells.

Function	Antibody	Antibodies bind to specific foreign particles, such as viruses and bacteria, to help protect the body.
	Enzyme	Enzymes carry out almost all of the thousands of chemical reactions that take place in cells. They also assist with the formation of new molecules by reading the genetic information stored in DNA.
	Messenger	Messenger proteins, such as some types of hormones, transmit signals to coordinate biological processes between different cells, tissues, and organs.
	Structural component	These proteins provide structure and support for cells. On a larger scale, they also allow the body to move.
	Transport/ storage	These proteins bind and carry atoms and small molecules within cells and throughout the body.

References

36. DNA Structure

DNA is the genetic material passed from parent to offspring for all life on Earth. The three letters "DNA" have now become associated with crime solving, paternity testing, human identification, and genetic testing. DNA can be retrieved from hair, blood, or saliva. With the exception of identical twins, each person's DNA is unique and it is possible to detect differences between human beings on the basis of their unique DNA sequence.

DNA analysis has many practical applications beyond forensics and paternity testing. DNA testing is used for tracing genealogy and identifying pathogens. In the medical field, DNA is used in diagnostics, new vaccine development, and cancer therapy. It is now possible to determine predisposition for many diseases by analyzing genes.

In the 1950s, Francis Crick and James Watson worked together to determine the structure of DNA at the University of Cambridge, England. Other scientists like Linus Pauling and Maurice Wilkins were also actively exploring this field. Pauling had discovered the secondary structure of proteins using X-ray crystallography. In Wilkins' lab, researcher Rosalind Franklin was using X-ray diffraction methods to understand the structure of DNA. Watson and Crick were able to piece together the puzzle of the DNA molecule on the basis of Franklin's data because Crick had also studied X-ray diffraction (**Figure 1**).

(a)

(b)

Figure 1 *The work of pioneering scientists (a) James Watson, Francis Crick, and Maclyn McCarty led to our present day understanding of DNA. Scientist Rosalind Franklin discovered (b) the X-ray diffraction pattern of DNA, which helped to elucidate its double helix structure. (credit a: modification of work by Marjorie McCarty, Public Library of Science)*

Unfortunately, Watson and Crick gained access to Franklin's data without her knowledge or approval. In 1962, James Watson, Francis Crick, and Maurice Wilkins were awarded the Nobel Prize in Medicine. Unfortunately, by then Franklin had died (of ovarian cancer, likely caused by exposure to X-rays), and Nobel prizes are not awarded posthumously (after death). This is actually a really interesting story of "sexism in the sciences" – there's a movie called "The Secret of Photo 51" that you can find on YouTube if you're interested.

Based on Rosalind Franklin's X-ray diffraction photograph, and work by other scientists, Watson and Crick proposed that DNA is made up of two strands of **nucleotides** that are twisted around each other to form a right-handed helix. The nucleotides are joined together in a chain by covalent bonds. Scientists already knew that nucleotides contain the same three important components: a **nitrogenous base**, a **deoxyribose** (5-carbon sugar), and a **phosphate group** (**Figure 2**). The nucleotide is named depending on the nitrogenous base: adenine (A), thymine (T), cytosine (C), and guanine (G).

Watson and Crick's model proposed that the two strands of nucleotides interact through base pairing between the nucleotides: A pairs with T and G pairs with C. Adenine and thymine are **complementary base pairs**, and cytosine and guanine are also complementary base pairs. The base pairs are stabilized by hydrogen bonds (a weak type of bond that forms between partially positive and partially negative atoms). Adenine and thymine form two hydrogen bonds and cytosine and guanine form three hydrogen bonds.

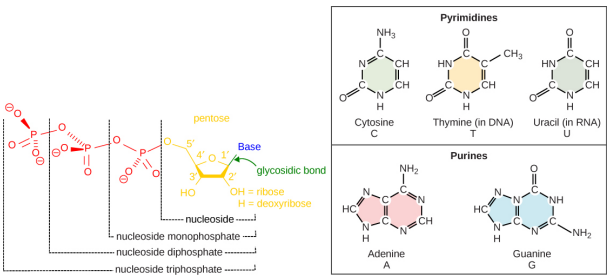

Figure 2 *Each nucleotide is made up of a sugar, a phosphate group, and a nitrogenous base. The sugar is deoxyribose in DNA and ribose in RNA.*

The two strands of a DNA double-helix are **anti-parallel** in nature; that is, the phosphate end of one strand points in one direction, while the sugar end of the other strand points in that direction. The

sugar and phosphate of the nucleotides form the backbone of the structure, while the nitrogenous bases are stacked inside.

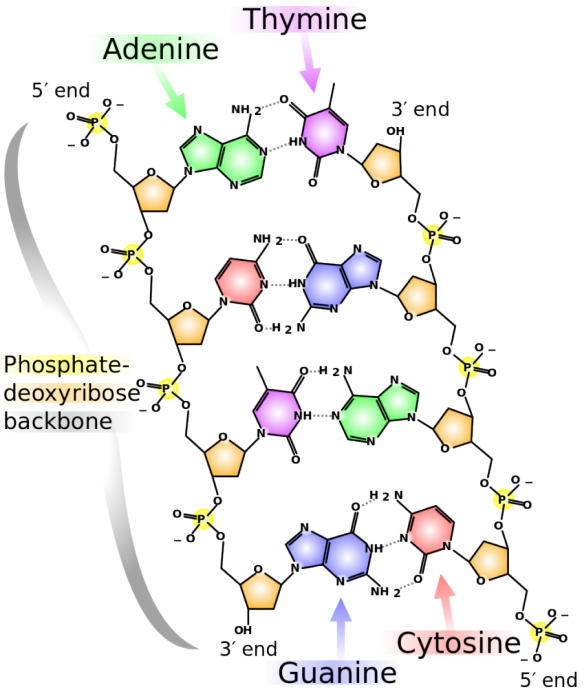

Figure 3 *Structure of DNA. Notice that adenine (a purine) and thymine (a pyrimidine) are connected together with 2 hydrogen bonds, while guanine (a purine) and cytosine (a pyrimidine) are connected by three hydrogen bonds. There is a 5′ and 3′ end to both chains of nucleotides, which are antiparallel to each other. Photo credit Madeline Price Ball; Wikimedia.*

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OpenStax, Biology. OpenStax CNX. December 21, 2017 http://cnx.org/contents/s8Hh0oOc@9.10:QhGQhr4x@6/Biological-Molecules

37. How DNA is arranged in a cell

DNA is a working molecule; it must be replicated (copied) when a cell is ready to divide, and it must be "read" to produce the molecules, such as proteins, to carry out the functions of the cell. For this reason, the DNA is protected and packaged in very specific ways. Because they must carry so much information, DNA molecules can be very long. Stretched end-to-end, the DNA molecules in a single human cell would come to a length of about 2 meters (roughly 6 feet). Thus, the DNA for a cell must be packaged in a very ordered way to fit and function within a structure (the cell) that is not visible to the naked eye.

A cell's complete complement of DNA is called its **genome**. In prokaryotes (bacteria), the genome is composed of a single, double-stranded DNA molecule in the form of a loop or circle. The region in the cell containing this genetic material is called a **nucleoid (Figure 1).** Some prokaryotes also have smaller loops of DNA called **plasmids** that are not essential for normal growth.

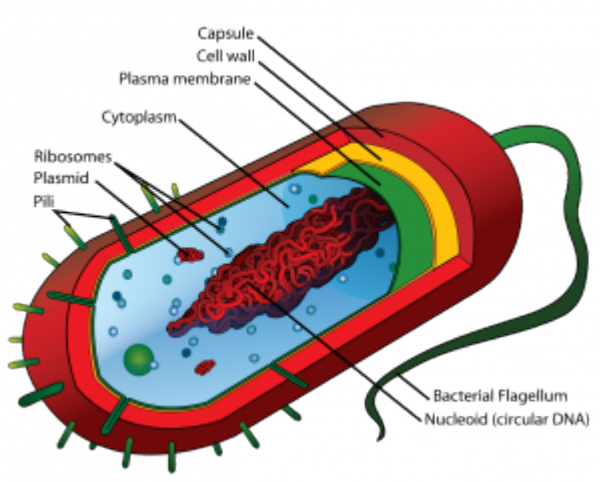


Figure 1 *An average prokaryotic cell. Note that the DNA is not surrounded by a membrane to create a nucleus. Photo credit Lady of Hats; Wikipedia.*

The size of the genome in one of the most well-studied prokaryotes, *Escherichia coli*, is 4.6 million base pairs. This would extend a distance of about 1.6 mm if stretched out. Compare that to the length of an E. coli cell, which is approximately 1-2μm long. 1.6mm = 1600μm: so how does all this DNA fit inside a tiny cell? The DNA is twisted beyond the double helix in what is known as supercoiling. Some proteins are known to be involved in the supercoiling; other proteins and enzymes help in maintaining the supercoiled structure.

Eukaryotes, such as animals and plants, have **chromosomes** that consist of linear DNA molecules. Chromosomes can be seen as thread-like structures located inside the nucleus of eukaryotic cells. Each chromosome is made of protein and a single linear double-helix of DNA (**Figure 2**). The term chromosome comes from the Greek words for color (chroma) and body (soma). Scientists gave this name to chromosomes because they are cell structures, or bodies, that are strongly stained by some colorful dyes used in research.

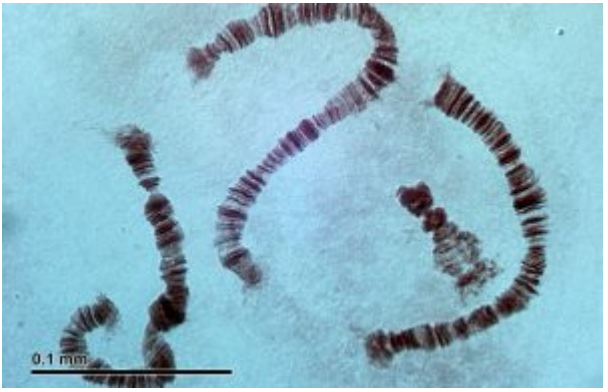


Figure 2 *Linear chromosomes from the salivary glands of nonbiting midge larvae. Photo credit Joseph Resichig; Wikimedia.*

Eukaryotes typically have much more DNA than prokaryotes: the human genome is roughly 3 *billion* base pairs while the E. coli genome is roughly 4 *million*.For this reason, eukaryotes employ a different type of packing strategy to fit their DNA inside the **nucleus** (**Figure 3**). At the most basic level, DNA is wrapped around proteins

known as **histones**. The DNA wrapped around histones wraps and stacks through several additional levels of complexity. These thicker more compact structures are what you have seen before in pictures labeled “chromosomes”.

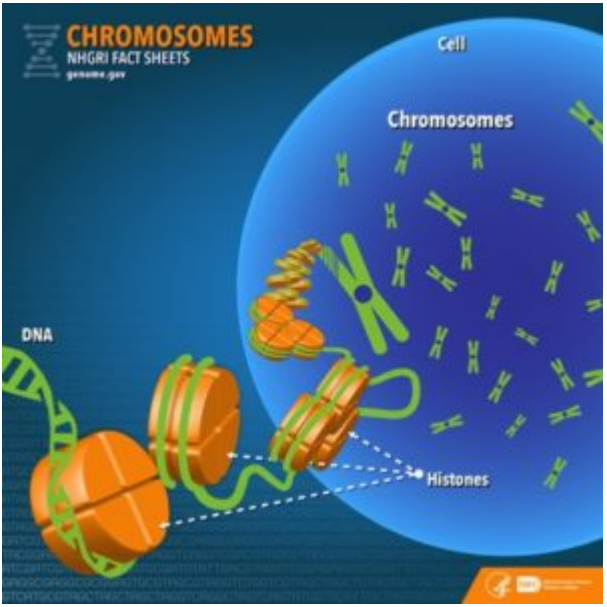
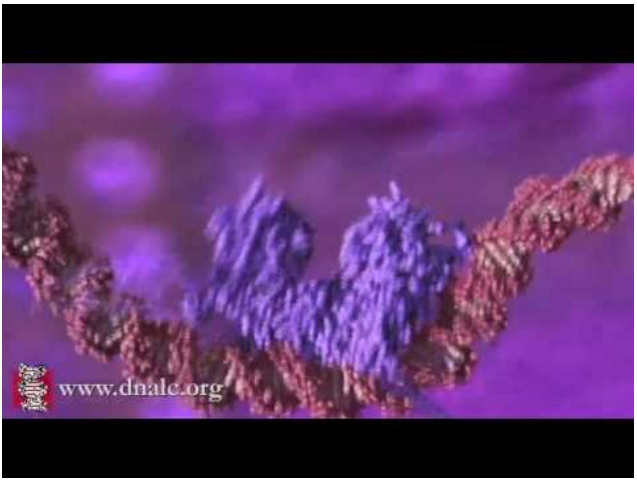


Figure 3: *The basic structure of eukaryotic chromosomes inside the nucleus of a cell (“Chromosomes” by National Human Genome Research Institute is in the Public Domain)*



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To summarize:

- Prokaryotes have relatively small amounts of DNA (millions of basepairs) found in one circular genome, which is located in the cytoplasm in the nucleoid.
- Eukaryotes have larger amounts of DNA (billions of basepairs) found in several linear chromosomes, which are located inside the nucleus.

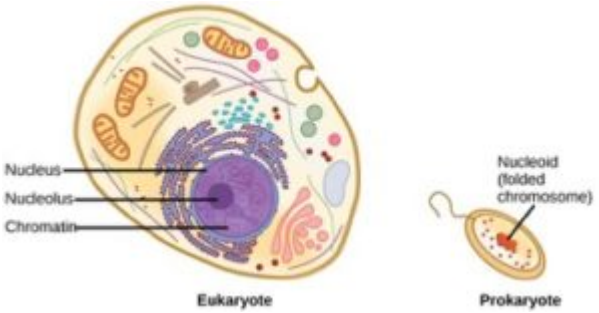

Figure 5: *A eukaryote contains a well-defined nucleus, whereas in prokaryotes, the chromosome lies in the cytoplasm in an area called the nucleoid.*

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https://openoregon.pressbooks.pub/mhccbiology112/?p=144

References

OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:8v2Xzdco@5/The-Structure-of-DNA

"Genetics Home Reference: Help Me Understand Genetics"by , National Institutes of Health: U.S> National Library of Medicineis in the Public Domain

38. Genes Direct the Production of Proteins

Most genes contain the information needed to make functional molecules called proteins. A few genes produce other molecules that help the cell assemble proteins. The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: transcription and translation. Together, transcription and translation are known as gene expression.

During the process of transcription, the information stored in a gene's DNA is transferred to a similar molecule called RNA (ribonucleic acid) in the cell nucleus. Both RNA and DNA are made up of a chain of nucleotide bases, but they have slightly different chemical properties. The type of RNA that contains the information for making a protein is called messenger RNA (mRNA) because it carries the information, or message, from the DNA out of the nucleus into the cytoplasm.

Translation, the second step in getting from a gene to a protein, takes place in the cytoplasm. The mRNA interacts with a specialized complex called a ribosome, which "reads" the sequence of mRNA bases. Each sequence of three bases, called a codon, usually codes for one particular amino acid. Remember that amino acids are the building blocks of proteins. A type of RNA called transfer RNA (tRNA) assembles the protein, one amino acid at a time. Protein assembly continues until the ribosome encounters a "stop" codon (a sequence of three bases that does not code for an amino acid).

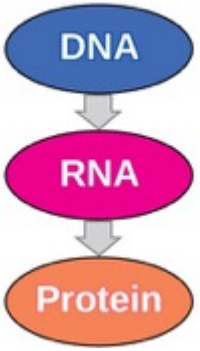


Figure 1: The Central Dogma – DNA is used to make RNA is used to make protein

The flow of information from DNA to RNA to proteins is one of the fundamental principles of molecular biology. It is so important that it is sometimes called the "central dogma."

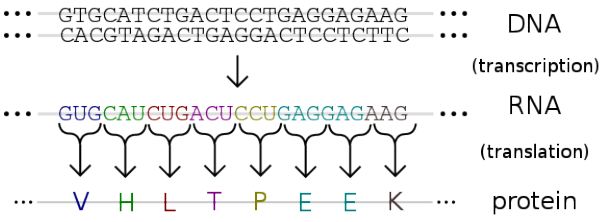
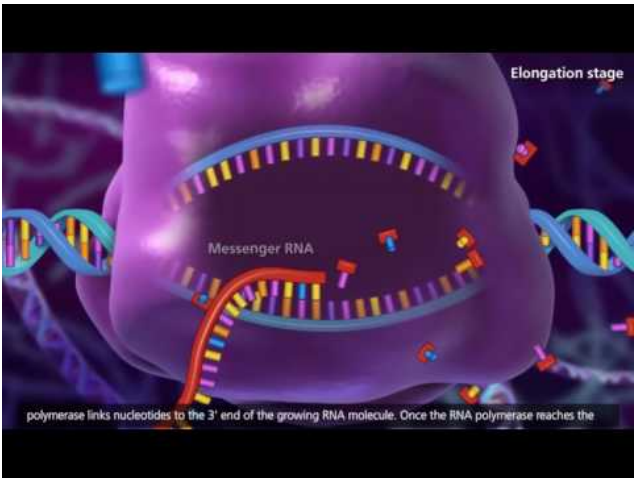


Figure 2 The Central Dogma: DNA is transcribed to produce RNA, which is translated to produce a protein. Genetic Code by Madprime, Wikimedia, Public Domain



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References

39. Transcription: from DNA to RNA

Both prokaryotes and eukaryotes perform fundamentally the same process of transcription, with the important difference of the membrane-bound nucleus in eukaryotes. With the genes bound in the nucleus, transcription occurs in the nucleus of the cell and the mRNA transcript must be transported to the cytoplasm. The prokaryotes, which include bacteria and archaea, lack membrane-bound nuclei and other organelles, and transcription occurs in the cytoplasm of the cell.

Transcription requires the DNA double helix to partially unwind in the region of mRNA synthesis. The DNA sequence onto which the proteins and enzymes involved in transcription bind to initiate the process is called a **promoter**. In most cases, promoters exist upstream of the genes they regulate. The specific sequence of a promoter is very important because it determines whether the corresponding gene is transcribed all of the time, some of the time, or hardly at all.

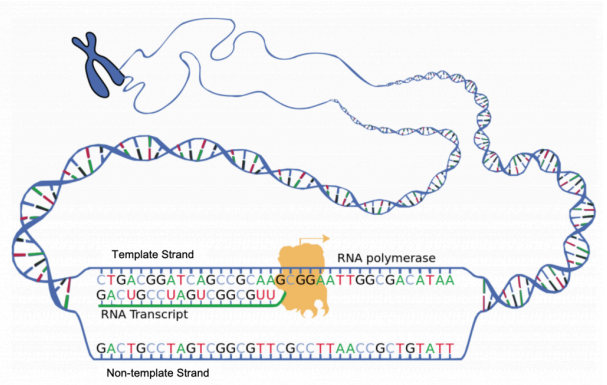

Figure 2: The initiation of transcription begins when DNA is unwound, forming a transcription bubble. Enzymes and other proteins involved in transcription bind at the promoter. Note the base-pairing between the RNA transcript and the template strand of DNA. From: Wikimedia; public domain.

Transcription always proceeds from one of the two DNA strands, which is called the **template strand**. The mRNA product is complementary to the template strand and is almost identical to the other DNA strand, called the **non-template strand**, with the exception that RNA contains a uracil (U) in place of the thymine (T) found in DNA. This means that the base-pairing rules between a DNA molecule and an RNA molecule are:

DNA	RNA
A	U
T	A
C	G
G	C

An enzyme called **RNA polymerase** proceeds along the DNA template adding nucleotides by base pairing with the DNA template in a manner similar to DNA replication.

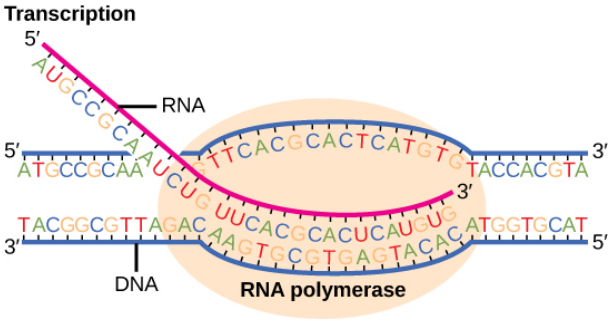

Figure 3: During elongation, RNA polymerase tracks along the DNA template, synthesizes mRNA in the 5′ to 3′ direction, and unwinds then rewinds the DNA as it is read. Again, notice the base-pairing between the template strand of DNA and the newly forming RNA.

Once a gene is transcribed, the RNA polymerase needs to be instructed to dissociate from the DNA template and liberate the newly made mRNA.

In a prokaryotic cell, by the time transcription ends, the transcript

would already have been used to begin making copies of the encoded protein because the processes of transcription and translation can occur at the same time since both occur in the cytoplasm (**Figure 4**). In contrast, transcription and translation cannot occur simultaneously in eukaryotic cells since transcription occurs inside the nucleus and translation occurs outside in the cytoplasm.

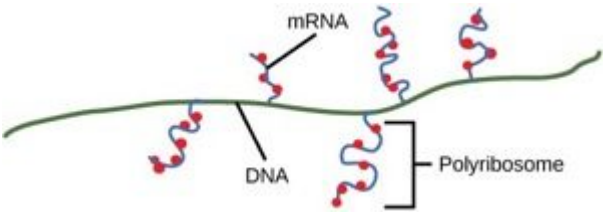

Figure 4: Multiple polymerases can transcribe a single bacterial gene while numerous ribosomes concurrently translate the mRNA transcripts into polypeptides. In this way, a specific protein can rapidly reach a high concentration in the bacterial cell.

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References

OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:TkuNUJis@3/Transcription

40. Eukaryotic RNA Processing

Eukaryotic mRNAs must undergo several processing steps before they can be transferred from the nucleus to the cytoplasm and translated into a protein. The additional steps involved in eukaryotic mRNA maturation create a molecule that is much more stable than a prokaryotic mRNA. Eukaryotic mRNAs typically last for several hours, whereas the typical prokaryotic mRNA lasts no more than five seconds.

The mRNA transcript is coated in **RNA-stabilizing proteins** to prevent it from degrading while it is processed and exported out of the nucleus.

A special nucleotide "cap" is added to one end of the growing transcript, which also helps prevent degradation and helps the cell recognize this molecule as an mRNA that should be translated.

Once transcription is complete, an enzyme adds a string of approximately 200 adenine residues to the end of the mRNA, called the **poly-A tail**. This modification further protects the pre-mRNA from degradation and signals to cellular factors that the transcript needs to be exported to the cytoplasm.

Eukaryotic genes are composed of protein-coding sequences called **exons** (*ex*-on signifies that they are *ex*pressed) and *in*tervening sequences called **introns** (*in*t-ron denotes their *in*tervening role; you can also think of them as *in*terrupting sequences). Introns are removed from the pre-mRNA during processing. Intron sequences in mRNA do not encode amino acids that become part of proteins. It is essential that all of a pre-mRNA's introns be completely and precisely removed before protein synthesis so that the exons join together to code for the correct amino acids. If the process errs by even a single nucleotide, the sequence of the rejoined exons would be shifted, and the resulting

protein would be nonfunctional. The process of removing introns and reconnecting exons is called **splicing** (**Figure 5**). Introns are removed and degraded while the pre-mRNA is still in the nucleus.

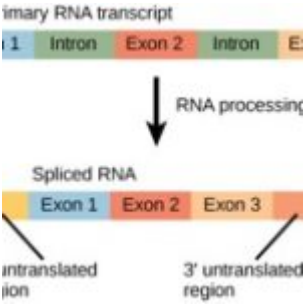

Figure 5: Eukaryotic mRNA contains introns that must be spliced out. A 5′ cap and 3′ tail are also added.

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OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:TkuNUJis@3/Transcription

41. Translation: From RNA to Protein

The synthesis of proteins is one of a cell's most energy-consuming metabolic processes. In turn, proteins account for more mass than any other component of living organisms (with the exception of water), and proteins perform a wide variety of the functions of a cell. The process of translation, or protein synthesis, involves decoding an mRNA message into a polypeptide product. Amino acids are connected together by covalent bonds in lengths ranging from approximately 50 amino acids to more than 1,000.

The Protein Synthesis Machinery

In addition to the mRNA template, many other molecules contribute to the process of translation. However, the general structures and functions of the protein synthesis machinery are comparable from bacteria to human cells. Translation requires the input of an mRNA template, ribosomes, tRNAs, and various enzymatic factors (**Figure 6**).

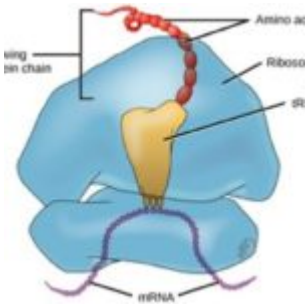

Figure 6: The protein synthesis machinery includes the large and small subunits of the ribosome, mRNA, and tRNA. (credit: modification of work by NIGMS, NIH)

Ribosomes are the part of the cell which reads the information in the mRNA molecule and joins amino acids together in the correct order. In *E. coli*, there are 200,000 ribosomes present in every cell at any given time. A ribosome is a very large, complex macromolecule. Ribosomes are located in the cytoplasm in prokaryotes and in the cytoplasm and endoplasmic reticulum of eukaryotes. Ribosomes are made up of two subunits that come together for translation, rather like a hamburger bun comes together around the meat (the mRNA). The small subunit is responsible for binding the mRNA template, whereas the large subunit sequentially binds **tRNAs**, a type of RNA molecule that brings amino acids to the growing chain of the polypeptide. Each mRNA molecule can be simultaneously translated by many ribosomes, all synthesizing protein in the same direction.

Depending on the species, 40 to 60 types of **tRNA** exist in the cytoplasm. Serving as adaptors, specific tRNAs bind to sequences on the mRNA template and add the corresponding amino acid to the polypeptide chain. Therefore, tRNAs are the molecules that actually "translate" the language of RNA into the language of proteins. For each tRNA to function, it must have its specific amino acid bonded to it. In the process of tRNA "charging," each tRNA molecule is bonded to its correct amino acid.

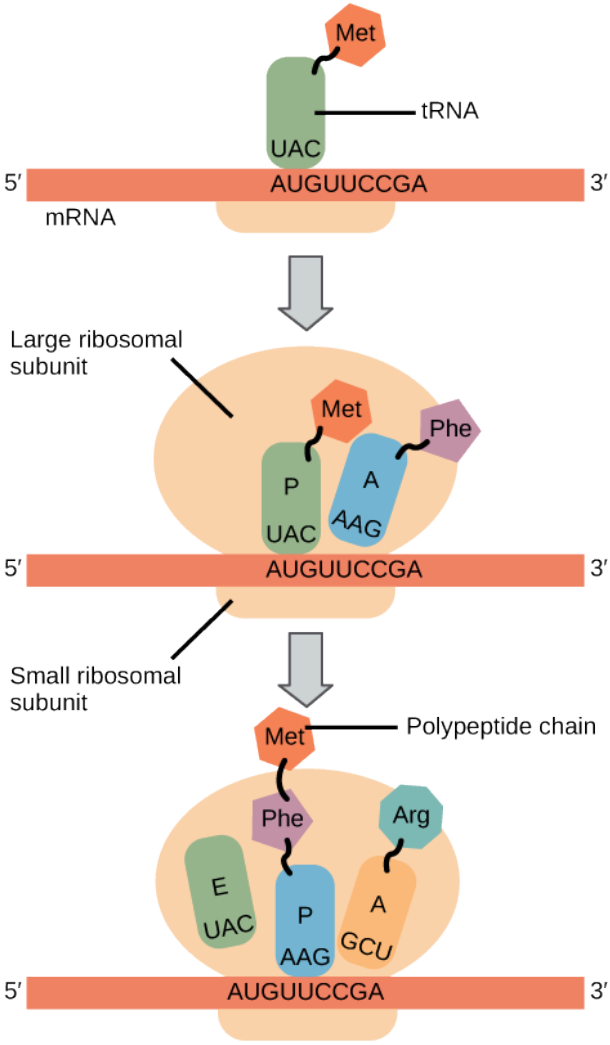

Figure 7: Translation begins when a tRNA anticodon recognizes a codon on the mRNA. The large ribosomal subunit joins the small subunit, and a second tRNA is recruited. As the mRNA moves relative to the ribosome, the polypeptide chain is formed. Entry of a release factor into the A site terminates translation and the components dissociate.

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References

OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:FUH9XUkW@6/Translation

42. The Genetic Code

To summarize what we know to this point, the cellular process of transcription generates messenger RNA (mRNA), a mobile molecular copy of one or more genes with an alphabet of A, C, G, and uracil (U). Translation of the mRNA template converts nucleotide-based genetic information into a protein product. Protein sequences consist of 20 commonly occurring amino acids; therefore, it can be said that the protein alphabet consists of 20 letters. Each amino acid is defined by a three-nucleotide sequence called the triplet **codon**. The relationship between a nucleotide codon and its corresponding amino acid is called the **genetic code**.

Given the different numbers of "letters" in the mRNA and protein "alphabets," combinations of nucleotides corresponded to single amino acids. Using a three-nucleotide code means that there are a total of 64 (4 × 4 × 4) possible combinations; therefore, a given amino acid is encoded by more than one nucleotide triplet (**Figure 8**).

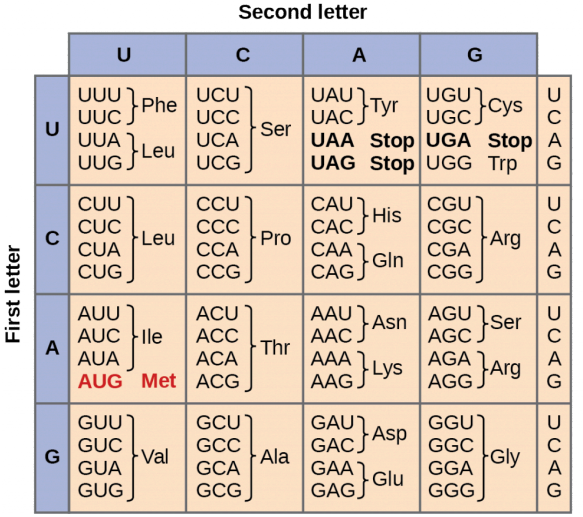


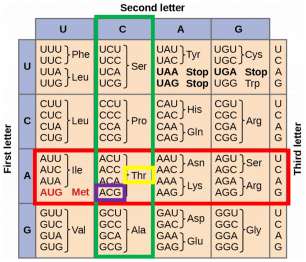
Figure 8: This figure shows the genetic code for translating each nucleotide triplet, or codon, in mRNA into an amino acid or a termination signal in a nascent protein. (credit: modification of work by NIH)

Three of the 64 codons terminate protein synthesis and release the polypeptide from the translation machinery. These triplets are called **stop codons**. Another codon, AUG, also has a special function. In addition to specifying the amino acid methionine, it also serves as the **start codon** to initiate translation. The reading frame for translation is set by the AUG start codon near the 5′ end of the mRNA. The genetic code is universal. With a few exceptions, virtually all species use the same genetic code for protein synthesis, which is powerful evidence that all life on Earth shares a common origin.

Using the Codon Table

Codon tables, such as the one in Figure 8, give the amino acids that are coded for by **mRNA** codons, not DNA codons. If you are given a DNA sequence, you must first transcribe it to produce the mRNA, then you can translate it into an amino acid sequence using the codon table.

Figure 9 shows two different codon tables: one square, and one round. Both convey the same information. This example shows how to use both tables to determine the amino acid coded for by the DNA sequence TGC. After transcription, the mRNA produced would have the sequence ACG. To use the square table, you begin with the first base (A), which shown in red. Then, you identify the second base (C), which is shown in green. In the box where the first and second bases intersect, you find the third base (G), which is shown in purple. This identifies the amino acid coded for by the mRNA codon ACG as Thr (the three-letter abbreviation for the amino acid threonine). To use the round table, start in the center with the first base (A), circled in red. Move outward to the second base (C), circled in green. Another step outward to the third base (G), which is circled in purple. This again identifies the amino acid coded for by the mRNA codon ACG as Threonine (abbreviated Thr or T).



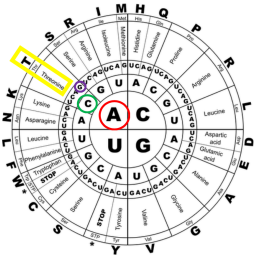


Figure 9 Using the codon table. Square codon table is a modification of work from the NIH and is in the Public Domain. Round codon table is also Public Domain.

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OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:FUH9XUkW@6/Translation

43. Prokaryotic versus Eukaryotic Gene Expression

To understand how gene expression is regulated, we must first understand how a gene becomes a functional protein in a cell. The process occurs in both prokaryotic and eukaryotic cells, just in slightly different fashions.

Because prokaryotic organisms lack a cell nucleus, the processes of transcription and translation occur almost simultaneously. When the protein is no longer needed, transcription stops. As a result, the primary method to control what type and how much protein is expressed in a prokaryotic cell is through the regulation of DNA transcription into RNA. All the subsequent steps happen automatically. When more protein is required, more transcription occurs. Therefore, in prokaryotic cells, the control of gene expression is almost entirely at the transcriptional level.

Eukaryotic cells, in contrast, have intracellular organelles and are much more complex. Recall that in eukaryotic cells, the DNA is contained inside the cell's nucleus and it is transcribed into mRNA there. The newly synthesized mRNA is then transported out of the nucleus into the cytoplasm, where ribosomes translate the mRNA into protein. The processes of transcription and translation are physically separated by the nuclear membrane; transcription occurs only within the nucleus, and translation only occurs outside the nucleus in the cytoplasm. The regulation of gene expression can occur at all stages of the process (**Figure 2**):

- Epigenetic level: regulates how tightly the DNA is wound around histone proteins to package it into chromosomes
- Transcriptional level: regulates how much transcription takes place
- Post-transcriptional level: regulates aspects of RNA processing

(such as splicing) and transport out of the nucleus

- Translational level: regulates how much of the RNA is translated into protein
- Post-translational level: regulates how long the protein lasts after it has been made and whether the protein is processed into an active form

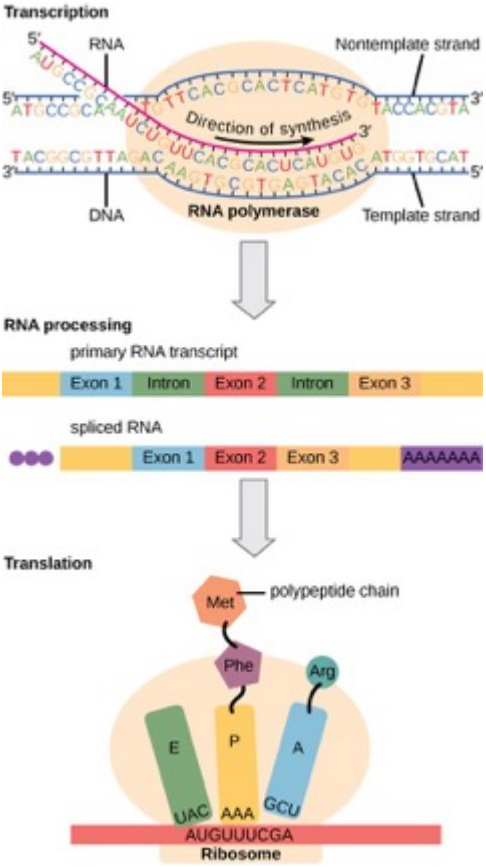

Figure 2: Eukaryotic gene expression is regulated during transcription and RNA processing, which take place in the nucleus, as well as during protein translation, which takes place in the cytoplasm. Further regulation may occur through post-translational modifications of proteins.

The differences in the regulation of gene expression between prokaryotes and eukaryotes are summarized in **Table 1**.

Table 1: Differences in the Regulation of Gene Expression of Prokaryotic and Eukaryotic Organisms

Prokaryotic organisms	Eukaryotic organisms
Lack nucleus	Contain nucleus
RNA transcription and protein translation occur almost simultaneously	RNA transcription occurs prior to protein translation, and it takes place in the nucleus. RNA translation to protein occurs in the cytoplasm. RNA post-processing includes addition of a 5′ cap, poly-A tail, and excision of introns and splicing of exons.
Gene expression is regulated primarily at the transcriptional level	Gene expression is regulated at many levels (epigenetic, transcriptional, post-transcriptional, translational, and posttranslational)

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OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

44. Gene Regulation

Each cell expresses, or turns on, only a fraction of its genes. "Expresses" or "turns on" means that protein is being produced from that gene. The rest of the genes are repressed, or turned off (no protein is being produced from those genes). The process of turning genes on and off is known as **gene regulation**. Gene regulation is an important part of normal development. Genes are turned on and off in different patterns during development to make a brain cell look and act different from a liver cell or a muscle cell, for example. Gene regulation also allows cells to react quickly to changes in their environments. Although we know that the regulation of genes is critical for life, this complex process is not yet fully understood.

For a cell to function properly, necessary proteins must be synthesized at the proper time. All organisms and cells control or regulate the transcription and translation of their DNA into protein. The process of turning on a gene to produce RNA and protein is called **gene expression**. Whether in a simple unicellular organism or in a complex multicellular organism, each cell controls when and how its genes are expressed. For this to occur, there must be a mechanism to control when a gene is expressed to make RNA and protein, how much of the protein is made, and when it is time to stop making that protein because it is no longer needed.

Cells in multicellular organisms are specialized; cells in different tissues look very different and perform different functions. For example, a muscle cell is very different from a liver cell, which is very different from a skin cell. These differences are a consequence of the expression of different sets of genes in each of these cells. All cells have certain basic functions they must perform for themselves, such as converting the energy in sugar molecules into energy in ATP. Therefore, there is a set of "housekeeping" genes that are expressed in all cells. Each type of cell also has many genes that are not expressed because the cell does not need to perform those

functions. Specific cells also express many genes that are not expressed by other cells so that they can carry out their specialized functions. In addition, cells will turn on or off certain genes at different times in response to changes in the environment or at different times during the development of the organism. Unicellular organisms, both eukaryotic and prokaryotic, also turn on and off genes in response to the demands of their environment so that they can respond to special conditions.

Figure 1 The unique color pattern of this cat's fur is caused by either the orange or the black allele of a gene being randomly silenced (turned off).

The control of gene expression is extremely complex. Malfunctions in this process are detrimental to the cell and can lead to the development of many diseases, including cancer.

Epigenetic Regulation

DNA modifications that do not change the DNA sequence can affect gene activity. Chemical compounds that are added to single genes can regulate their activity; these modifications are known as **epigenetic** changes. The **epigenome** comprises all of the chemical compounds that have been added to the entirety of one's DNA (genome) as a way to regulate the activity (expression) of all the genes within the genome. The chemical compounds of the epigenome are not part of the DNA sequence, but are on or attached to DNA ("epi-" means above in Greek). Epigenomic modifications remain as cells divide and in some cases can be inherited through the generations. Environmental influences, such as a person's diet and exposure to pollutants, can also impact the epigenome.

Epigenetic changes can help determine whether genes are turned on or off and can influence the production of proteins in certain cells, ensuring that only necessary proteins are produced. For example, proteins that promote bone growth are not produced in muscle cells. Patterns of epigenome modification vary among individuals, different tissues within an individual, and even different cells.

The human genome encodes over 20,000 genes, which means that each of the 23 pairs of human chromosomes contains thousands of genes. The DNA in the nucleus of each cell is precisely wound, folded, and compacted into chromosomes so that it will fit inside the nuclear membrane. It is also organized so that specific segments can be accessed as needed by a specific cell type.

The first level of organization, or packing, is the winding of DNA strands around **histone** proteins. Histones package and order DNA into structural units called **nucleosome** complexes, which can control the access of proteins to the DNA regions (Figure 1**a**). Under the electron microscope, this winding of DNA around histone

proteins to form nucleosomes looks like small beads on a string (Figure 1**b**). These beads (histone proteins) can move along the string (DNA) and change the structure of the molecule.

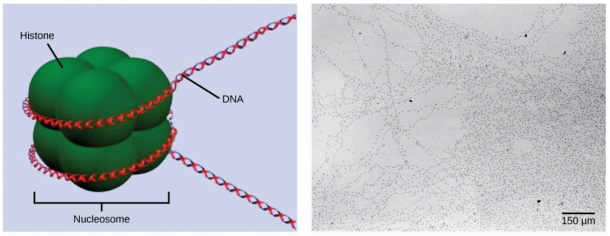


Figure 1 *DNA is folded around histone proteins to create (a) nucleosome complexes. These nucleosomes control the access of proteins to the underlying DNA. When viewed through an electron microscope (b), the nucleosomes look like beads on a string. (credit "micrograph": modification of work by Chris Woodcock)*

If DNA encoding a specific gene is to be transcribed into RNA, the nucleosomes surrounding that region of DNA can slide down the DNA to open that specific chromosomal region and allow for the transcriptional machinery (RNA polymerase) to initiate transcription. Nucleosomes can move to open the chromosome structure to expose a segment of DNA, but do so in a very controlled manner.

Active open regions of chromatin are called **euchromatin (Figure 2).** Regions of the genome that are transcriptionally active are typically euchromatic. Tightly wound regions of chromatin are called **heterochromatin.** Heterochromatic regions of the genome are typically silenced and transcriptionally inactive.

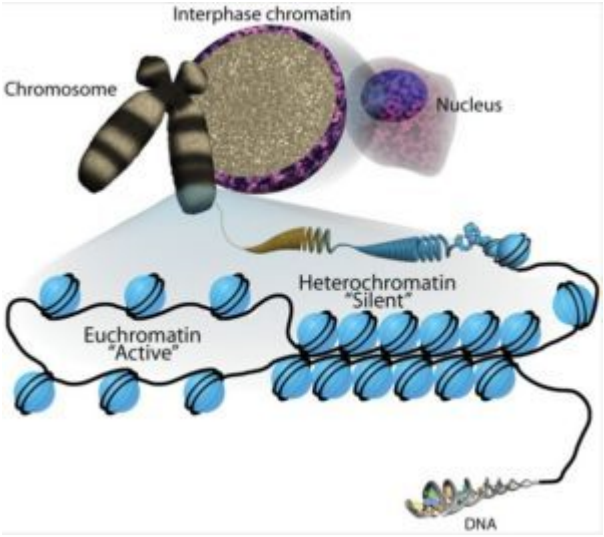


Figure 2 *The difference in chromatin packaging between an active (euchromatic) and inactive (heterochromatic) region of DNA.*

Modifications to DNA and histones

How the histone proteins move, and whether the DNA is wrapped loosely or tightly around them, is dependent on signals found on both the histone proteins and on the DNA. These signals are chemical tags added to histone proteins and DNA that tell the histones if a chromosomal region should be open or closed. These tags are not permanent, but may be added or removed as needed. They are chemical modifications (phosphate, methyl, or acetyl groups) that are attached to specific amino acids in the protein or to the nucleotides of the DNA. The tags do not alter the DNA base sequence, but they do alter how tightly wound the DNA is around the histone proteins.

This type of gene regulation is called epigenetic regulation. Epigenetic means "around or above genetics." The changes that occur to the histone proteins and DNA do not alter the nucleotide sequence and are not permanent. Instead, these changes are temporary, although they can and often do persist through multiple rounds of cell division. They alter the chromosomal structure (open euchromatin or closed heterochromatin) as needed, but do not change the sequence of bases within the DNA.

A gene can be turned on or off depending upon the location and modifications to the histone proteins and DNA. If a gene is to be transcribed, the histone proteins and DNA are modified surrounding the chromosomal region encoding that gene. This opens the chromosomal region (it becomes euchromatic) to allow access for RNA polymerase and other proteins, called transcription factors, to bind to the promoter region, located just upstream of the gene, and initiate transcription. If a gene is to remain turned off, or silenced, the histone proteins and DNA have different modifications that signal a closed chromosomal configuration. In this closed configuration (heterochromatin), the RNA polymerase and

transcription factors do not have access to the DNA and transcription cannot occur (Figure 2).

DNA Methylation

A common type of epigenomic modification is called **methylation.**Methylation involves attaching small molecules called methyl groups, each consisting of one carbon atom and three hydrogen atoms, to DNA nucleotides or the amino acids that make up the histone proteins.

When DNA is methylated, the methyl group is typically added to cytosine nucleotides. This occurs within very specific regions called CpG islands. These are stretches with a high frequency of cytosine and guanine dinucleotide DNA pairs (CG) found in the promoter regions of genes. When this configuration exists, the cytosine member of the pair can be methylated (a methyl group is added). This modification changes how the DNA interacts with proteins, including the histone proteins that control access to the region. When methyl groups are added to a particular gene, that gene is turned off or silenced, and no protein is produced from that gene (Figure 3).

"Histone Code" Hypothesis

The **histone code hypothesis**is the hypothesis that transcription of a gene is in part regulated by modifications made to histone proteins, primarily on their somewhat floppy ends (their "tails"). Many of the histone tail modifications correlate very well to chromatin structure and both histone modification state and chromatin structure correlate well to gene expression levels. The most important concept in the histone code hypothesis is that the

histone modifications serve to recruit other proteins by specific recognition of the modified histone, rather than through simply stabilizing or destabilizing the interaction between histone and the underlying DNA. These recruited proteins then act to alter chromatin structure actively or to promote transcription.

The histone code has the potential to be massively complex. There are at least 20 modifications that are made to histone tails that have been relatively well characterized, and there is the potential for many more that we have not discovered. Each histone can be modified on multiple amino acids, with multiple different chemical modifications. The information that can be stored in the histone code dwarfs the amount that is stored in the order of the bases in the human genome.

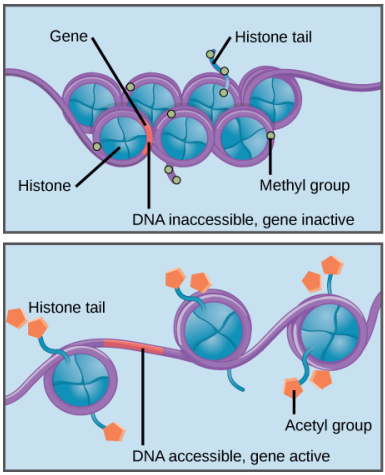
Histone Methlyation

A portion of the histone protein known as the histone tail can have methyl groups (CH_3) added to it. This is the same modification that is made to cytosine nucleotides in DNA. The specific amino acid in the histone tail that gets methylated is very important for determining whether it will tighten or loosen chromatin structure. Modification to several amino acids in the tail is correlated with euchromatin and active transcription, while modification to other amino acids is correlated with heterochromatin and gene silencing. You should know that histones can be methylated, but we can't use histone methylation as a predictor for euchromatin or heterochromatin.

Histone Acetylation

Histone tails can also be modified by the addition of an acetyl group

(this process is known as acetylation). If you remember from cellular respiration, an acetyl group (such as that found in acetyl-CoA) is a 2-carbon molecule. When histone tails are acetylated, this typically causes the tails to loosen from around the DNA, allowing the chromatin to loosen (Figure 3).



Methylation of DNA and histones causes nucleosomes to pack tightly together. Transcription factors cannot bind the DNA, and genes are not expressed.

Histone acetylation results in loose packing of nucleosomes. Transcription factors can bind the DNA and genes are expressed.

Figure 3 Nucleosomes can slide along DNA. When nucleosomes are spaced closely together (top), transcription factors cannot bind and gene expression is turned off. When the nucleosomes are spaced far apart (bottom), the DNA is exposed. Transcription factors can bind, allowing gene expression to occur. Modifications to the histones and DNA affect nucleosome spacing.

Other modifications

There are many other modifications that can be made to histone proteins in addition to methylation and acetylation. Histone tails can be phosphorylated or ubiquitinated (where a small protein called ubiquitin is attached). Histone phosphorylation seems to be related to DNA repair. Ubiquitination has been shown to be associated with both transcriptional activation or inactivation, depending on the specific location.

Epigenetic Changes

Because errors in the epigenetic process, such as modifying the wrong gene or failing to add a compound to a gene, can lead to abnormal gene activity or inactivity, they can cause genetic disorders. Conditions including cancers, metabolic disorders, and degenerative disorders have all been found to be related to epigenetic errors.

Cancerous cells often have regions of DNA that show different levels of methylation compared to normal cells. Some genes are methylated and silenced in cancerous cells, while they are unmethylated and active in normal cells. Other genes are active in cancerous cells, but inactive in normal cells. Each specific cancer in each specific individual can show different patterns of methylation, although there are similarities between many different types of cancer.

Scientists continue to explore the relationship between the genome and the chemical compounds that modify it. In particular, they are studying what effect the modifications have on gene function, protein production, and human health.

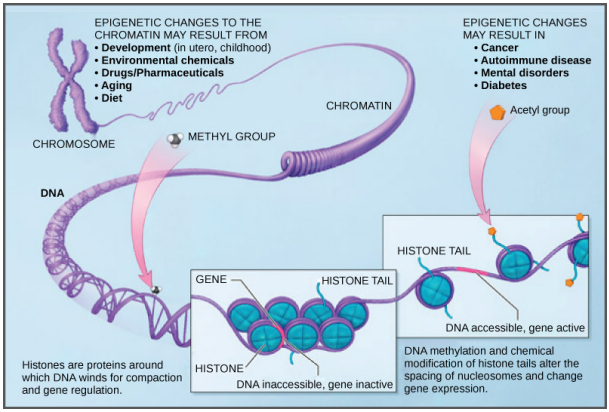


Figure 4 Histone proteins and DNA nucleotides can be modified chemically. Modifications affect nucleosome spacing and gene expression. (credit: modification of work by NIH)

Transcriptional Regulation

Gene expression can be regulated at the transcriptional level. This means that the process of transcription can be turned on or off. In both prokaryotic and eukaryotic cells, transcription requires RNA polymerase to bind to a sequence upstream of a gene to initiate transcription. Prokaryotes almost always regulate gene expression at the transcriptional level.

In eukaryotes, the eukaryotic RNA polymerase requires other proteins, or transcription factors, to facilitate transcription initiation. Transcription factors are proteins that bind to the promoter sequence and other regulatory sequences to control the transcription of the target gene. RNA polymerase by itself cannot initiate transcription in eukaryotic cells. Transcription factors must bind to the promoter region first and recruit RNA polymerase to the site for transcription to be established.

- If transcription factors are not allowed to bind, transcription can not take place, which means gene expression is turned off.

- In some eukaryotic genes, there are regions that help increase or enhance transcription called enhancers. When transcription factors bind to these enhancer regions, they can increase rates of transcription, which means gene expression is turned up.
- Transcriptional repressors can bind to promoter or enhancer regions and block transcription. This means that gene expression is turned off.

Post-transcriptional Regulation

After RNA is transcribed, it must be processed into a mature form before translation can begin. This processing after an RNA molecule has been transcribed, but before it is translated into a protein, is called post-transcriptional modification. As with the epigenetic and transcriptional stages of processing, this post-transcriptional step can also be regulated to control gene expression in the cell. If the RNA is not processed, shuttled, or translated, then no protein will be synthesized.

Alternative RNA Splicing

In the 1970s, genes were first observed that exhibited **alternative RNA splicing**. Alternative RNA splicing is a mechanism that allows different protein products to be produced from one gene when different combinations of introns (and sometimes exons) are removed from the transcript (**Figure 1**). This alternative splicing can be haphazard, but more often it is controlled and acts as a mechanism of gene regulation, with the frequency of different splicing alternatives controlled by the cell as a way to control the production of different protein products in different cells, or at different stages of development. Alternative splicing is now

understood to be a common mechanism of gene regulation in eukaryotes; according to one estimate, 70% of genes in humans are expressed as multiple proteins through alternative splicing.

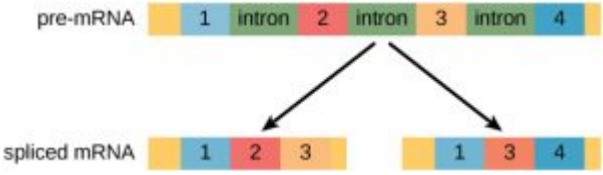


Figure 1 Pre-mRNA can be alternatively spliced to create different proteins.

How could alternative splicing evolve? Introns have a beginning and ending recognition sequence, and it is easy to imagine the failure of the splicing mechanism to identify the end of an intron and find the end of the next intron, thus removing two introns and the intervening exon. In fact, there are mechanisms in place to prevent such exon skipping, but mutations are likely to lead to their failure. Such "mistakes" would more than likely produce a nonfunctional protein. Indeed, the cause of many genetic diseases is alternative splicing rather than mutations in a sequence. However, alternative splicing would create a protein variant without the loss of the original protein, opening up possibilities for adaptation of the new variant to new functions. Gene duplication has played an important role in the evolution of new functions in a similar way—by providing genes that may evolve without eliminating the original functional protein.

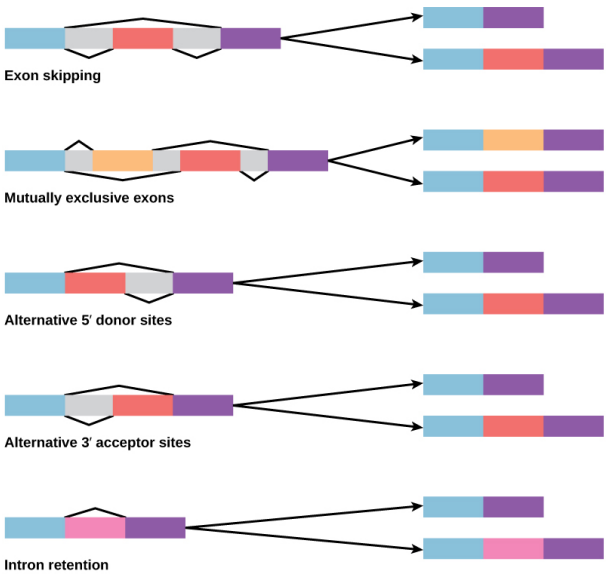


Figure 2 There are five basic modes of alternative splicing.

Control of RNA Stability

Before the mRNA leaves the nucleus, it is given two protective "caps" that prevent the end of the strand from degrading during its journey. The 5′ cap, which is placed on the 5′ end of the mRNA, is usually composed of a methylated guanosine triphosphate molecule (GTP). The poly-A tail, which is attached to the 3′ end, is usually composed of a series of adenine nucleotides. Once the RNA is transported to the cytoplasm, the length of time that the RNA remains there can be controlled. Each RNA molecule has a defined lifespan and decays at a specific rate. This rate of decay can influence how much protein is in the cell. If the RNA decays more rapidly, translation has less time to occur, so less protein will be produced. Conversely, if RNA decays less rapidly, more protein will be produced. This rate of decay is referred to as the RNA stability. If the RNA is stable, it will be detected for longer periods of time in the

cytoplasm. Binding of proteins to the RNA can influence its stability (Figure 3).

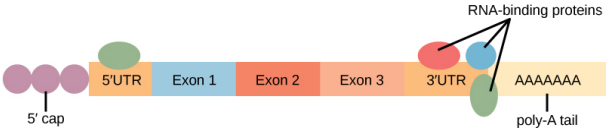


Figure 3 The protein-coding region of mRNA is flanked by 5′ and 3′ untranslated regions (UTRs). The presence of RNA-binding proteins at the 5′ or 3′ UTR influences the stability of the RNA molecule.

Translational Regulation

Like transcription, translation is controlled by proteins that bind and initiate the process. In translation, the complex that assembles to start the process is referred to as the initiation complex. Regulation of the formation of this complex can increase or decrease rates of translation.

Post-translational Regulation

Proteins can be chemically modified with the addition of groups including methyl, phosphate, acetyl, and ubiquitin groups. The addition or removal of these groups from proteins regulates their activity or the length of time they exist in the cell. Sometimes these

modifications can regulate where a protein is found in the cell—for example, in the nucleus, the cytoplasm, or attached to the plasma membrane.

Chemical modifications occur in response to external stimuli such as stress, the lack of nutrients, heat, or ultraviolet light exposure. These changes can alter epigenetic accessibility, transcription, mRNA stability, or translation—all resulting in changes in expression of various genes. This is an efficient way for the cell to rapidly change the levels of specific proteins in response to the environment. Because proteins are involved in every stage of gene regulation, the phosphorylation of a protein (depending on the protein that is modified) can alter accessibility to the chromosome, can alter translation (by altering transcription factor binding or function), can change nuclear shuttling (by influencing modifications to the nuclear pore complex), can alter RNA stability (by binding or not binding to the RNA to regulate its stability), can modify translation (increase or decrease), or can change post-translational modifications (add or remove phosphates or other chemical modifications).

The addition of an ubiquitin group to a protein marks that protein for degradation. Ubiquitin acts like a flag indicating that the protein lifespan is complete. These proteins are moved to the proteasome, an organelle that functions to remove proteins, to be degraded (Figure 2). One way to control gene expression, therefore, is to alter the longevity of the protein.

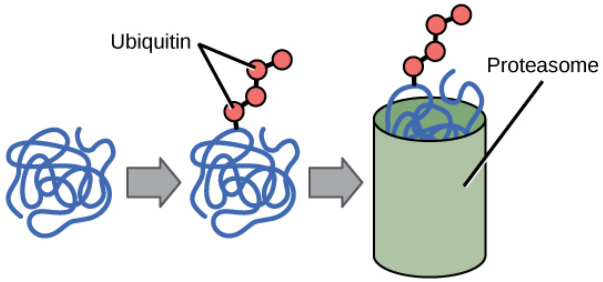


Figure 4 Proteins with ubiquitin tags are marked for degradation within the proteasome.

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PART VIII

MUTATIONS

Learning Objectives

By the end of this section, you will be able to:

- Describe how mutations affect protein synthesis and its products.

In both prokaryotes and eukaryotes, the major purpose of DNA is to provide the information needed to construct the **proteins** necessary for the cell can perform all of its functions. Proteins are large, complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs.

The information to make proteins is stored in an organism's DNA. Each protein is coded for by a specific section of DNA called a **gene.** A gene is the section of DNA required to produce one protein. Genes are typically hundreds or thousands of base pairs in length because they code for proteins made of hundreds or thousands of amino acids.

A gene **mutation** is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

Since the DNA sequence found within a gene controls protein synthesis. If the DNA sequence is altered, this can alter the amino

acid sequence within a protein. This can have a variety of potential effects, which will be discussed in this chapter.

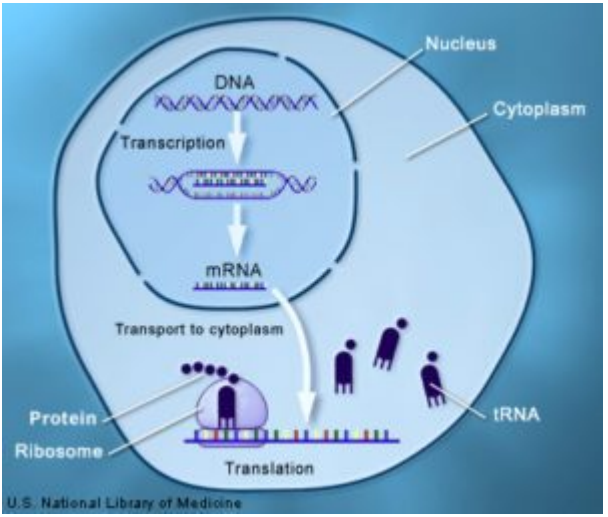
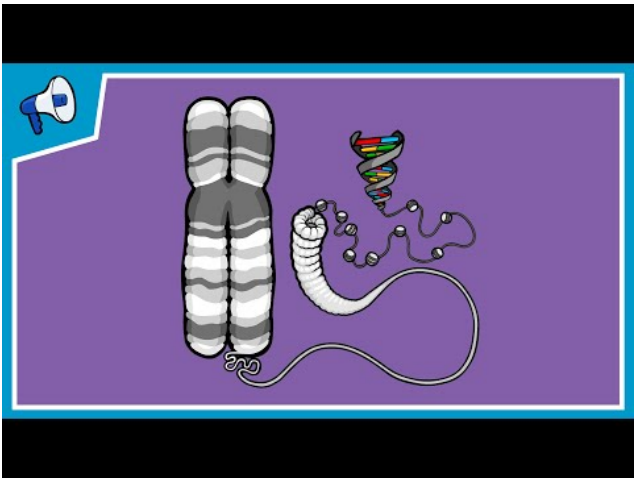


Figure 1 The process of protein synthesis first creates an mRNA copy of a DNA sequence during the process of transcription . This mRNA is translated into a sequence of amino acids by the ribosome. In this way, the information encoded in the sequence of bases in the DNA making up a gene is used to produce a protein.



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45. Review of Protein Synthesis

In order to understand the potential effect of mutations, we must first recall how the information in DNA is used to produce a protein. Each protein is coded for by a gene, which is typically hundreds or thousands of base pairs in length. The information in the gene specifies the order in which the amino acids will be assembled into the protein.

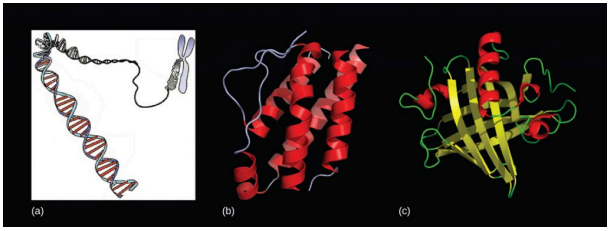

Figure 1 Genes, which are carried on (a) chromosomes, are linearly organized instructions for making the RNA and protein molecules that are necessary for all of processes of life. The (b) interleukin-2 protein and (c) alpha-2u-globulin protein are just two examples of the array of different molecular structures that are encoded by genes. (credit "chromosome: National Human Genome Research Institute; credit "interleukin-2": Ramin Herati/ Created from PDB 1M47 and rendered with Pymol; credit "alpha-2u-globulin": Darren Logan/

rendered with AISMIG) The journey from gene to protein is complex and tightly controlled within each cell. It consists of two major steps: **transcription** and **translation.**Together, transcription and translation are known as **gene expression**.

Transcription

During the process of **transcription,** the information stored in a gene's DNA is used as a blueprint to produce a similar molecule called RNA (ribonucleic acid) in the cell nucleus. Both RNA and DNA are made up of a chain of nucleotide bases, but they have slightly different chemical properties (Figure 2).

- Both RNA and DNA contain a 5-carbon sugar, but the sugar differs: it is deoxyribose in DNA and ribose in RNA (DNA stands for deoxyribonucleic acid; RNA stands for ribonucleic acid).
- DNA and RNA also differ in the nitrogenous bases they contain. DNA contains A, T, C, and G. RNA contains A, C, and G, but no thymine. Instead it contains a base called uracil (U).
- DNA is almost always double-stranded (a double helix), while RNA is typically single stranded.

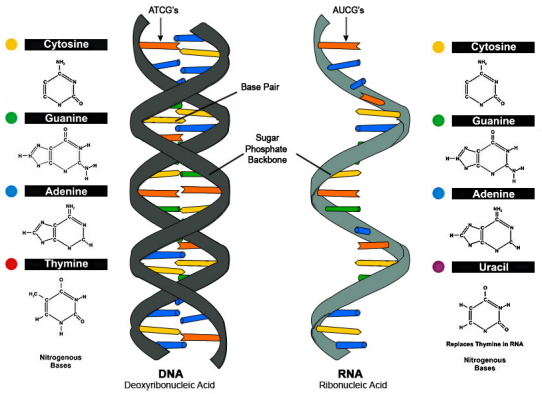

Figure 2 DNA vs RNA. Photo credit Zappys Technology Solution; Flickr.

The type of RNA that contains the information for making a protein is called messenger RNA (mRNA) because it carries the information, or message, from the DNA out of the nucleus into the cytoplasm. During transcription, this mRNA copy is made from a DNA molecule. This is possible because of the base-pairing rules: A with T (or U) and C with G. The hydrogen bonds connecting the base pairs in a DNA molecule are broken, and an enzyme creates a chain of RNA nucleotides that correspond to the DNA sequence.

In eukaryotes, transcription occurs in the nucleus (because that's where the DNA is). In prokaryotes, transcription occurs in the cytoplasm because there is no nucleus.

RNA Processing

After prokaryotes produce an mRNA, it can be immediately translated since both processes occur in the cytoplasm. In fact, transcription and translation can occur at the same time – as an mRNA is being transcribed, it can also begin to be translated.

Eukaryotes require a more complex process since the mRNA must move from the nucleus to the cytoplasm. Additionally, eukaryotic mRNAs are typically modified in several different ways: portions of the mRNA that do not code for amino acids are removed ("spliced" out), and the 5′ and 3′ ends are modified to help with recognition and mRNA stability. After these modifications are made, the mature mRNA is transported to the cytoplasm.

Translation

Translation, the second step in getting from a gene to a protein, takes place in the cytoplasm. The mRNA interacts with a specialized complex called a **ribosome,** which "reads" the sequence of mRNA bases. In conjunction with a type of RNA called transfer RNA (tRNA), the protein is assembled according to the instructions in the mRNA molecule. Each sequence of three bases in the mRNA, called a **codon,** usually codes for one particular amino acid. Remember that amino acids are the building blocks of proteins. Protein assembly continues until the ribosome encounters a "stop" codon (a sequence of three bases that does not code for an amino acid).

Recall that ribosomes are located in two different places in eukaryotic cells: free-floating in the cytoplasm and attached to the rough endoplasmic reticulum. The final destination of the protein determines where it will be synthesized.

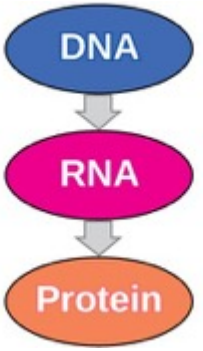

Figure 3:*The Central Dogma – DNA is used to make RNA is used to make protein*

The flow of information from DNA to RNA to proteins is one of the fundamental principles of molecular biology. It is so important that it is sometimes called the "central dogma" (Figures 3 and 4).

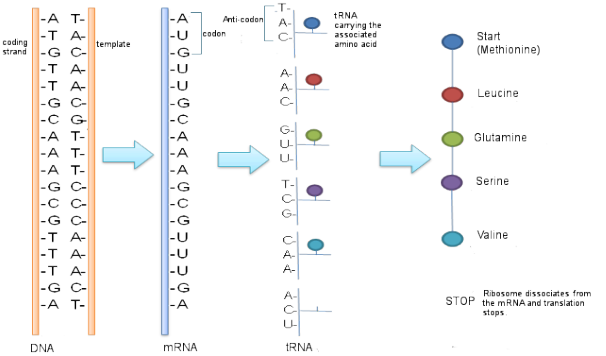

Figure 4: More detail on the central dogma. ("Overview of Protein Synthesis" by Becky Boone is licensed under CC BY-SA 2.0)

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References

46. How Mutations Occur

A gene **mutation** is a permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people. Mutations range in size; they can affect anywhere from a single DNA building block (base pair) to a large segment of a chromosome that includes multiple genes.

Recall that the DNA sequence found within a gene controls protein synthesis. If the DNA sequence is altered, this can alter the amino acid sequence within a protein.

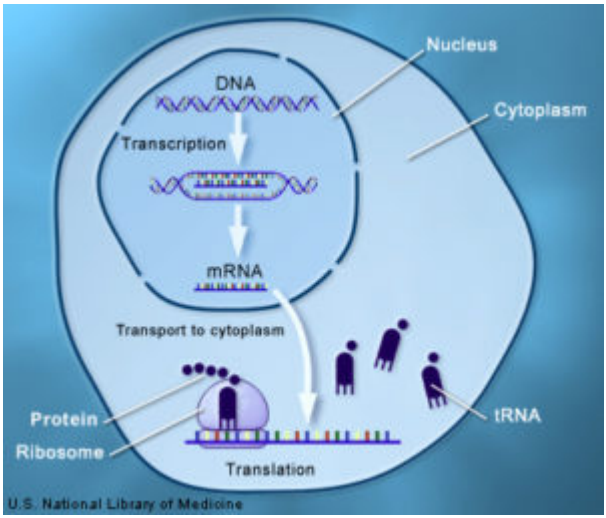

Figure : The process of protein synthesis first creates an mRNA copy of a DNA sequence during the process of transcription . This mRNA is translated into a sequence of amino acids by the ribosome. In this way, the information encoded in the sequence of bases in the DNA making up a gene is used to produce a protein.

Gene mutations can be classified in two major ways:

- **Hereditary mutations** are inherited from a parent and are present throughout a person's life in virtually every cell in the body. These mutations are also called germline mutations because they are present in the parent's egg or sperm cells, which are also called germ cells. When an egg and a sperm cell unite, the resulting fertilized egg cell receives DNA from both parents. If this DNA has a mutation, the child that grows from the fertilized egg will have the mutation in each of his or her cells.
- **Acquired (or somatic) mutations** occur at some time during a person's life and are present only in certain cells, not in every cell in the body. These changes can be caused by environmental factors such as ultraviolet radiation from the sun, or can occur if a mistake is made as DNA copies itself during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed on to the next generation.

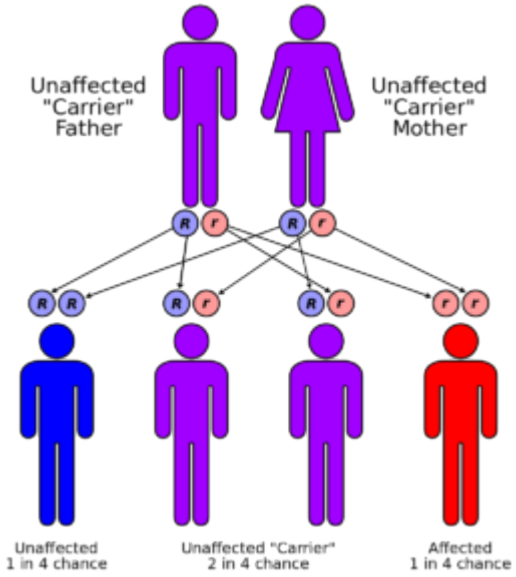

Figure: The red individual has inherited two mutated alleles of a gene from their parents. This is an example of a hereditary mutation.

Genetic changes that are described as ***de novo* (new) mutations** can be either hereditary or somatic. In some cases, the mutation occurs in a person's egg or sperm cell but is not present in any of the person's other cells. In other cases, the mutation occurs in the fertilized egg shortly after the egg and sperm cells unite. It is often impossible to tell exactly when a de novo mutation happened. As the fertilized egg divides, each resulting cell in the growing embryo will have the mutation. *De novo* mutations may explain genetic disorders in which an affected child has a mutation in every cell in the body but the parents do not, and there is no family history of the disorder.

Somatic mutations that happen in a single cell early in embryonic development can lead to a situation called mosaicism. These genetic changes are not present in a parent's egg or sperm cells, or in the fertilized egg, but happen a bit later when the embryo includes several cells. As all the cells divide during growth and development, cells that arise from the cell with the altered gene will have the

mutation, while other cells will not. Depending on the mutation and how many cells are affected, mosaicism may or may not cause health problems.

Most disease-causing gene mutations are uncommon in the general population. However, other genetic changes occur more frequently. Genetic alterations that occur in more than 1 percent of the population are called **polymorphisms**. They are common enough to be considered a normal variation in the DNA. Polymorphisms are responsible for many of the normal differences between people such as eye color, hair color, and blood type. Although many polymorphisms have no negative effects on a person's health, some of these variations may influence the risk of developing certain disorders.

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47. Genetic disorders

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. Sometimes, gene mutations prevent one or more of these proteins from working properly. By changing a gene's instructions for making a protein, a mutation can cause the protein to malfunction or to be missing entirely. When a mutation alters a protein that plays a critical role in the body, it can disrupt normal development or cause a medical condition. A condition caused by mutations in one or more genes is called a **genetic disorder**.

In some cases, gene mutations are so severe that they prevent an embryo from surviving until birth. These changes occur in genes that are essential for development, and often disrupt the development of an embryo in its earliest stages. Because these mutations have very serious effects, they are incompatible with life.

It is important to note that genes themselves do not cause disease—genetic disorders are caused by mutations that make a gene function improperly. For example, when people say that someone has "the cystic fibrosis gene," they are usually referring to a mutated version of the *CFTR* gene, which causes the disease. All people, including those without cystic fibrosis, have a version of the *CFTR* gene. These different versions of a gene are called **alleles.** Someone who has cystic fibrosis will have alleles of the CFTR gene that contain mutations which lead to the genetic disorder. Someone who does not have cystic fibrosis will have alleles of the CFTR gene that do not contain mutations.

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References

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48. Do all gene mutations affect health and development?

No; only a small percentage of mutations cause genetic disorders—most have no impact on health or development. For example, some mutations alter a gene's DNA sequence but do not change the function of the protein made by the gene.

Often, gene mutations that could cause a genetic disorder are repaired by certain enzymes before the gene is expressed and an altered protein is produced.

Each cell has a number of pathways through which enzymes recognize and repair mistakes in DNA. Because DNA can be damaged or mutated in many ways, DNA repair is an important process by which the body protects itself from disease.

A very small percentage of all mutations actually have a positive effect. These mutations lead to new versions of proteins that help an individual better adapt to changes in his or her environment. For example, a beneficial mutation could result in a protein that protects an individual and future generations from a new strain of bacteria.

Because a person's genetic code can have a large number of mutations with no effect on health, diagnosing genetic conditions can be difficult. Sometimes, genes thought to be related to a particular genetic condition have mutations, but whether these changes are involved in development of the condition has not been determined; these genetic changes are known as variants of unknown significance (VOUS). Sometimes, no mutations are found in suspected disease- related genes, but mutations are found in other genes whose relationship to a particular genetic condition is

unknown. It is difficult to know whether these variants are involved in the disease.

Figure: This lobster contains a mutation that causes it to be blue. This is estimated to occur in roughly one in two million lobsters.

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49. Types of mutations

The DNA sequence of a gene can be altered in a number of ways. Gene mutations have varying effects on health, depending on where they occur and whether they alter the function of essential proteins. The types of mutations include:

Silent mutation: Not all changes in DNA sequence will result in a change in the amino acid that gets inserted into a protein. Mutations in the coding sequence that do not change an amino acid are called silent mutations.

Missense mutation: This type of mutation is a change in one DNA base pair that results in the substitution of one amino acid for another in the protein made by a gene.

Nonsense mutation: A nonsense mutation is also a change in one DNA base pair. Instead of substituting one amino acid for another, however, the mutation causes the insertion of an early stop codon. This stop codon signals the cell to stop building a protein prematurely. This type of mutation results in a truncated (shortened) protein that may function improperly or not at all.

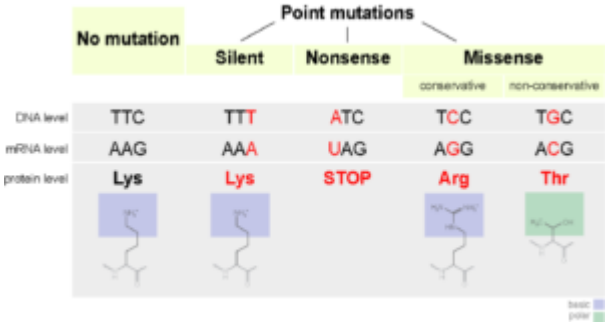

Figure: Some mutations do not change the sequence of amino acids in a protein. Some swap one amino acid for another. Others introduce an early stop codon into the sequence causing the protein to be truncated.

Insertion or Deletion: An insertion changes the number of DNA bases in a gene by adding a piece of DNA. A deletion removes a piece of DNA. Insertions or deletions may be small (one or a few base pairs within a gene) or large (an entire gene, several genes, or a large section of a chromosome). In any of these cases, the protein made by the gene may not function properly.

Duplication: A duplication consists of a piece of DNA that is abnormally copied one or more times. This type of mutation may alter the function of the resulting protein.

Frameshift mutation: This type of mutation occurs when the addition or loss of DNA bases changes a gene's reading frame. A reading frame consists of groups of 3 bases that each code for one amino acid. A frameshift mutation shifts the grouping of these bases and changes the code for amino acids. The resulting protein is usually nonfunctional. Insertions, deletions, and duplications can all be frameshift mutations.

Repeat expansion: Nucleotide repeats are short DNA sequences that are repeated a number of times in a row. For example, a trinucleotide repeat is made up of 3-base- pair sequences, and a tetranucleotide repeat is made up of 4-base-pair sequences. A repeat expansion is a mutation that increases the number of times that the short DNA sequence is repeated. This type of mutation can cause the resulting protein to function.

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50. Changes in number of genes or chromosomes

Changes in numbers of genes

People have two copies of most genes, one copy inherited from each parent. In some cases, however, the number of copies varies—meaning that a person can be born with one, three, or more copies of particular genes. Less commonly, one or more genes may be entirely missing. This type of genetic difference is known as copy number variation (CNV).

Copy number variation results from insertions, deletions, and duplications of large segments of DNA. These segments are big enough to include whole genes. Variation in gene copy number can influence the activity of genes and ultimately affect many body functions.

Researchers were surprised to learn that copy number variation accounts for a significant amount of genetic difference between people. More than 10 percent of human DNA appears to contain these differences in gene copy number. While much of this variation does not affect health or development, some differences likely influence a person's risk of disease and response to certain drugs. Future research will focus on the consequences of copy number variation in different parts of the genome and study the contribution of these variations to many types of disease.

Changes in Numbers of Chromosomes.

Human cells normally contain 23 pairs of chromosomes, for a total of 46 chromosomes in each cell. A change in the number of chromosomes can cause problems with growth, development, and function of the body's systems. These changes can occur during the formation of reproductive cells (eggs and sperm), in early fetal development, or in any cell after birth. A gain or loss of chromosomes from the normal 46 is called **aneuploidy**.

A common form of aneuploidy is **trisomy,** or the presence of an extra chromosome in cells. "Tri-" is Greek for "three"; people with trisomy have three copies of a particular chromosome in cells instead of the normal two copies. Down syndrome is an example of a condition caused by trisomy. People with Down syndrome typically have three copies of chromosome 21 in each cell, for a total of 47 chromosomes per cell.

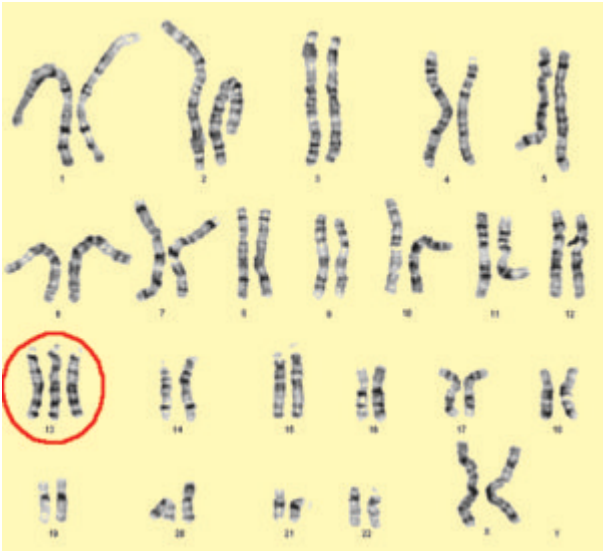

Figure 1 This karyotype, which is a picture of all the chromosome s from one individual, is from a person who has Trisomy 13.

Monosomy, or the loss of one chromosome in cells, is another kind of aneuploidy. "Mono-" is Greek for "one"; people with monosomy have one copy of a particular chromosome in cells instead of the normal two copies. Turner syndrome is a condition caused by monosomy. Women with Turner syndrome usually have only one copy of the X chromosome in every cell, for a total of 45 chromosomes per cell.

Rarely, some cells end up with complete extra sets of chromosomes. Cells with one additional set of chromosomes, for a total of 69 chromosomes, are called **triploid.** Cells with two additional sets of chromosomes, for a total of 92 chromosomes, are called tetraploid. A condition in which every cell in the body has an extra set of chromosomes is not compatible with life.

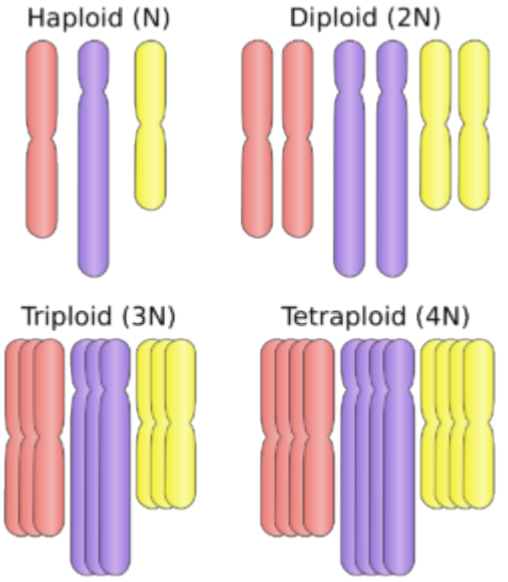

Figure 2 "Ploid" refers to the number of copies of each chromosome found in a somatic cell.

Figure 3 Human and other animal cells do not develop if they have an entire extra set of chromosome s. In contrast, plants often have entire copied sets of chromosome s. This strawberry is an example of a plant that is tetraploid.

In some cases, a change in the number of chromosomes occurs only in certain cells. When an individual has two or more cell populations with a different chromosomal makeup, this situation is called **chromosomal mosaicism**. Chromosomal mosaicism occurs from an error in cell division in cells other than eggs and sperm. Most commonly, some cells end up with one extra or missing chromosome (for a total of 45 or 47 chromosomes per cell), while other cells have the usual 46 chromosomes. Mosaic Turner syndrome is one example of chromosomal mosaicism. In females with this condition, some cells have 45 chromosomes because they are missing one copy of the X chromosome, while other cells have the usual number of chromosomes.

Many cancer cells also have changes in their number of chromosomes. These changes are not inherited; they occur in

somatic cells (cells other than eggs or sperm) during the formation or progression of a cancerous tumor.

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51. Multifactorial Disorders and Genetic Predispositions

Multifactorial Disorders

Researchers are learning that nearly all conditions and diseases have a genetic component. Some disorders, such as sickle cell disease and cystic fibrosis, are caused by mutations in a single gene. The causes of many other disorders, however, are much more complex. Common medical problems such as heart disease, diabetes, and obesity do not have a single genetic cause—they are likely associated with the effects of multiple genes in combination with lifestyle and environmental factors. Conditions caused by many contributing factors are called complex or **multifactorial disorders**.

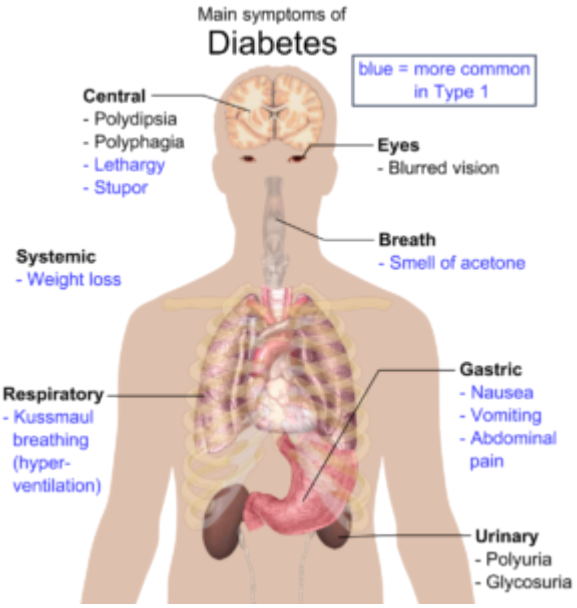

Figure 1 The main symptoms of diabetes, a multifactorial disorder

Although complex disorders often cluster in families, they do not have a clear- cut pattern of inheritance. This makes it difficult to determine a person's risk of inheriting or passing on these disorders. Complex disorders are also difficult to study and treat because the specific factors that cause most of these disorders have not yet been identified. Researchers continue to look for major contributing genes for many common complex disorders.

Genetic Predispositions

A **genetic predisposition**(sometimes also called genetic

susceptibility) is an increased likelihood of developing a particular disease based on a person's genetic makeup. A genetic predisposition results from specific genetic variations that are often inherited from a parent. These genetic changes contribute to the development of a disease but do not directly cause it. Some people with a predisposing genetic variation will never get the disease while others will, even within the same family.

Genetic variations can have large or small effects on the likelihood of developing a particular disease. For example, certain mutations in the *BRCA1* or *BRCA2* genes greatly increase a person's risk of developing breast cancer and ovarian cancer. Variations in other genes, such as *BARD1* and *BRIP1*, also increase breast cancer risk, but the contribution of these genetic changes to a person's overall risk appears to be much smaller.

Current research is focused on identifying genetic changes that have a small effect on disease risk but are common in the general population. Although each of these variations only slightly increases a person's risk, having changes in several different genes may combine to increase disease risk significantly. Changes in many genes, each with a small effect, may underlie susceptibility to many common diseases, including cancer, obesity, diabetes, heart disease, and mental illness.

In people with a genetic predisposition, the risk of disease can depend on multiple factors in addition to an identified genetic change. These include other genetic factors (sometimes called modifiers) as well as lifestyle and environmental factors. Although a person's genetic makeup cannot be altered, some lifestyle and environmental modifications (such as having more frequent disease screenings and maintaining a healthy weight) may be able to reduce disease risk in people with a genetic predisposition.

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52. Genetics and statistics

Statistical data can provide general information about how common a condition is, how many people have the condition, or how likely it is that a person will develop the condition. Statistics are not personalized, however—they offer estimates based on groups of people. By taking into account a person's family history, medical history, and other factors, a genetics professional can help interpret what statistics mean for a particular patient.

Some statistical terms are commonly used when describing genetic conditions and other disorders. These terms include:

Statistical term	**Description**
Incidence	The incidence of a gene mutation or a genetic disorder is the number of people who are born with the mutation or disorder in a specified group per year. Incidence is often written in the form "1 in [a number]" or as a total number of live births.
Prevalence	The prevalence of a gene mutation or a genetic disorder is the total number of people in a specified group at a given time who have the mutation or disorder. This term includes both newly diagnosed and pre-existing cases in people of any age. Prevalence is often written in the form "1 in [a number]" or as a total number of people who have a condition.
Mortality	Mortality is the number of deaths from a particular disorder occurring in a specified group per year. Mortality is usually expressed as a total number of deaths.
Lifetime risk	Lifetime risk is the average risk of developing a particular disorder at some point during a lifetime. Lifetime risk is often written as a percentage or as "1 in [a number]." It is important to remember that the risk per year or per decade is much lower than the lifetime risk. In addition, other factors may increase or decrease a person's risk as compared with the average.

Use of Statistics Terms

- About 1 in 200,000 people in the United States are born with syndrome A each year.
- An estimated 15,000 infants with syndrome B were born last year worldwide.
- Approximately 1 in 100,000 people in the United States have syndrome A at the present time.
- About 100,000 children worldwide currently have syndrome B.
- An estimated 12,000 people worldwide died from syndrome C in 2002.
- Approximately 1 percent of people in the United States develop disorder D during their lifetimes.
- The lifetime risk of developing disorder D is 1 in 100.

References

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PART IX

ENZYME CATALYZED REACTIONS

Learning Objectives

By the end of this section, you will be able to:

- Explain the role of enzyme-catalyzed reactions in cellular metabolism.

Figure 1 A hummingbird needs energy to maintain prolonged flight. The bird obtains its energy from taking in food and transforming the energy contained in food molecules into forms of energy to power its flight through a series of biochemical reactions. (credit: modification of work by Cory Zanker)

Virtually every task performed by living organisms requires energy. Energy is needed to perform heavy labor and exercise, but humans also use energy while thinking, and even during sleep. In fact, the living cells of every organism constantly use energy. Nutrients and other molecules are imported into the cell have many different potential paths: metabolized (broken down) and used for energy, synthesized into new molecules, modified if needed, transported around the cell, and even distributed to the entire organism. For example, the large proteins that make up muscles are built from smaller molecules imported from dietary amino acids. Complex carbohydrates are broken down into simple sugars that the cell uses for energy. Just as energy is required to both build and demolish a building, energy is required for the synthesis and breakdown of

molecules as well as the transport of molecules into and out of cells. In addition, processes such as ingesting and breaking down pathogenic bacteria and viruses, exporting wastes and toxins, and movement of the cell require energy.

References

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53. Energy

In general, **energy** is defined as the ability to do work, or to create some kind of change. Energy exists in different forms. For example, electrical energy, light energy, and heat energy are all different types of energy.

Cellular processes such as the building and breaking down of complex molecules occur through stepwise chemical reactions. Some of these chemical reactions are spontaneous and release energy, whereas others require energy to proceed.

Just as living things must continually consume food to replenish their energy supplies, cells must continually produce more energy to replenish that used by the many energy-requiring chemical reactions that constantly take place. Together, all of the chemical reactions that take place inside cells, including those that consume or generate energy, are referred to as the cell's **metabolism**.

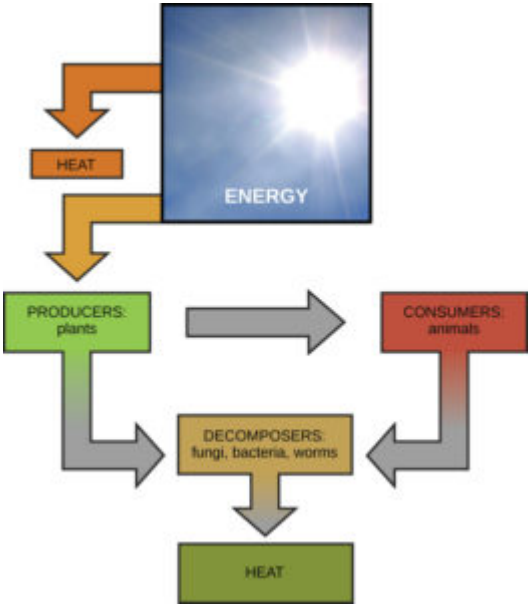

Figure 1 Ultimately, most life forms get their energy from the sun. Plants use photosynthesis to capture sunlight, and herbivores eat the plants to obtain energy. Carnivores eat the herbivores, and eventual decomposition of plant and animal material contributes to the nutrient pool.

In biological organisms, energy is exchanged between the organism and their surroundings. This can occur as they use energy from the sun to perform photosynthesis or consume food (energy-storing molecules) and then release energy to the environment by doing work and releasing heat. Like all things in the physical world, energy is subject to physical laws. The laws of thermodynamics govern the transfer of energy in and among all systems in the universe.

The First Law of Thermodynamics states that the total amount of energy in the universe is constant and conserved. In other words, there has always been, and always will be, exactly the same amount of energy in the universe. According to the first law of thermodynamics, *energy may be transferred from place to place or transformed into different forms, but it cannot be created or*

destroyed. Transfers and transformations of energy take place around us all the time, but now you know that when this happens, no energy is created or destroyed. Light bulbs transform electrical energy into light and heat energy. Gas stoves transform chemical energy from natural gas into heat energy. Plants perform one of the most biologically useful energy transformations on earth: that of converting the energy of sunlight to chemical energy stored within organic molecules. In all of these energy conversions, no energy is created or destroyed.

The challenge for all living organisms is to obtain energy from their surroundings in forms that are usable to do cellular work. Living cells have evolved to meet this challenge. Chemical energy stored within molecules such as sugars and fats is transferred and transformed through a series of cellular chemical reactions into energy within molecules of **ATP** (adenosine triphosphate). Energy in ATP molecules is easily accessible to do work. Examples of the types of work that cells need to do include building complex molecules, transporting materials, powering the motion of cilia or flagella, and contracting muscle fibers to create movement.

A living cell's primary tasks of obtaining, transforming, and using energy to do work may seem simple. However, these tasks are harder than they appear. The **second law of thermodynamics** explains why: a*ll energy transfers and transformations are never completely efficient*. This means that in every energy transfer, some amount of energy is lost in a form that is unusable. In most cases, this form is heat energy. Thermodynamically, **heat energy** is defined as the energy transferred from one system to another that is not work. For example, when a light bulb is turned on, some of the energy being converted from electrical energy into light energy is lost as heat energy. Likewise, some energy is lost as heat energy during cellular metabolic reactions.

Potential and Kinetic Energy

When an object is in motion, there is energy associated with that object. Think of a wrecking ball. Even a slow-moving wrecking ball can do a great deal of damage to other objects. Energy associated with objects in motion is called **kinetic energy** (**Figure 5**). A speeding bullet, a walking person, and the rapid movement of molecules in the air (which produces heat) all have kinetic energy.

Now what if that same motionless wrecking ball is lifted two stories above ground with a crane? If the suspended wrecking ball is unmoving, is there energy associated with it? The answer is yes. The energy that was required to lift the wrecking ball did not disappear, but is now stored in the wrecking ball by virtue of its position and the force of gravity acting on it. This type of energy is called **potential energy** (**Figure 5**). If the ball were to fall, the potential energy would be transformed into kinetic energy until all of the potential energy was exhausted when the ball rested on the ground. Wrecking balls also swing like a pendulum; through the swing, there is a constant change of potential energy (highest at the top of the swing) to kinetic energy (highest at the bottom of the swing). Other examples of potential energy include the energy of water held behind a dam or a person about to skydive out of an airplane.

Figure 5 Still water has potential energy; moving water, such as in a waterfall or a rapidly flowing river, has kinetic energy. (credit "dam": modification of work by "Pascal"/Flickr; credit "waterfall": modification of work by Frank Gualtieri)

Potential energy is not only associated with the location of matter, but also with the *structure* of matter. A spring on the ground has potential energy if it is compressed; so does a rubber band that is pulled taut. On a molecular level, the bonds that hold the atoms of molecules together exist in a particular structure that has potential energy. Cellular pathways *require* energy to synthesize complex molecules from simpler ones and other pathways *release* energy when these complex molecules are broken down. The fact that energy can be released by the breakdown of certain chemical bonds implies that those bonds have potential energy. In fact, there is potential energy stored within the bonds of all the food molecules we eat, which is eventually harnessed for use. This is because these bonds can release energy when broken. The type of potential energy that exists within chemical bonds, and is released when those bonds are broken, is called **chemical energy**. Chemical energy

is responsible for providing living cells with energy from food. The release of energy occurs when the molecular bonds within food molecules are broken.

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54. Metabolic Pathways

Consider the metabolism (both the creation and breakdown) of sugar. This is a classic example of one of the many cellular processes that use and produce energy. Living things consume sugars as a major energy source, because sugar molecules have a great deal of energy stored within their bonds. For the most part, photosynthesizing organisms like plants produce these sugars. During photosynthesis, plants use energy (originally from sunlight) to convert carbon dioxide gas (CO_2) into sugar molecules (like glucose: $C_6H_{12}O_6$). They consume carbon dioxide and produce oxygen as a waste product. This reaction is summarized as:

$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$

Because this process involves synthesizing an energy-storing molecule, it requires energy input to proceed. During photosynthesis, the energy from the sun is stored within molecules of **adenosine triphosphate (ATP)**, which is the primary energy currency of all cells. Just as the dollar is used as currency to buy goods, cells use molecules of ATP as energy currency to perform immediate work. Energy-storage molecules such as glucose and fat are consumed so that they can be broken down to use their energy. The reaction that harvests the energy of a sugar molecule in cells requiring oxygen to survive can be summarized by the reverse reaction to photosynthesis. In this reaction, oxygen is consumed and carbon dioxide is released as a waste product. The reaction is summarized as:

$C_6H_{12}O_6 + 6O_2 \rightarrow 6H_2O + 6CO_2$

Both of these reactions involve many steps.

The processes of making and breaking down sugar molecules illustrate two examples of metabolic pathways. A **metabolic pathway**is a series of chemical reactions that takes a starting molecule and modifies it, step-by-step, through a series of metabolic intermediates, eventually yielding a final product. In the

example of sugar metabolism, the first metabolic pathway synthesized sugar from smaller molecules, and the other pathway broke sugar down into smaller molecules. These two opposite processes—the first requiring energy and the second producing energy—are referred to as **anabolic** pathways (building polymers) and **catabolic** pathways (breaking down polymers into their monomers), respectively. Consequently, metabolism is composed of synthesis (anabolism) and degradation (catabolism) (**Figure 3**).

It is important to know that the chemical reactions of metabolic pathways do not take place on their own. Each reaction step is facilitated, or catalyzed, by a protein called an **enzyme**. Enzymes are important for catalyzing all types of biological reactions—those that require energy as well as those that release energy.

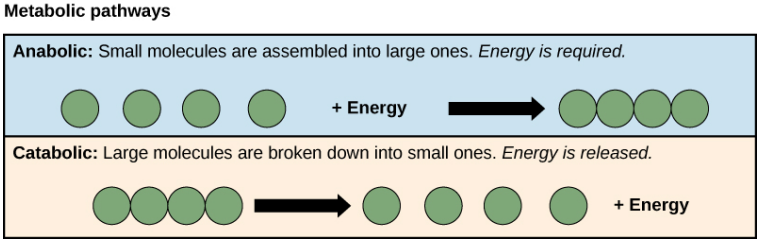

Figure 3 Catabolic pathways are those that generate energy by breaking down larger molecules. Anabolic pathways are those that require energy to synthesize larger molecules. Both types of pathways are required for maintaining the cell's energy balance.

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55. Activation Energy

Chemical reactions can be divided into two types based on whether they require energy to proceed or release energy as they proceed.

Endergonic reactions absorb energy. In this case, the products have more energy than the reactants. These chemical reactions are nonspontaneous – they require an input of energy in order to occur. The products of these reactions have more stored energy than the starting molecules. These products can be thought of as energy-storing molecules. An endergonic reaction will not take place on its own without the addition of energy.

Exergonic reactions release energy. Think: *ex*ergonic means energy is *ex*iting the system. These reactions are also referred to as spontaneous reactions – they will occur by themselves without an input of energy. Their products have less stored energy than the starting molecules. An important distinction must be drawn between the term spontaneous and the idea of a chemical reaction occurring immediately. Contrary to the everyday use of the term, a spontaneous reaction is not one that suddenly or quickly occurs. The rusting of iron is an example of a spontaneous reaction that occurs slowly, little by little, over time.

One more important concept must be considered regarding exergonic reactions. Exergonic reactions require a small amount of energy input to get going, before they can proceed with their energy-releasing steps. This small amount of energy input necessary for all chemical reactions to occur is called the **activation energy**. Think of a firecracker: it won't explode until you add a small amount of energy by lighting the fuse. The energy added by lighting the fuse can be compared to the activation energy of a chemical reaction.

References

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56. Enzymes

A substance that helps a chemical reaction to occur is called a *catalyst*, and the molecules that catalyze biochemical reactions are called **enzymes**. Most enzymes are proteins and perform the critical task of lowering the activation energies of chemical reactions inside the cell. Most of the reactions critical to a living cell happen too slowly at normal temperatures to be of any use to the cell. Without enzymes to speed up these reactions, life could not persist. Enzymes do this by binding to the reactant molecules and holding them in such a way as to make the chemical bond-breaking and -forming processes take place more easily.

It is important to remember that enzymes do not change whether a reaction is exergonic (produces energy, spontaneous) or endergonic (requires energy, non-spontaneous). This is because they do not change the free energy of the reactants or products (i.e. they do not change the amount of energy stored within a molecule of reactant or within a molecule of the product). They only reduce the activation energy required for the reaction to proceed (**Figure 1**). In addition, an enzyme itself is unchanged by the reaction it catalyzes. Once one reaction has been catalyzed, the enzyme is able to participate in other reactions.

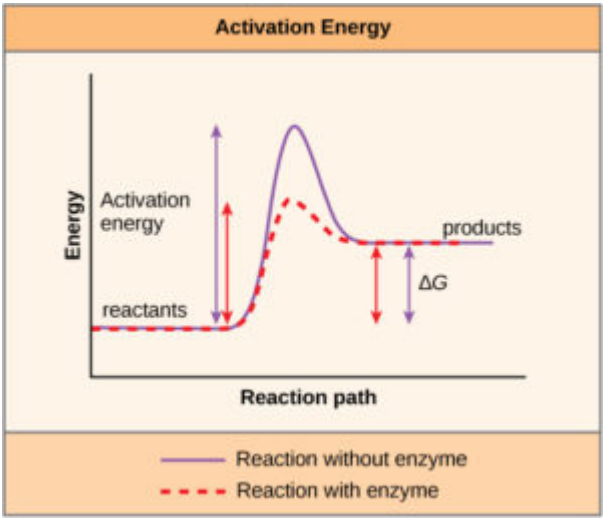


Figure 1 Enzymes lower the activation energy of the reaction but do not change the free energy of the reaction.

The chemical reactants to which an enzyme binds are called the enzyme's **substrates**. There may be one or more substrates, depending on the particular chemical reaction. In some reactions, a single reactant substrate is broken down into multiple products. In others, two substrates may come together to create one larger molecule. Two reactants might also enter a reaction and both become modified, but they leave the reaction as two products. The location within the enzyme where the substrate binds is called the enzyme's **active site**. The active site is where the "action" happens. Since enzymes are proteins, there is a unique combination of amino acid side chains within the active site. Each side chain is characterized by different properties. They can be large or small, weakly acidic or basic, hydrophilic or hydrophobic, positively or negatively charged, or neutral. The unique combination of side chains creates a very specific chemical environment within the active site. This specific environment is suited to bind to one specific chemical substrate (or substrates).

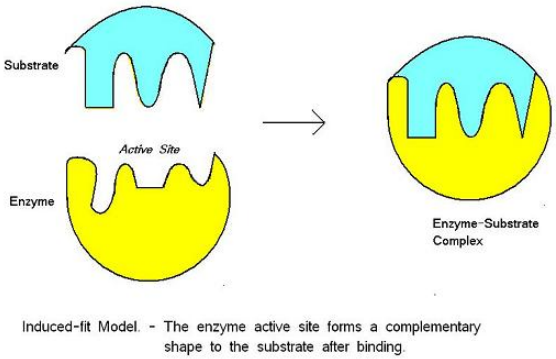
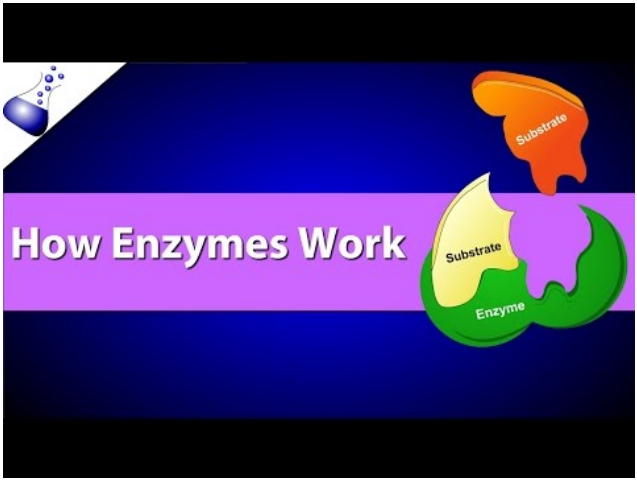


Figure 2 The substrate binds to the enzyme at the active site. Credit: Induced Fit Model; Stephjc; wikimedia; public domain.



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For many years, scientists thought that enzyme-substrate binding took place in a simple "lock and key" fashion. This model asserted that the enzyme and substrate fit together perfectly in one instantaneous step. However, current research supports a model called **induced fit** (**Figure 4**). The induced-fit model expands on the lock-and-key model by describing a more dynamic binding between enzyme and substrate. As the enzyme and substrate come together, their interaction causes a slight shift in the enzyme's structure that forms an ideal binding arrangement between enzyme and substrate.

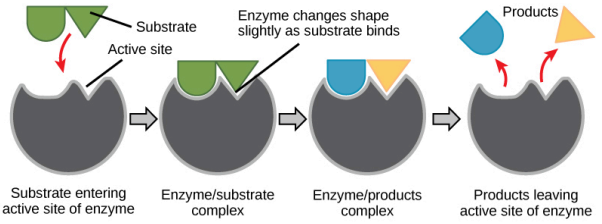
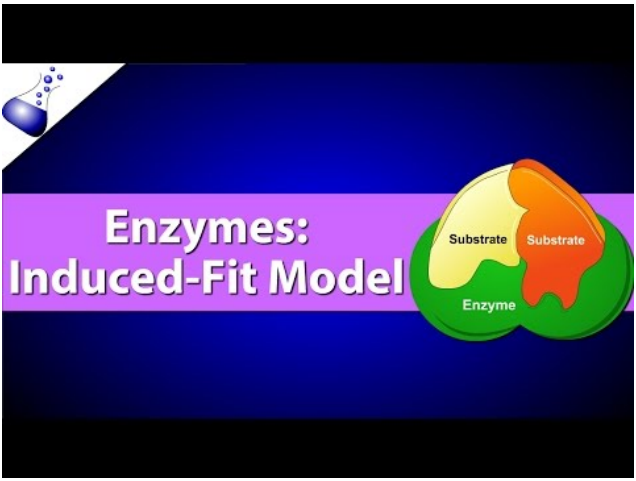


Figure 3 The induced-fit model is an adjustment to the lock-and-key model and explains how enzymes and substrates undergo dynamic modification s during the transition state to increase the affinity of the substrate for the active site.



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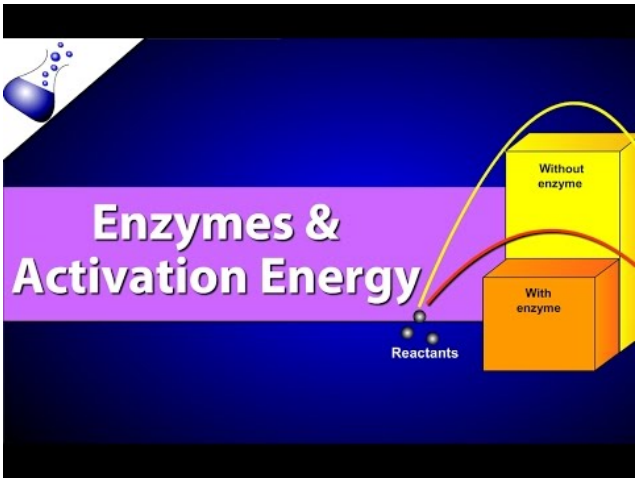
When an enzyme binds its substrate, an enzyme-substrate complex is formed. This complex lowers the activation energy of the reaction and promotes its rapid progression in one of multiple possible ways.

- On a basic level, enzymes promote chemical reactions that involve more than one substrate by bringing the substrates together in an optimal orientation for reaction.
- Enzymes promote the reaction of their substrates is by creating an optimal environment within the active site for the reaction to occur. The chemical properties that emerge from the particular arrangement of amino acid R groups (side chains) within an active site create the perfect environment for an enzyme's specific substrates to react.
- The enzyme-substrate complex can also lower activation energy by compromising the bond structure so that it is easier

to break.

- Finally, enzymes can also lower activation energies by taking part in the chemical reaction itself. In these cases, it is important to remember that the enzyme will always return to its original state by the completion of the reaction.

One of the hallmark properties of enzymes is that they remain ultimately unchanged by the reactions they catalyze. After an enzyme has catalyzed a reaction, it releases its product(s) and can catalyze a new reaction.



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57. Changes in Enzyme Activity

It would seem ideal to have a scenario in which all of an organism's enzymes existed in abundant supply and functioned optimally under all cellular conditions, in all cells, at all times. However, this is not true for a variety of reasons. First, it would require a lot of energy to produce all an organism's enzymes all the time. Also, cellular needs and conditions constantly vary from cell to cell, and change within individual cells over time. The required enzymes of stomach cells differ from those of fat storage cells, skin cells, blood cells, and nerve cells. Furthermore, a digestive organ cell works much harder to process and break down nutrients during the time that closely follows a meal compared with many hours after a meal. As these cellular demands and conditions vary, so must the amounts and functionality of different enzymes.

Since the rates of biochemical reactions are controlled by activation energy, and enzymes lower and determine activation energies for chemical reactions, the relative amounts and functioning of the variety of enzymes within a cell ultimately determine which reactions will proceed and at what rates. This determination is tightly controlled in cells.

Regulation

Enzymes can also be regulated in ways that either promote or reduce enzyme activity. There are many kinds of molecules that inhibit or promote enzyme function, and various mechanisms by which they do so.

- In some cases of enzyme inhibition, an inhibitor molecule is similar enough to a substrate that it can bind to the active site and simply block the substrate from binding.
- In other cases, an inhibitor molecule binds to the enzyme in a location other than the active site, called an allosteric site, but still manages to block substrate binding to the active site (Figure 4).
- Some inhibitor molecules bind to enzymes in a location where their binding causes a change in the shape of the enzyme that makes the enzyme less likely to bind to its substrate.
- There are also activator molecules that can increase the ability of an enzyme to bind to its substrate.

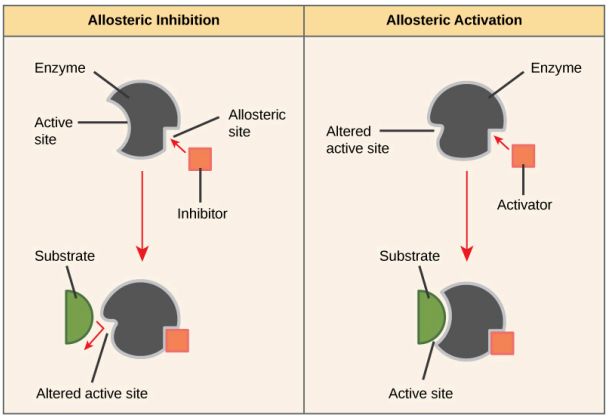

Figure 4 Allosteric inhibition works by indirectly inducing a conformatio nal change to the active site such that the substrate no longer fits. In contrast, in allosteric activation, the activator molecule modifies the shape of the active site to allow a better fit of the substrate.

Cofactors and Coenzymes

Many enzymes do not work optimally, or even at all, unless bound to other specific non-protein helper molecules. They may bond either temporarily through ionic or hydrogen bonds, or permanently through stronger covalent bonds. Binding to these molecules promotes optimal shape and function of their respective enzymes – they activate the enzyme. Two examples of these types of helper molecules are *cofactors* and *coenzymes*. Cofactors are inorganic ions such as ions of iron and magnesium. Coenzymes are organic helper molecules, those with a basic atomic structure made up of carbon and hydrogen. Like enzymes, these molecules participate in reactions without being changed themselves and are ultimately recycled and reused. Vitamins are the source of coenzymes. Some vitamins are the precursors of coenzymes and others act directly as coenzymes. Vitamin C is a direct coenzyme for multiple enzymes that take part in building the important connective tissue, collagen. Therefore, enzyme function is, in part, regulated by the abundance of various cofactors and coenzymes, which may be supplied by an organism's diet or, in some cases, produced by the organism.

Effect of environmental conditions

Enzyme activity is subject to influences of the local environment. In a cold environment, enzymes function more slowly because the molecules are moving more slowly. The substrate bumps into the enzyme less frequently. As the temperature increases, molecules move more quickly, so the enzyme functions at a higher rate. Increasing temperature generally increases reaction rates, enzyme-catalyzed or otherwise. You may have noticed that sugar dissolves faster in hot coffee than in cold ice tea – this is because the molecules are moving more quickly in hot coffee, which increases

the rate of the reaction. However, temperatures that are too high will reduce the rate at which an enzyme catalyzes a reaction. This is because hot temperatures will eventually cause the enzyme to **denature,** an irreversible change in the three-dimensional shape and therefore the function of the enzyme (**Figure 5**).

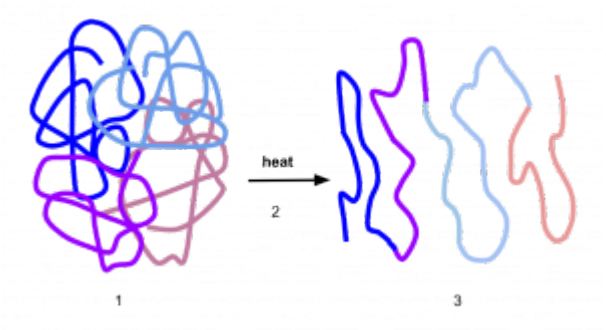

Figure 5 Denaturation causes a protein to lose its 3-dimensional shape. Picture by Scurran15, Denaturation, CC SA 4.0

Denaturation is caused by the breaking of the bonds that hold the enzyme together in its three-dimensional shape. Heat can break hydrogen and ionic bonds, which disrupts the shape of the enzyme and will change the shape of the active site. Cold temperatures do not denature enzymes because cold does not cause chemical bonds to break.

Figure 6 Heat applied to an egg during cooking irreversibly denatures the proteins. (credit: "K-Wall"/Flickr)

Enzymes are suited to function best within a certain temperature, pH, and salt concentration range. In addition to high temperatures, extreme pH and salt concentrations can cause enzymes to denature. Both acidic and basic pH can cause enzymes to denature because the presence of extra H+ ions (in an acidic solution) or OH- ions (in a basic solution) can modify the chemical structure of the amino acids forming the protein, which can cause the chemical bonds holding the three-dimensional structure of the protein to break. High salt concentrations can also cause chemical bonds within the protein to break in a similar matter.

Typically, enzymes function optimally in the environment where they are typically found and used. For example, the enzyme amylase is found in saliva, where it functions to break down starch (a polysaccharide – carbohydrate chain) into smaller sugars. Note that in this example, amylase is the enzyme, starch is the substrate, and smaller sugars are the product. The pH of saliva is typically between 6.2 and 7.6, with roughly 6.7 being the average. The optimum pH of amylase is between 6.7 and 7.0, which is close to neutral (Figure 3). The optimum temperature for amylase is close to 37°C (which is human body temperature).

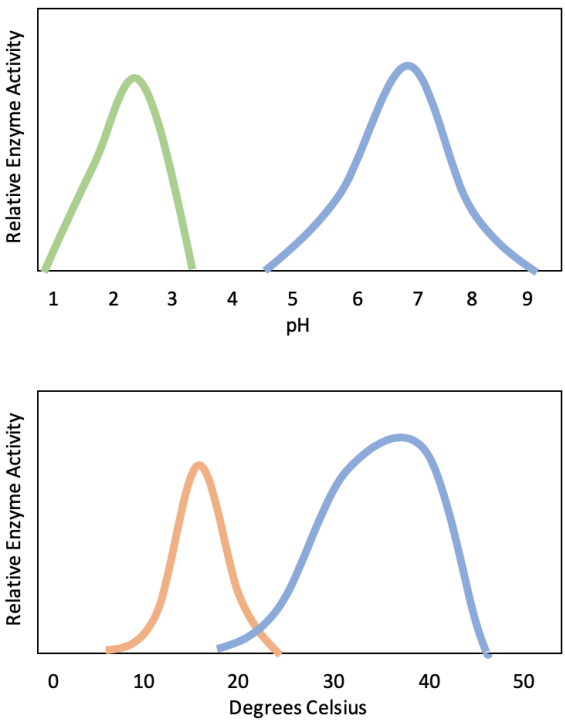

Figure 3 The effect of pH and temperature on the activity of an enzyme. Amylase is shown in blue in both graphs. (top) Amylase (blue) has an optimum pH of about 7. The green enzyme, which has an optimum pH of about 2.3, might function in the stomach where it is very acidic. (bottom) Amylase (blue) has an optimum temperature of about 37 degrees C. The orange enzyme, which has an optimum temperature of about 15 degrees C (about 60F) might function in a plant found outdoors.

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58. Feedback Inhibition in Metabolic Pathways

Molecules can regulate enzyme function in many ways. The major question remains, however: What are these molecules and where do they come from? Some are cofactors and coenzymes, as you have learned. What other molecules in the cell provide enzymatic regulation such as allosteric modulation, and competitive and non-competitive inhibition? Perhaps the most relevant sources of regulatory molecules, with respect to enzymatic cellular metabolism, are the products of the cellular metabolic reactions themselves. In a most efficient and elegant way, cells have evolved to use the products of their own reactions for feedback inhibition of enzyme activity. **Feedback inhibition** involves the use of a reaction product to regulate its own further production (**Figure 11**). The cell responds to an abundance of the products by slowing down production during anabolic or catabolic reactions. Such reaction products may inhibit the enzymes that catalyzed their production through the mechanisms described above.

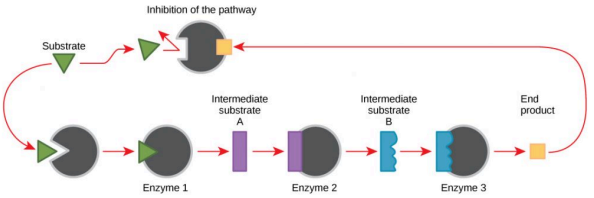

Figure 11 Metabolic pathways are a series of reactions catalyzed by multiple enzymes. Feedback inhibition, where the end product of the pathway inhibits an upstream process, is an important regulatory mechanism in cells.

The production of both amino acids and nucleotides is controlled through feedback inhibition. Additionally, ATP is an allosteric regulator of some of the enzymes involved in the catabolic breakdown of sugar, the process that creates ATP. In this way, when ATP is in abundant supply, the cell can prevent the production of ATP. On the other hand, ADP serves as a positive allosteric regulator (an allosteric activator) for some of the same enzymes that are inhibited by ATP. Thus, when relative levels of ADP are high compared to ATP, the cell is triggered to produce more ATP through sugar catabolism.

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59. Enzymes and Disease

Because enzymes are so important in all metabolic processes, when they malfunction, it can create big problems for the organism. Here are some examples of genetic disorders that are caused by an enzyme that is not working correctly:

Maple syrup urine disease

Maple syrup urine disease is an inherited disorder in which the body is unable to process certain protein building blocks (amino acids) properly. The condition gets its name from the distinctive sweet odor of affected infants' urine. It is also characterized by poor feeding, vomiting, lack of energy (lethargy), abnormal movements, and delayed development. If untreated, maple syrup urine disease can lead to seizures, coma, and death.

Mutations in the BCKDHA, BCKDHB, and DBT genes can cause maple syrup urine disease. Each of these three genes provides the instructions to make one protein. The proteins work together as part of an enzyme complex. The enzyme complex is essential for breaking down the amino acids leucine, isoleucine, and valine, which are present in many kinds of food, particularly protein-rich foods such as milk, meat, and eggs.

Mutations in any of these three genes reduce or eliminate the function of the enzyme complex, preventing the normal breakdown of leucine, isoleucine, and valine. As a result, these amino acids and their byproducts build up in the body. Because high levels of these substances are toxic to the brain and other organs, their accumulation leads to the serious health problems associated with maple syrup urine disease.

Tay Sachs Disease

Tay-Sachs disease is a rare inherited disorder that progressively destroys nerve cells (neurons) in the brain and spinal cord.

The most common form of Tay-Sachs disease becomes apparent in infancy. Infants with this disorder typically appear normal until the age of 3 to 6 months, when their development slows and muscles used for movement weaken. Affected infants lose motor skills such as turning over, sitting, and crawling. They also develop an exaggerated startle reaction to loud noises. As the disease progresses, children with Tay-Sachs disease experience seizures, vision and hearing loss, intellectual disability, and paralysis. An eye abnormality called a cherry-red spot, which can be identified with an eye examination, is characteristic of this disorder. Children with this severe infantile form of Tay-Sachs disease usually live only into early childhood.

Mutations in the HEXA gene cause Tay-Sachs disease. The HEXA gene provides instructions for making part of an enzyme called beta-hexosaminidase A, which plays a critical role in the brain and spinal cord. This enzyme is located in lysosomes (remember that these are the organelles that break down toxic substances and act as recycling centers). Within lysosomes, beta-hexosaminidase A helps break down a fatty substance called GM2 ganglioside.

Mutations in the HEXA gene disrupt the activity of beta-hexosaminidase A, which prevents the enzyme from breaking down GM2 ganglioside. As a result, this substance accumulates to toxic levels, particularly in neurons in the brain and spinal cord. Progressive damage caused by the buildup of GM2 ganglioside leads to the destruction of these neurons, which causes the signs and symptoms of Tay-Sachs disease. Because Tay-Sachs disease impairs the function of a lysosomal enzyme, this condition is sometimes referred to as a lysosomal storage disorder.

Phenylketonuria

Phenylketonuria (commonly known as PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. Phenylalanine is an amino acid that is obtained through the diet. It is found in all proteins and in some artificial sweeteners (aspartame – found in Nutrasweet and Equal) . If PKU is not treated, phenylalanine can build up to harmful levels in the body, causing intellectual disability and other serious health problems.

The signs and symptoms of PKU vary from mild to severe. The most severe form of this disorder is known as classic PKU. Infants with classic PKU appear normal until they are a few months old. Without treatment, these children develop permanent intellectual disability. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Untreated individuals may have a musty or mouse-like odor as a side effect of excess phenylalanine in the body. Children with classic PKU tend to have lighter skin and hair than unaffected family members and are also likely to have skin disorders such as eczema.

Less severe forms of this condition, sometimes called variant PKU and non-PKU hyperphenylalaninemia, have a smaller risk of brain damage. People with very mild cases may not require treatment with a low-phenylalanine diet.

Mutations in the PAH gene cause phenylketonuria. The PAH gene provides instructions for making an enzyme called phenylalanine hydroxylase. This enzyme converts the amino acid phenylalanine to other important compounds in the body. If gene mutations reduce the activity of phenylalanine hydroxylase, phenylalanine from the diet is not processed effectively. As a result, this amino acid can build up to toxic levels in the blood and other tissues. Because nerve cells in the brain are particularly sensitive to phenylalanine levels, excessive amounts of this substance can cause brain damage.

Classic PKU, the most severe form of the disorder, occurs when phenylalanine hydroxylase enzyme activity is severely reduced or

absent. People with untreated classic PKU have levels of phenylalanine high enough to cause severe brain damage and other serious health problems. Mutations in the PAH gene that allow the enzyme to retain some activity result in milder versions of this condition, such as variant PKU or non-PKU hyperphenylalaninemia.

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PART X

HOW CELLS OBTAIN ENERGY

Learning Objectives

By the end of this section, you will begin to be able to:

- Compare energy-generating processes within different types of cells.

All living organisms require energy to perform their life processes. Energy, as you learned earlier in the chapter about enzymes, is the ability to do work or to create some kind of change. You are familiar with or have learned about many processes that can require energy:

- Movement
- Reproduction
- Maintaining homeostasis of many different conditions
- Acquiring and digesting food
- Producing proteins

Just as living things must continually consume food to replenish their energy supplies, cells must continually produce more energy to replenish that used by the many energy-requiring chemical reactions that constantly take place. Together, all of the chemical reactions that take place inside cells, including those that consume or generate energy, are referred to as the cell's **metabolism**.

A living cell cannot store significant amounts of free energy. Free

energy is energy that is not stored in molecules. Excess free energy would result in an increase of heat in the cell, which would denature enzymes and other proteins, and destroy the cell. Instead, a cell must be able to store energy safely and release it for use only as needed. Living cells accomplish this using ATP, which can be used to fill any energy need of the cell. How? It functions like a rechargeable battery.

When ATP is broken down, energy is released. This energy is used by the cell to do work. For example, in the mechanical work of muscle contraction, ATP supplies energy to move the contractile muscle proteins.

ATP Structure and Function

ATP is a complex-looking molecule, but for our purposes you can think of it as a rechargeable battery. ATP, the fully charged form of our battery, is made up of three phosphates (the "TP" part of ATP means "tri phosphate") attached to a sugar and an adenine (the "A" part of ATP) (**Figure 1**). When the last phosphate is broken off of the ATP, energy is released. The result is a single phosphate and a molecule called ADP ("D" stands for "di" which means two).

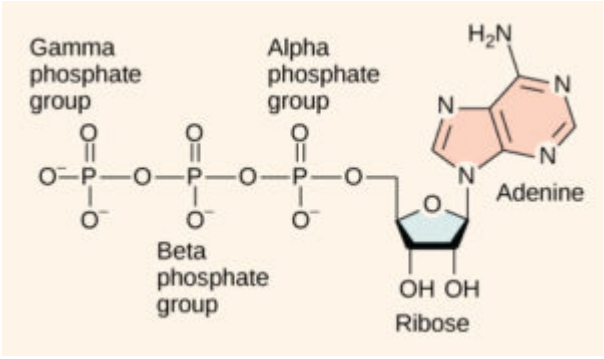
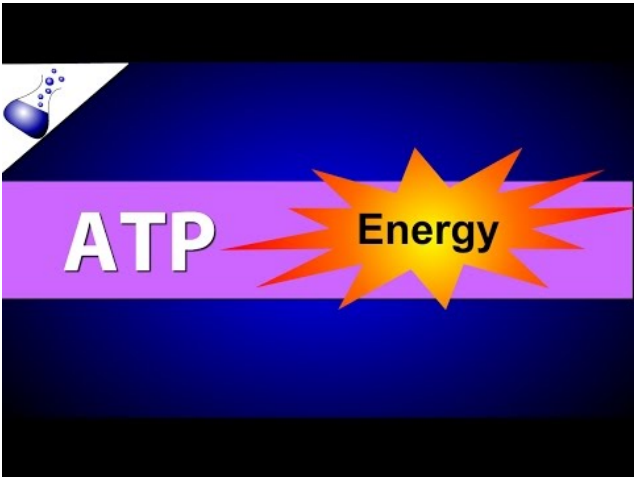


Figure 1*The structure of ATP shows the basic components of a two-ring adenine, five-carbon ribose sugar, and three phosphate groups.*

A large amount of energy is required in order to recharge a molecule of ADP into ATP. This energy is stored in the bond between the second and third phosphates. When this bond is broken, the energy is released in a way that the cell can use it.



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60. From Mouth to Molecule: Digestion

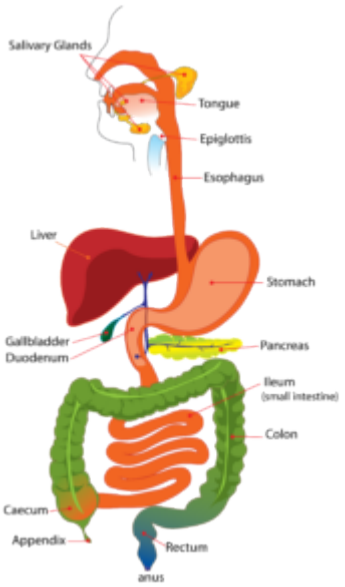
While plants can produce their own energy using the process of photosynthesis, animals (and other organisms that can't do photosynthesis) must eat to get energy from food molecules. Just like energy can be stored in the chemical bond between the second and third phosphate of an ATP molecule, energy can also be stored in the chemical bonds that make up food molecules. Most of the energy that we use comes from molecules of glucose, a simple sugar.

Food energy is chemical energy that animals (including humans) derive from their food through the process of cellular respiration. Cellular respiration involves either joining oxygen from air with the molecules of food (aerobic respiration) or reorganizing the atoms within the molecules in the absence of oxygen (anaerobic respiration).

Humans and other animals need a minimum intake of food energy to sustain their metabolism and to drive their muscles. Foods are composed chiefly of carbohydrates, fats, proteins, water, vitamins, and minerals. Carbohydrates, fats, proteins, and water represent virtually all the weight of food, with vitamins and minerals making up only a small percentage of the weight. In fact, carbohydrates, fats, and proteins comprise ninety percent of the dry weight of foods. Organisms derive food energy mainly from carbohydrates and fats present in the diet, and to a smaller extent proteins and other organic molecules. Some diet components that provide little or no food energy, such as water, minerals, vitamins, cholesterol, and fiber, may still be necessary to health and survival for other reasons. Water, minerals, vitamins, and cholesterol are not broken down; they are used by the body in the form in which they are taken in, so they cannot be used for energy. Fiber, a type of carbohydrate,

cannot be completely digested by the human body so energy is not released from fiber when it is digested. Instead, it moves mostly intact through the digestive system.

After you put food into your mouth, you begin to break it down mechanically using your teeth. Enzymes in your saliva begin breaking the food molecules down as well. After you swallow your food, it is further broken down by additional enzymes in the stomach, followed by the small intestine. In the small intestine, the fully broken-down food is absorbed into the blood. The majority of the nutrients (about 95%) are absorbed in the small intestine. Water is reabsorbed from the remaining material in the colon. Then the residual waste is eliminated during defecation.



The human digestive system. (Credit: Leysi24, from Wikimedia. Creative Commons Attribution-Share Alike 3.0 Unported)

Once in the bloodstream, nutrients enter individual cells. Glucose is too large to diffuse through the cell membrane and is typically transported inside cells by proteins. After molecules enter a cell, the

breakdown process to produce energy in the form of ATP can be completed.

References

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61. Metabolism

An organism's metabolism is the sum total of all the chemical reactions that occur within the organism. These chemical reactions fall into two basic categories:

- Anabolism: building polymers (large molecules that the cell needs).
- Catabolism: breaking down polymers to release energy.

This means that metabolism is composed of synthesis (anabolism) and degradation (catabolism) (**Figure 1**).

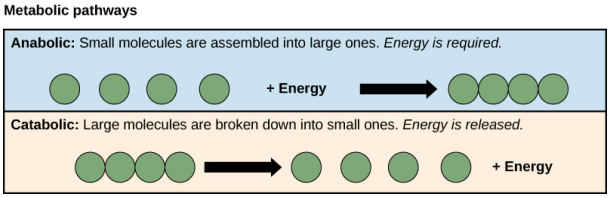


Figure 1*Catabolic pathways are those that generate energy by breaking down larger molecules. Anabolic pathways are those that require energy to synthesize larger molecules. Both types of pathways are required for maintaining the cell's energy balance.*

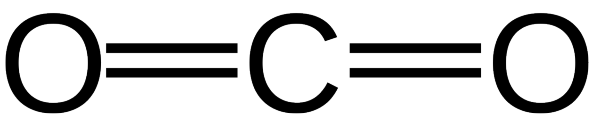
It is important to know that the chemical reactions of metabolic

pathways do not take place on their own. Each reaction step is facilitated, or catalyzed, by a protein called an **enzyme**. Enzymes are important for catalyzing all types of biological reactions—those that require energy as well as those that release energy. Refer back to the chapter on enzymes if you need a reminder about this topic.

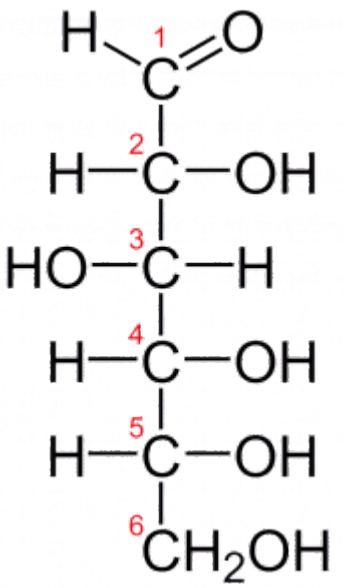
Consider the metabolism of sugar (a carbohydrate). This is a classic example of one of the many cellular processes that use and produce energy. Living things consume sugars as a major energy source, because sugar molecules have a great deal of energy stored within their bonds. For the most part, photosynthesizing organisms like plants produce these sugars. During photosynthesis, plants use energy (originally from sunlight) to convert carbon dioxide gas (CO_2) into sugar molecules (like glucose: $C_6H_{12}O_6$). They consume carbon dioxide and produce oxygen as a waste product. This reaction is summarized as:

$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$

Recall from chemistry that the abbreviation "CO_2" means "one carbon atom covalently bonded to two oxygen atoms." Water, "H_2O" is two hydrogen atoms covalently bonded to one oxygen atom. And "$C_6H_{12}O_6$" has 6 carbon atoms, 12 hydrogen atoms, and 6 oxygen atoms that are covalently bonded together.



Carbon dioxide (CO2) contains one carbon atom covalently bonded to two oxygen atoms. Credit: wikimedia



Glucose contains 6 carbons, 6 oxygens, and 12 hydrogen atoms. Credit: Ben, 2006. Wikimedia. Public domain.

The process of producing glucose from carbon dioxide and water requires an energy input to proceed because glucose contains more energy in its molecular bonds than carbon dioxide does. This means that the process of producing glucose is endergonic.

In contrast, energy-storage molecules such as glucose are consumed to be broken down to use their energy. The reaction that harvests the energy of a sugar molecule in cells requiring oxygen to survive can be summarized by the reverse reaction to photosynthesis. In this reaction, oxygen is consumed and carbon dioxide is released as a waste product. The reaction is summarized as:

$C_6H_{12}O_6 + 6O_2 -> 6H_2O + 6CO_2$

Both of these reactions involve many steps.

The processes of making and breaking down sugar molecules illustrate two examples of metabolic pathways. A **metabolic pathway** is a series of chemical reactions that takes a starting

molecule and modifies it, step-by-step, through a series of metabolic intermediates, eventually yielding a final product. In the example of sugar metabolism, the first metabolic pathway synthesized sugar from smaller molecules (anabolism), and the other pathway broke sugar down into smaller molecules (catabolism).

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62. An Overview of Cellular Respiration

Glucose and other molecules from food are broken down to release energy in a complex series of chemical reactions that together are called **cellular respiration**.

Cellular respiration is a set of metabolic reactions and processes that take place in the cells of organisms to convert biochemical energy from nutrients into ATP, and then release waste products. The reactions involved in respiration are catabolic reactions, which break large molecules into smaller ones, releasing energy in the process. These processes require a large number of enzymes which each perform one specific chemical reaction. Because of the laws of thermodynamics discussed in the enzyme chapter, every time energy is converted from one form to another, some of the energy is lost as heat. That means that during each of these enzyme-catalyzed reactions, some of the original energy from the sugar molecule is lost as heat.

Aerobic Respiration

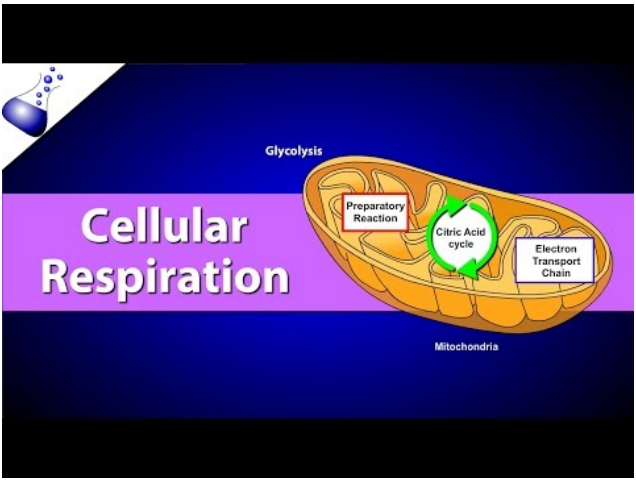
Aerobic respiration requires oxygen. This is the reason why we breathe oxygen in from the air. This type of respiration releases a large amount of energy from glucose that can be stored as ATP. Aerobic respiration happens all the time in animals and plants, where most of the reactions occur in the mitochondria. Even some prokaryotes can perform aerobic respiration (although since prokaryotes don't contain mitochondria, the reactions are slightly different). The overall chemical formula for aerobic respiration can be written as:

$C_6H_{12}O_2 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$ + (approximately) 38 ATP

Translating that formula into English: One molecule of glucose can be broken down in the presence of oxygen gas to produce waste products of carbon dioxide (which we breathe out) and water. This process has an overall release of energy which is captured and stored in 38 molecules of ATP.

Aerobic respiration is a complex process that can be divided into three basic stages: glycolysis, the citric acid cycle, and oxidative phosphorylation. The next several sections in the textbook address the details of these stages, but here is a basic summary:

- During **glycolysis,** 6-carbon glucose is broken in half and a small amount of energy is transferred to ATP and other energy carrier molecules.
- One carbon atom is broken off of each of the two halves of the glucose molecule (3-carbon molecules known as pyruvate) and released as carbon dioxide. This leaves two 2-carbon molecules called acetyls, which are attached to Coenzyme A to make acetyl-CoA.
- Acetyl-CoA enters the **citric acid cycle**, where it is completely broken down into carbon dioxide and all the energy from the molecule is transferred to ATP and other energy carrier molecules. The carbon atoms are released as carbon dioxide.
- The energy carrier molecules produced during glycolysis and the citric acid cycle are used to power the **electron transport chain and chemiosmosis** (together known as **oxidative phosphorylation**). The end result of this is the majority of ATP produced during aerobic respiration.



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Anaerobic Processes

Anaerobic Cellular Respiration

Some organisms (mostly bacteria) perform anaerobic cellular respiration. During anaerobic cellular respiration, cells use the same three basic stages: glycolysis, the citric acid cycle, and the electron transport chain / chemiosmosis, but another molecule is used in place of oxygen gas. This is not a common form of cellular respiration and isn't used by humans, so we will not be focusing on it.

Just as a side note here, typically when "anaerobic respiration" is mentioned in videos and animations, they are *not* talking about this process. They are talking about fermentation (below).

Fermentation

Fermentation is also a form of cellular respiration that occurs in the absence of oxygen. There are several different types of fermentation, which will be discussed in more detail later. Fermentation releases a much smaller amount of energy than aerobic respiration. In fact, it does not release enough energy to power human cells for long – think about how long a person can live if they are not able to breathe. Fermentation occurs in muscle cells during hard exercise (after the oxygen has been used up). It also occurs in yeast when brewing beer. Many prokaryotes perform anaerobic respiration.

All types of fermentation involve glycolysis, and none of them go through the citric acid cycle or oxidative phosphorylation. Instead, various other methods are used to regenerate the molecules needed for glycolysis, For now, we will summarize them all using this chemical formula:

$C_6H_{12}O_2$ NAD+ → various waste products + NADH + 2 ATP

NAD+ and NADH are two states of a molecule that will carry energy during this process. It will be addressed further in a later section. For right now, just know that NADH carries energy (similar to ATP) and NAD+ is the form that carries less energy (similar to ADP).

Aerobic vs anaerobic respiration

	Aerobic	Fermentation
Requires oxygen?	Yes	No
Glucose breakdown	Complete	Incomplete
End products	CO_2 and H_2O	Animal cells: lactic acid Plant cells and yeast: carbon dioxide and ethanol
ATP produced	About 38	2

Aerobic respiration is much more efficient than fermentation. One molecule of glucose can generate up to 38 molecules of ATP if aerobic respiration is used. In contrast, only 2 molecules of ATP are generated in fermentation.

To put it another way, a cellular process which requires 100 molecules of ATP:

- Will require about 2.5 molecules of glucose to be broken down using aerobic respiration (100 / 38 = 2.63)
- Will require 50 molecules of glucose to be broken down using fermentation (100 / 2 = 50)

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References

Wikipedia.

63. Glycolysis

You have read that nearly all of the energy used by living things comes to them in the bonds of the sugar, glucose. **Glycolysis** is the first step in the breakdown of glucose to extract energy for cell metabolism. Many living organisms carry out glycolysis as part of their metabolism. Glycolysis takes place in the cytoplasm of most prokaryotic and all eukaryotic cells.

Glycolysis begins with a molecule of glucose ($C_6H_{12}O_6$). Various enzymes are used to break glucose down into two molecules of pyruvate ($C_3H_4O_3$, basically a glucose molecule broken in half). This process releases a small amount of energy.

Glycolysis consists of two distinct phases. In the first part of the glycolysis pathway, energy is used to make adjustments so that the six-carbon sugar molecule can be split evenly into two three-carbon pyruvate molecules. In the second part of glycolysis, ATP and nicotinamide-adenine dinucleotide (NADH) are produced (**Figure 2**).

If the cell cannot catabolize (break down) the pyruvate molecules further, it will harvest only two ATP molecules from one molecule of glucose. For example, mature mammalian red blood cells are only capable of glycolysis, which is their sole source of ATP. If glycolysis is interrupted, these cells would eventually die.

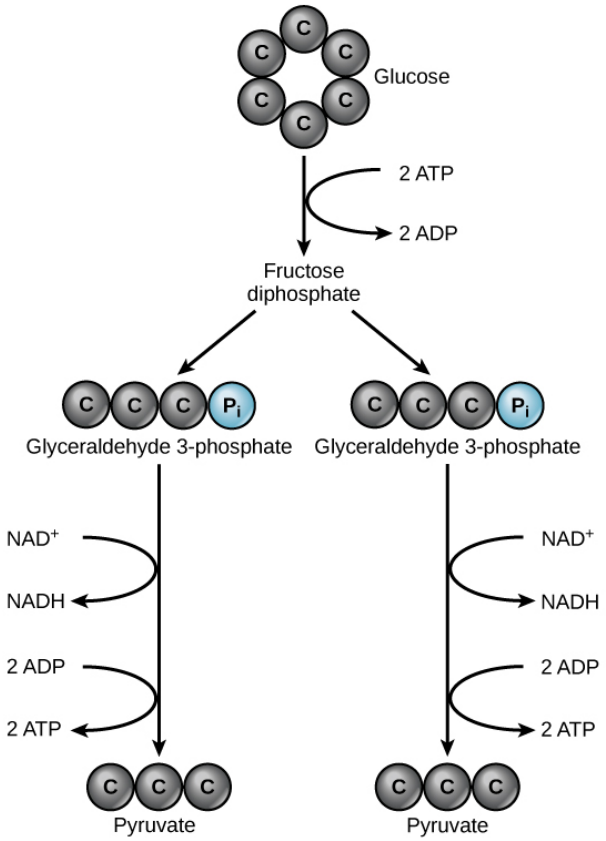

Figure 2 In glycolysis, a 6-carbon glucose molecule is converted into two 3-carbon pyruvate molecules.

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64. The Citric Acid Cycle

In eukaryotic cells, the pyruvate molecules produced at the end of glycolysis are transported into mitochondria. Mitochondria are sites of cellular respiration; In the presence of oxygen, aerobic respiration will proceed. In the mitochondria, pyruvate is first transformed into a two-carbon acetyl group by removing a molecule of carbon dioxide. This acetyl group is attached to a carrier compound called coenzyme A (CoA), which is made from vitamin B5. The resulting 2-carbon compound is called **acetyl CoA**. (**Figure 3**). Acetyl CoA can be used in a variety of ways by the cell, but its major function is to deliver the acetyl group derived from pyruvate to the next pathway in glucose catabolism.

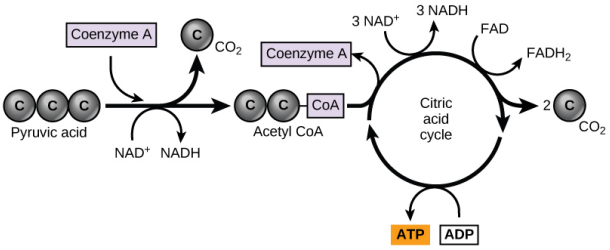

Figure 3 The Citric Acid Cycle

Like the conversion of pyruvate to acetyl CoA, the **citric acid cycle** in eukaryotic cells takes place in the matrix of the mitochondria. Unlike glycolysis, the citric acid cycle is a closed loop: The last part of the pathway regenerates the compound used in the first step. The eight steps of the cycle are a series of chemical reactions that produces the following from each molecule of pyruvate (remember that there are 2 molecules of pyruvate produced per molecule of glucose that originally went into glycolysis):

- 2 carbon dioxide molecules
- 1 ATP molecule (or an equivalent)
- 3 NADH and 2 $FADH_2$, which carry energy to the last part of the aerobic respiration pathway.

Part of this is considered an **aerobic** pathway (oxygen-requiring) because the NADH and $FADH_2$ produced must transfer their electrons to the next pathway in the system, which will use oxygen. If oxygen is not present, this transfer does not occur. The citric acid cycle does NOT occur in anaerobic respiration.

The citric acid cycle is also sometimes called the TCA cycle or the Krebs cycle. These names can be used interchangeably – they all refer to the same process.

More Details

Two carbon atoms come into the citric acid cycle from each acetyl group. Two carbon dioxide molecules are released on each turn of the cycle; however, these do not contain the same carbon atoms contributed by the acetyl group on that turn of the pathway. The two acetyl-carbon atoms will eventually be released on later turns of the cycle; in this way, all six carbon atoms from the original glucose molecule will be eventually released as carbon dioxide. It takes two turns of the cycle to process the equivalent of one glucose molecule. Each turn of the cycle forms three high-energy NADH molecules and one high-energy $FADH_2$ molecule. These high-energy carriers will connect with the last portion of aerobic respiration to produce ATP molecules. One ATP (or an equivalent) is also made in each cycle. Several of the intermediate compounds in the citric acid cycle can be used in synthesizing non-essential amino acids; therefore, the cycle is both anabolic and catabolic.

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65. Oxidative Phosphorylation

You have just read about two pathways in glucose catabolism—glycolysis and the citric acid cycle—that generate ATP. Most of the ATP generated during the aerobic catabolism of glucose, however, is not generated directly from these pathways. Rather, it derives from a process that begins with passing electrons through a series of chemical reactions to a final electron acceptor, oxygen. This is the only place in aerobic respiration where $O_2$is actually required. These reactions take place in specialized protein complexes located in the inner membrane of the mitochondria of eukaryotic organisms and on the inner part of the cell membrane of prokaryotic organisms. The energy of the electrons is used to generate ATP. The entirety of this process is called **oxidative phosphorylation**.

During oxidative phosphorylation:

- The energy from NADH and $FADH_2$is used up.
- Oxygen gas is converted into water.
- 30-36 ATP are recharged from ADP

Electron Transport Chain

The electron transport chain (**Figure 1**) is the last component of aerobic respiration and is the only part of metabolism that uses atmospheric oxygen. Oxygen continuously diffuses into plants for this purpose. In animals, oxygen enters the body through the respiratory system. Electron transport is a series of chemical reactions that resembles a bucket brigade in that electrons are

passed rapidly from one component to the next, to the endpoint of the chain where oxygen is the final electron acceptor and water is produced. There are four complexes composed of proteins, labeled I through IV in **Figure 1**, and the aggregation of these four complexes, together with associated mobile, accessory electron carriers, is called the **electron transport chain**. The electron transport chain is present in multiple copies in the **inner mitochondrial membrane** of eukaryotes and in the plasma membrane of prokaryotes. In each transfer of an electron through the electron transport chain, the electron loses energy, but with some transfers, the energy is stored as potential energy by using it to pump hydrogen ions (H^+, protons) across the inner mitochondrial membrane into the **intermembrane space**, creating an **electrochemical gradient**. An electrochemical gradient consists of two parts: a difference in solute concentration across the membrane combined with a difference in charge across the membrane. Here, the electrochemical gradient is made up of a higher concentration of H+ in the inner membrane space compared to the mitochondrial matrix.

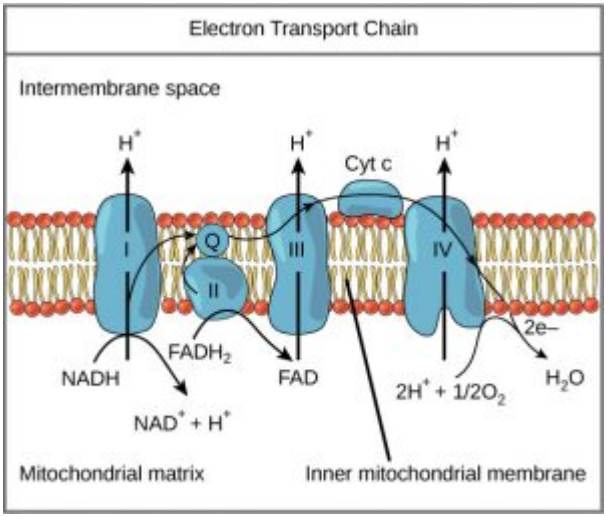

Figure 1*The electron transport chain is a series of electron transporters embedded in the inner mitochondrial membrane that shuttles electrons from NADH and* $FADH_2$ *to molecular oxygen. In the process, protons are pumped from the mitochondrial matrix to the intermembrane space, and oxygen is reduced to form water.*

Electrons from NADH and $FADH_2$ are passed to protein complexes in the electron transport chain. As they are passed from one complex to another (there are a total of four), the electrons lose energy, and some of that energy is used to pump hydrogen ions from the mitochondrial matrix into the intermembrane space. In the fourth protein complex, the electrons are accepted by oxygen, the terminal acceptor. The oxygen with its extra electrons then combines with two hydrogen ions, further enhancing the electrochemical gradient, to form water. If there were no oxygen present in the mitochondrion, the electrons could not be removed from the system, and the entire electron transport chain would back up and stop. The mitochondria would be unable to generate new ATP in

this way, and the cell would ultimately die from lack of energy. This is the reason we must breathe to draw in new oxygen. This is the only place where oxygen is required during the processes of aerobic respiration.

In the electron transport chain, the free energy from the series of reactions just described is used to pump hydrogen ions across the membrane. The uneven distribution of H+ ions across the membrane establishes an electrochemical gradient, owing to the H+ ions' positive charge and their higher concentration on one side of the membrane.

Hydrogen ions diffuse from the intermembrane space through the inner membrane into the mitochondrial matrix through an integral membrane protein called **ATP synthase** (**Figure 2**). This complex protein acts as a tiny generator, turned by the force of the hydrogen ions diffusing through it, down their electrochemical gradient from the intermembrane space, where there are many mutually repelling hydrogen ions to the matrix, where there are few. The turning of the parts of this molecular machine regenerate ATP from ADP. This flow of hydrogen ions across the membrane through ATP synthase is called **chemiosmosis**.

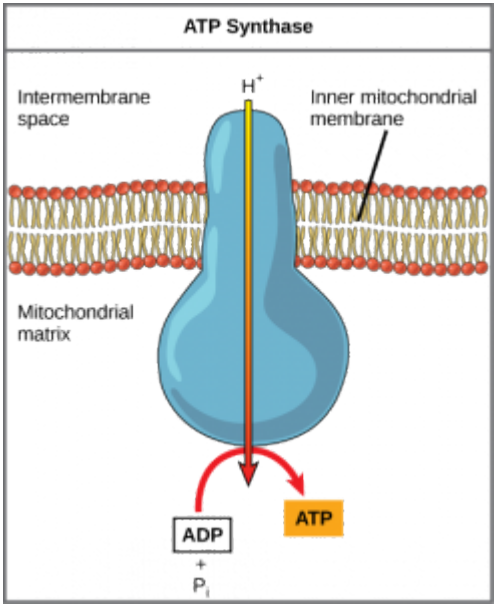

Figure 2ATP *synthase is a complex, molecular machine that uses a proton (H+) gradient to form ATP from ADP and inorganic phosphate (Pi). (Credit: modification of work by Klaus Hoffmeier)*

Chemiosmosis (**Figure 2**) is used to generate 90 percent of the ATP made during aerobic glucose catabolism. The result of the reactions is the production of ATP from the energy of the electrons removed from hydrogen atoms. These atoms were originally part of a glucose molecule. At the end of the electron transport system, the electrons are used to reduce an oxygen molecule to oxygen ions. The extra electrons on the oxygen ions attract hydrogen ions (protons) from the surrounding medium, and water is formed. The electron transport chain and the production of ATP through chemiosmosis are collectively called **oxidative phosphorylation (Figure 3)**.

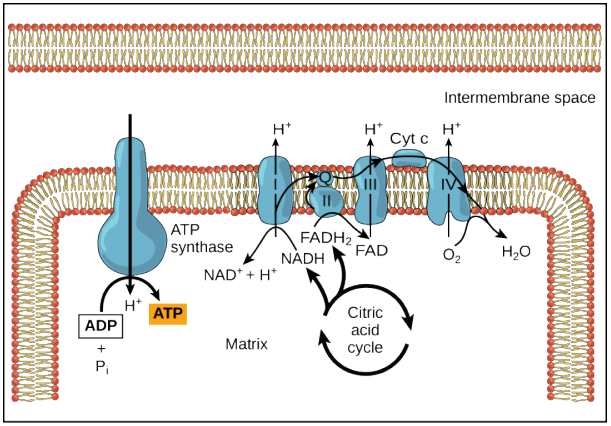

Figure 3*In oxidative phosphorylation, the pH gradient formed by the electron transport chain is used by ATP synthase to form ATP.*

ATP Yield

The number of ATP molecules generated from the catabolism of glucose varies. For example, the number of hydrogen ions that the electron transport chain complexes can pump through the membrane varies between species. Another source of variance stems from the shuttle of electrons across the membranes of the mitochondria because the NADH generated from glycolysis cannot easily enter mitochondria. Thus, electrons are picked up on the inside of mitochondria by either NAD^+or FAD^+. As you have learned earlier, these FAD^+molecules can transport fewer ions; consequently, fewer ATP molecules are generated when FAD^+acts as a carrier. $NAD^+$is used as the electron transporter in the liver and FAD^+acts in the brain.

Another factor that affects the yield of ATP molecules generated from glucose is the fact that intermediate compounds in these pathways are used for other purposes. Glucose catabolism connects with the pathways that build or break down all other biochemical compounds in cells, and the result is somewhat messier than the ideal situations described thus far. For example, sugars other than

glucose are fed into the glycolytic pathway for energy extraction. Moreover, the five-carbon sugars that form nucleic acids are made from intermediates in glycolysis. Certain nonessential amino acids can be made from intermediates of both glycolysis and the citric acid cycle. Lipids, such as cholesterol and triglycerides, are also made from intermediates in these pathways, and both amino acids and triglycerides are broken down for energy through these pathways. Overall, in living systems, these pathways of glucose catabolism extract about 34 percent of the energy contained in glucose.

Section Summary

The electron transport chain is the portion of aerobic respiration that uses free oxygen as the final electron acceptor of the electrons removed from the intermediate compounds in glucose catabolism. The electron transport chain is composed of four large, multiprotein complexes embedded in the inner mitochondrial membrane and two small diffusible electron carriers shuttling electrons between them. The electrons are passed through a series of reactions, with a small amount of free energy used at three points to transport hydrogen ions across a membrane. This process contributes to the gradient used in chemiosmosis. The electrons passing through the electron transport chain gradually lose energy until eventually they are donated to oxygen gas which accepts two protons (H+) and is converted into water. The end products of the electron transport chain are water and roughly 30-34 molecules of ATP. A number of intermediate compounds of the citric acid cycle can be diverted into the anabolism of other biochemical molecules, such as nonessential amino acids, sugars, and lipids. These same molecules can serve as energy sources for the glucose pathways.

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OpenStax, Biology. OpenStax CNX. September 16, 2017 https://cnx.org/contents/GFy_h8cu@10.118:7oTVAgrZ@7/Oxidative-Phosphorylation

66. Metabolism without Oxygen: Fermentation

In aerobic respiration, the final electron acceptor for the electron transport chain is an oxygen molecule, O_2. If aerobic respiration occurs, then approximately 30 molecules of ATP will be produced during the electron transport chain and chemiosmosis using the energy of the high-energy electrons carried by NADH or $FADH_2$to the electron transport chain. When NADH or $FADH_2$ give their high energy electrons to the electron transport chain, $NAD^+$and FAD are regenerated. These low energy molecules cycle back to glycolysis and/or the citric acid cycle, where they pick up more high energy electrons and allow the process to continue.

Glycolysis and the citric acid cycle can not occur if there is not NAD^+*present to pick up electrons as the reactions proceed.*When oxygen is present, this isn't a problem – all of the NADH and $FADH_2$ that were produced during glycolysis and the citric acid cycle are converted back into $NAD^+$and FAD after the electron transport chain. When no oxygen is present, the electron transport chain can't run because there is no oxygen to act as the final electron acceptor. This means that the ETC will not be accepting electrons from NADH as its source of power, so NAD^+will not be regenerated. Both glycolysis and the citric acid cycle require NAD^+ to accept electrons during their chemical reactions. In order for the cell to continue to generate *any*ATP, NADH must be converted back to $NAD^+$for use as an electron carrier. Anaerobic processes use different mechanisms, but all function to convert NAD^+back into NADH.

How is this done?

- Processes that use an organic molecule to regenerate $NAD^+$from NADH are collectively referred to as **fermentation**.

- In contrast, some living systems use an inorganic molecule (such as nitrate or sulfur) to regenerate NAD^+.

Both of these methods are called **anaerobic cellular respiration**. They do not require oxygen to achieve NAD^+regeneration and enable organisms to convert energy for their use in the absence of oxygen.

During anaerobic respiration, only glycolysis occurs. The 2 molecules of NADH that are generated during glycolysis are then converted back into NAD+ during anaerobic respiration so that glycolysis can continue. Since glycolysis only produces 2 ATP, anaerobic respiration is much less efficient than aerobic respiration (2 ATP molecules compared to 36-ish ATP molecules). However, 2 ATP molecules is much better for a cell than 0 ATP molecules. In anaerobic situations, the cell needs to continue performing glycolysis to generate 2 ATP per glucose because if a cell is not generating any ATP, it will die.

Note that the only part of aerobic respiration that physically uses oxygen is the electron transport chain. However, the citric acid cycle can not occur in the absence of oxygen because there is no way to regenerate the NAD+ used during this process.

Lactic Acid Fermentation

The fermentation method used by animals and some bacteria like those in yogurt is lactic acid fermentation (**Figure 1**). This occurs routinely in mammalian red blood cells and in skeletal muscle that does not have enough oxygen to allow aerobic respiration to continue (such as in muscles after hard exercise). The chemical reaction of lactic acid fermentation is the following:

Pyruvic acid + NADH ↔ lactic acid + NAD^+

The build-up of lactic acid causes muscle stiffness and fatigue. In muscles, lactic acid produced by fermentation must be removed by the blood circulation and brought to the liver for further metabolism. Once the lactic acid has been removed from the muscle and is circulated to the liver, it can be converted back to pyruvic acid and further catabolized (broken down) for energy.

Note that the purpose of this process is not to produce lactic acid (which is a waste product and is excreted from the body). The purpose is to convert NADH back into NAD^+so that glycolysis can continue so that the cell can produce 2 ATP per glucose.

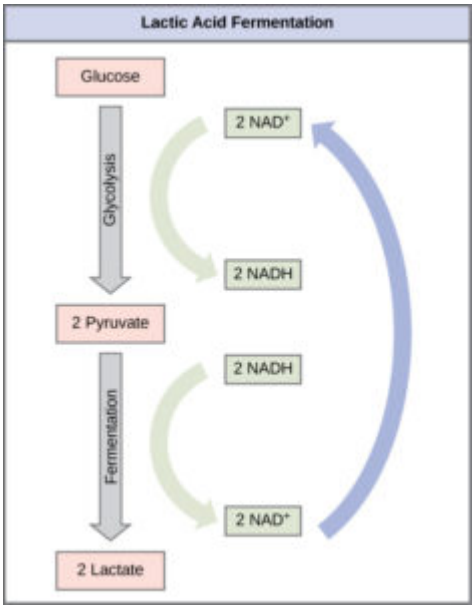

Figure 1 *Lactic acid fermentation is common in muscles that have become exhausted by use.*

Alcohol Fermentation

Another familiar fermentation process is alcohol fermentation (**Figure 2**), which produces ethanol, an alcohol. The alcohol fermentation reaction is the following:

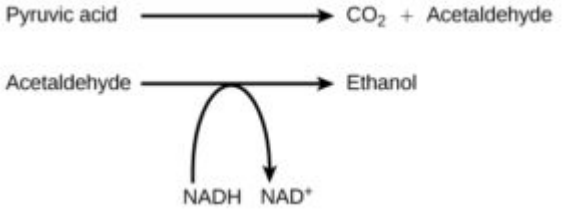

Figure 2 *The reaction resulting in alcohol fermentation is shown.*

The fermentation of pyruvic acid by yeast produces the ethanol found in alcoholic beverages (**Figure 3**). If the carbon dioxide produced by the reaction is not vented from the fermentation chamber, for example in beer and sparkling wines, it remains dissolved in the medium until the pressure is released. Ethanol above 12 percent is toxic to yeast, so natural levels of alcohol in wine occur at a maximum of 12 percent.

Figure 3 *Fermentation of grape juice to make wine produces CO_2as a byproduct. Fermentation tanks have valves so that pressure inside the tanks can be released.*

Again, the purpose of this process is not to produce ethanol, but rather to convert NADH back into NAD^+so that glycolysis can continue.

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67. Metabolism of Molecules Other Than Glucose

You have learned about the catabolism of glucose, which provides energy to living cells. But living things consume more than just glucose for food. How does a turkey sandwich, which contains various carbohydrates, lipids, and protein, provide energy to your cells?

Basically, all of these molecules from food are converted into molecules that can enter the cellular respiration pathway somewhere. Some molecules enter at glycolysis, while others enter at the citric acid cycle. This means that all of the catabolic pathways for carbohydrates, proteins, and lipids eventually connect into glycolysis and the citric acid cycle pathways. Metabolic pathways should be thought of as porous—that is, substances enter from other pathways, and other substances leave for other pathways. These pathways are not closed systems. Many of the products in a particular pathway are reactants in other pathways.

Carbohydrates

So far, we have discussed the carbohydrate from which organisms derive the majority of their energy: glucose. Many carbohydrate molecules can be broken down into glucose or otherwise processed into glucose by the body. **Glycogen,** a polymer of glucose, is a short-term energy storage molecule in animals (**Figure 1**). When there is plenty of ATP present, the extra glucose is converted into glycogen for storage. Glycogen is made and stored in the liver and muscle. Glycogen will be taken out of storage if blood sugar levels drop.

The presence of glycogen in muscle cells as a source of glucose allows ATP to be produced for a longer time during exercise.

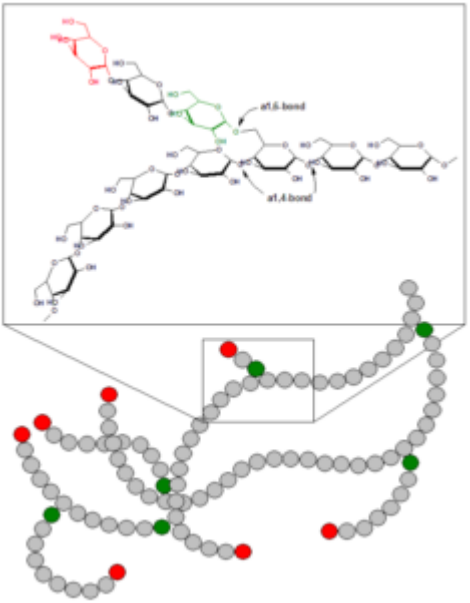

Figure 1*Glycogen is made of many molecules of glucose attached together into branching chains. Each of the balls in the bottom diagram represents one molecule of glucose. (Credit: Glycogen by BorisTM. This work has been released into the public domain)*

Most other carbohydrates enter the cellular respiration pathway during glycolysis. For example, **sucrose**is a disaccharide made from glucose and fructose bonded together. Sucrose is broken down in the small intestine. The glucose enters the beginning of glycolysis as previously discussed, while fructose can be slightly modified and enter glycolysis at the third step. **Lactose,**the disaccharide sugar found in milk, can be broken down by lactase enzyme into two smaller sugars: galactose and glucose. Like fructose, galactose can be slightly modified to enter glycolysis.

Because these carbohydrates enter near the beginning of glycolysis, their catabolism (breakdown) produces the same number of ATP molecules as glucose.

Proteins

Proteins are broken down by a variety of enzymes in cells. Most of the time, amino acids are recycled into new proteins and not used as a source of energy. This is because it is more energy efficient to reuse amino acids rather than making new ones from scratch. The body will use protein as a source of energy if:

- There are excess amino acids (you consume a lot of protein)
- The body is in a state of famine (you are starving and have no other source of energy available)

When proteins are used in the cellular respiration pathway, they are first broken down into individual amino acids. The amino group from each amino acid is removed (deaminated) and is converted into ammonia. In mammals, the liver synthesizes urea from two ammonia molecules and a carbon dioxide molecule. Thus, urea is the principal waste product in mammals from the nitrogen originating in amino acids, and it leaves the body in urine.

Once the amino acid has been deaminated, its chemical properties determine which intermediate of the cellular respiration pathway it will be converted into. These intermediates enter cellular respiration at various places in the Citric Acid Cycle (**Figure 2**).

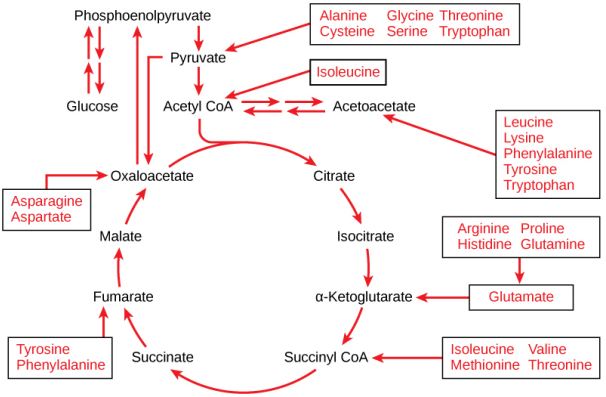

Figure 2 *The carbon skeletons of certain amino acids (indicated in boxes) derived from proteins can feed into the citric acid cycle. (credit: modification of work by Mikael Häggström)*

Lipids

Triglycerides (fats) are a form of long-term energy storage in animals. Triglycerides store about twice as much energy as carbohydrates. Triglycerides are made of glycerol and three fatty acids. Glycerol can enter glycolysis. Fatty acids are broken into two-carbon units that enter the citric acid cycle (**Figure 3**).

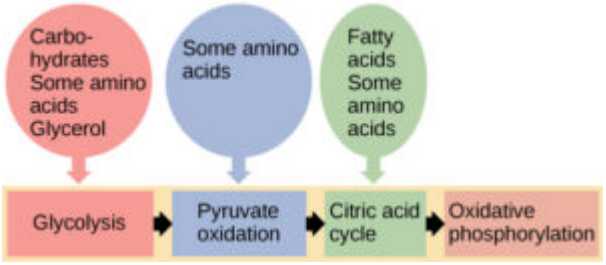

Figure 3 *Glycogen from the liver and muscles, together with fats, can feed into the catabolic pathways for carbohydrates.*

Remember that if oxygen is not available, glycolysis can occur but not the citric acid cycle or oxidative phosphorylation. Since fatty acids enter the pathway at the citric acid cycle, they can not be broken down in the absence of oxygen. This means that if cells are not performing aerobic cellular respiration, the body can not burn fat for energy. This is why posters about the "Fat Burning Zone" in a gym specify that you need to have a lower heart rate / breathing rate to burn more fat – cells that are not doing aerobic respiration can't burn fat for fuel!

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References

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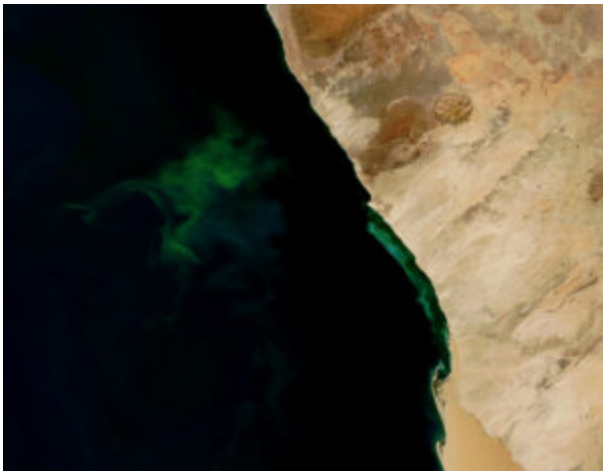
68. Anaerobic Cellular Respiration in Prokaryotes

Certain prokaryotes, including some species of bacteria and Archaea, use anaerobic respiration. For example, the group of Archaea called methanogens reduces carbon dioxide to methane to oxidize NADH. These microorganisms are found in soil and in the digestive tracts of ruminants, such as cows and sheep. Similarly, sulfate-reducing bacteria and Archaea, most of which are anaerobic (**Figure 8**), reduce sulfate to hydrogen sulfide to regenerate NAD^+ from NADH.



Other fermentation methods occur in bacteria. Many prokaryotes are facultatively anaerobic. This means that they can switch between aerobic respiration and fermentation, depending on the availability of oxygen. Certain prokaryotes, like *Clostridia* bacteria, are obligate anaerobes. Obligate anaerobes live and grow in the absence of molecular oxygen. Oxygen is a poison to these microorganisms and kills them upon exposure. It should be noted

that all forms of fermentation, except lactic acid fermentation, produce gas. The production of particular types of gas is used as an indicator of the fermentation of specific carbohydrates, which plays a role in the laboratory identification of the bacteria. The various methods of fermentation are used by different organisms to ensure an adequate supply of NAD^+ for the sixth step in glycolysis. Without these pathways, that step would not occur, and no ATP would be harvested from the breakdown of glucose.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 http://cnx.org/contents/b3c1e1d2-839c-42b0-a314-e119a8aafbdd@9.10

69. The Energy Cycle

Living things access energy by breaking down carbohydrate molecules. However, if plants make carbohydrate molecules, why would they need to break them down? Carbohydrates are storage molecules for energy in all living things. Although energy can be stored in molecules like ATP, carbohydrates are much more stable and efficient reservoirs for chemical energy. Photosynthetic organisms also carry out the reactions of respiration to harvest the energy that they have stored in carbohydrates, for example, plants have mitochondria in addition to chloroplasts.

You may have noticed that the overall reaction for photosynthesis:

$$\mathbf{6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2}$$

is the reverse of the overall reaction for cellular respiration:

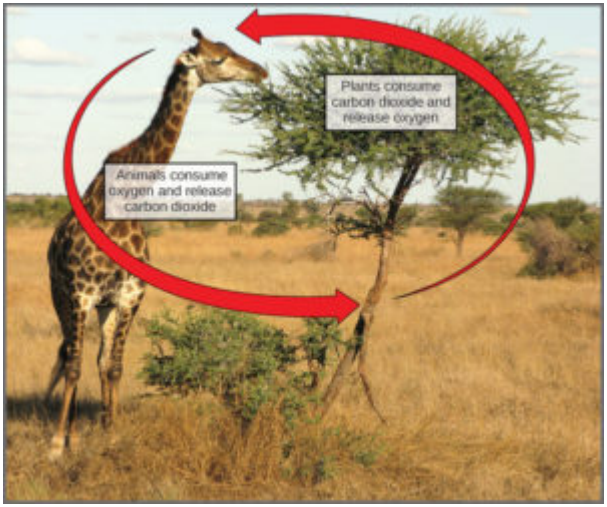
$$\mathbf{6O_2 + C_6H_{12}O_6 \rightarrow 6CO_2 + 6H_2O}$$

Photosynthesis produces oxygen as a byproduct, and respiration produces carbon dioxide as a byproduct.

In nature, there is no such thing as waste. Every single atom of matter is conserved, recycling indefinitely. Substances change form or move from one type of molecule to another, but never disappear (**Figure 16**).

CO_2 is no more a form of waste produced by respiration than oxygen is a waste product of photosynthesis. Both are byproducts of

reactions that move on to other reactions. Photosynthesis absorbs energy to build carbohydrates in chloroplasts, and aerobic cellular respiration releases energy by using oxygen to break down carbohydrates. Both organelles use electron transport chains to generate the energy necessary to drive other reactions. Photosynthesis and cellular respiration function in a biological cycle, allowing organisms to access life-sustaining energy that originates millions of miles away in a star.



The energy cycle

References

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PART XI

MEMBRANES AND THEIR FUNCTIONS

Learning Objectives

By the end of this section, you will be able to:

- Explain how the structure of cell membranes leads to its various functions including selective permeability and transport, and cell signaling.

The plasma membrane, which is also called the cell membrane, has many functions, but the most basic one is to define the borders of the cell and keep the cell functional. The plasma membrane is selectively permeable. This means that the membrane allows some materials to freely enter or leave the cell, while other materials cannot move freely, but require the use of a specialized structure, and occasionally, even energy investment for crossing.

References

Text adapted from: OpenStax, Concepts of Biology. OpenStax CNX. May 18, 2016 https://cnx.org/contents/GFy_h8cu@10.117:oaLwOnAf@2/Introduction

70. Structure of the Plasma Membrane

Cells closely control the exchange of substances in and out of the cell. Some substances are excluded, others are taken in, and still others are excreted – all in controlled quantities. Although the **plasma membrane (cell membrane)** encloses the cell's borders, it is far from being a static barrier; it is dynamic and constantly in flux. The plasma membrane must be sufficiently flexible to allow certain cells, such as red blood cells and white blood cells, to change shape as they pass through narrow capillaries. In addition to these more obvious functions, the surface of the plasma membrane carries markers which allow cells to recognize one another. This is vital as these markers play a role in the "self" versus "non-self" distinction of the immune response.

Fluid Mosaic Model

In 1972, S. J. Singer and Garth L. Nicolson proposed a new model of the plasma membrane. This theory, compared to earlier theories, best explains both microscopic observations and the function of the plasma membrane. This theory is called the **fluid mosaic model**. The model has evolved somewhat over time, but still best accounts for the structure and functions of the plasma membrane as we now understand them. The fluid mosaic model describes the structure of the plasma membrane as comprised of diverse components–including phospholipids, cholesterol, proteins, and carbohydrates–that are able to flow and change position, while maintaining the basic integrity of the membrane. Both phospholipid molecules and embedded proteins are able to move laterally in the

membrane. The fluidity of the plasma membrane is necessary for the activities of certain enzymes and transport molecules within the membrane.

Plasma membranes range from 5–10 nm thick. As a comparison, human red blood cells, visible via light microscopy, are approximately 8 μm thick, or approximately 1,000 times thicker than a plasma membrane.

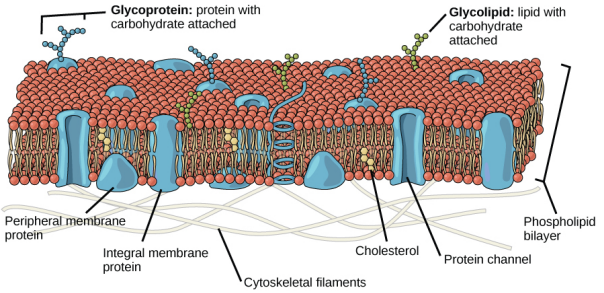
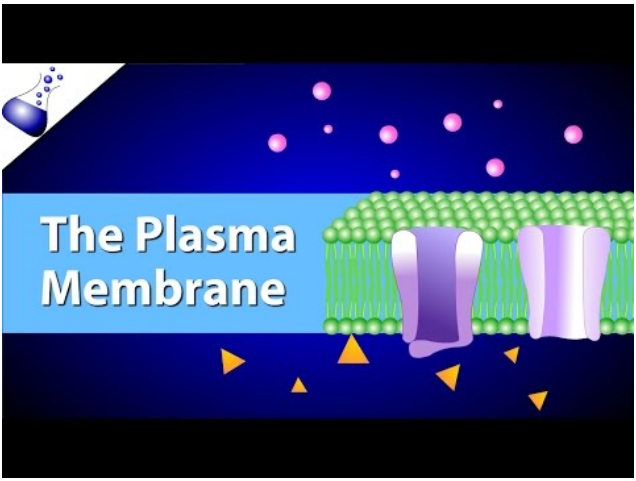


Figure 1 *The fluid mosaic model of the plasma membrane structure describes the plasma membrane as a fluid combination of phospholipids, cholesterol, proteins, and carbohydrates.*

Components of the Plasma Membrane

The plasma membrane is made up primarily of a bilayer of phospholipids with embedded proteins, carbohydrates, glycolipids, and glycoproteins, and, in animal cells, cholesterol (**Figure 1**).



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Phospholipids

The main fabric of the membrane is composed of two layers of phospholipid molecules, and the polar ends of these molecules (which look like a collection of balls in an artist's rendition of the model) (**Figure 2**) are in contact with aqueous fluid both inside and outside the cell. Thus, both surfaces of the plasma membrane are **hydrophilic** ("water loving"). In contrast, the interior of the membrane, between its two surfaces, is a **hydrophobic** ("water fearing") or nonpolar region because of the fatty acid tails. This region has no attraction for water or other polar molecules.

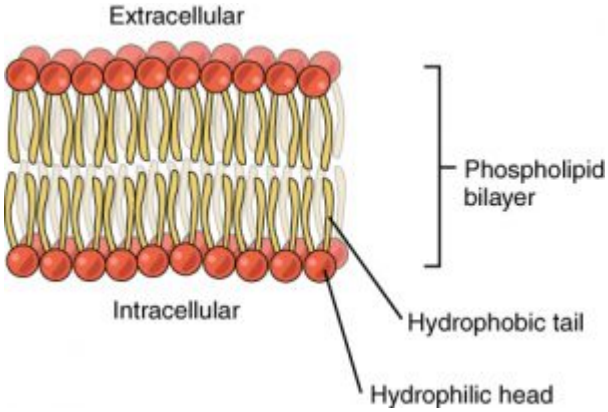


Figure 2 *Phospholipid bilayer. "Extracellular" = outside the cell; "Intracellular" = inside the cell. Photo credit: OpenStax Anatomy and Physiology.*

A phospholipid molecule (**Figure 3**) consists of a three-carbon glycerol backbone with two fatty acid molecules attached to carbons 1 and 2, and a phosphate-containing group attached to the third carbon. This arrangement gives the overall molecule an area described as its head (the phosphate-containing group), which has a polar character or negative charge, and an area called the tail (the fatty acids), which has no charge. The head can form hydrogen bonds, but the tail cannot.

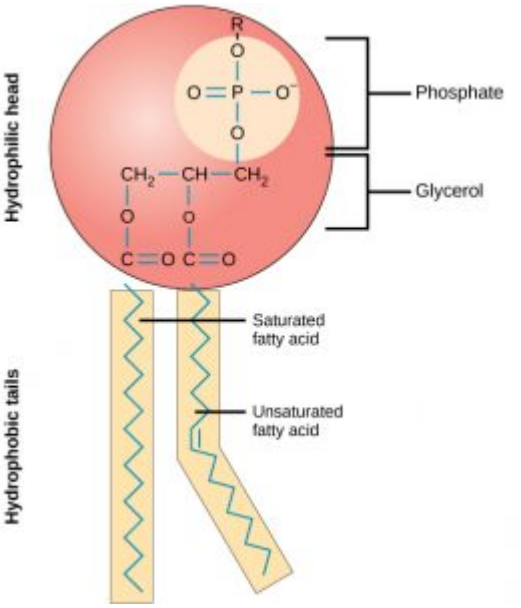


Figure 3 *This phospholipid molecule is composed of a hydrophilic head and two hydrophobic tails. The hydrophilic head group consists of a phosphate-containing group attached to a glycerol molecule. The hydrophobic tails, each containing either a saturated or an unsaturated fatty acid, are long hydrocarbon chains.*

Proteins

Proteins make up the second major chemical component of plasma membranes (see **Figure 1**). Proteins are embedded in the plasma membrane and can go all the way through the membrane or be found on one side or the other (**Figure 1**). Proteins may serve as enzymes, as structural attachments for the fibers of the cytoskeleton, or as part of the cell's recognition sites. Proteins that go all the way through the membrane can serve as channels or pumps to move materials into or out of the cell. Proteins are also found on either the exterior or interior surfaces of membranes

where they can be attached either to other proteins or to phospholipid molecules (**Figure 1**).

Five different types of proteins that are commonly associated with the cell membrane are described below.

Recognition (Identification) Proteins

Glycoproteins are proteins that have sugar molecules attached to them. Glycoproteins help cells recognize each other. The unique patterns of sugar molecules on the cell surface can be 'read' by corresponding glycoproteins on another cell. However, this process is different from how we read words. It's more like fitting a key into a lock; glycoproteins will often bind together if they're a match. This binding process communicates to the cell that it has found match. This is what helps our immune system recognize foreign invaders and then defend our body against them. The reverse is true, too. Viruses use glycoproteins to bind to and infect a host cell. Glycoprotein recognition also helps in reproduction.

Receptor Proteins

Cell surface receptors (membrane receptors, transmembrane receptors) are receptors that are embedded in the membranes of cells. A **receptor** is a type of recognition protein that can selectively bind a specific molecule outside the cell and this binding induces a chemical reaction within the cell. A ligand is the specific molecule that binds to and activates a receptor. The ligand molecules may be hormones, neurotransmitters, cytokines, growth factors, cell adhesion molecules, or nutrients; they react with the receptor to induce changes in the metabolism and activity of a cell.

Each receptor is structured to bind with a specific substance.

The binding of a specific substance to its receptor on the plasma membrane can activate processes within the interior of the cell – such as activating enzymes involved in metabolic pathways. These metabolic pathways might be vital for providing the cell with energy, making substances for the cell, or breaking down cellular waste or toxins for disposal. Likewise, extracellular hormones and neurotransmitters bind to plasma membrane receptors which transmit a signal into the cell to intracellular molecules. Some recognition sites are used by viruses as attachment points. Although they are highly specific, pathogens like viruses may evolve to exploit receptors to gain entry to a cell by mimicking the specific substance that the receptor is meant to bind. This specificity helps to explain why human immunodeficiency virus (HIV) or any of the five types of hepatitis viruses invade only specific cells.

Movement Proteins

Channel proteins allow the movement of materials from one side of the membrane to the other, without requiring energy. The molecule being moved is taken in on one side of the channel protein, and without using energy, the molecule is released into the cell. Channels are used for facilitated diffusion which is transport especially for large polar molecules and charged ions that cannot diffuse freely across cell membranes due to the hydrophobic nature of the fatty acid tails of the phospholipids that make up the bilayers.

Carrier proteins use energy to move molecules across the membrane. The chemical to be transported must first bind at a binding site on the carrier protein. Following binding, the carrier will take in and retain the material being moved. Next, the carrier protein changes shape so that the opening in the protein now faces the other side of the plasma membrane. The material being transported is then released on that side of the membrane.

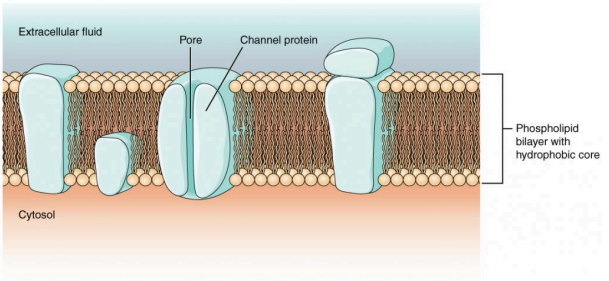


Figure 4 *Several membrane proteins. The channel protein in the center contains a pore or channel through which material can travel. From OpenStax Anatomy and Physiology*

Aquaporins also called water channels is a transmembrane protein that selectively conducts water molecules in and out of the cell, while preventing the passage of ions and other solutes. Water molecules travel through the pore of the channel in single file (Figure 5). The presence of aquaporins increases membrane permeability to water. Water molecules traverse through the pore of the channel in single file. The presence of water channels increases membrane permeability to water.

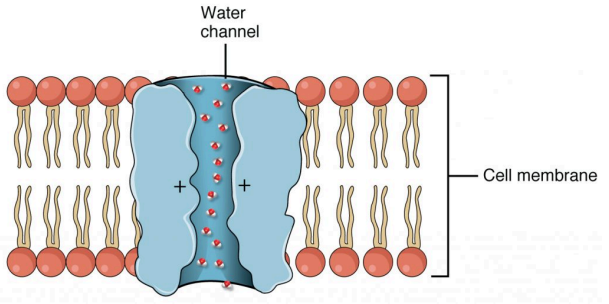
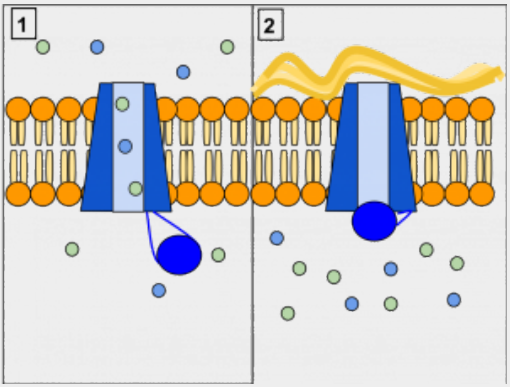


Figure 5 *The structure of an aquaporin or "water channel protein".*

Cystic Fibrosis is caused by a defect in an integral protein in the cell membrane which acts as a channel. The CFTR protein moves ions from one side of the membrane to another. When it is not functioning correctly, this causes very thick mucus to build up in the lungs and digestive tract.



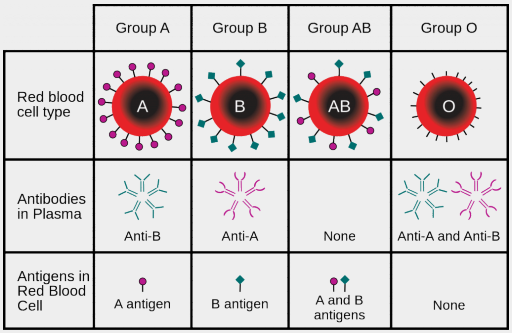
When the CFTR channel protein is functioning correctly (1), ions (small balls) are able to pass through the membrane. When it is not functioning correctly (2), ions are unable to cross the membrane. Photo credit: LBudd14, May, 2013. Wikimedia.

Carbohydrates

Carbohydrates are the third major component of plasma membranes. They are always found on the exterior surface of cells and are bound either to proteins (forming **glycoproteins**) or to lipids (forming **glycolipids**). These carbohydrate chains may consist of 2–60 monosaccharide units and may be either straight or branched.

Glycoproteins and glycolipids form specialized sites on the cell surface that allow cells to recognize each other. These sites have unique patterns that allow the cell to be recognized, much the way that the facial features unique to each person allow him or her to be recognized. This recognition function is very important to cells, as it allows the immune system to differentiate between body cells (called "self") and foreign cells or tissues (called "non-self"). Similar types of glycoproteins and glycolipids are found on the surfaces of viruses and may change frequently, preventing immune cells from recognizing and attacking them.

> The carbohydrates that make up glycoproteins are responsible for determining human A, B, O blood types. These glycoproteins are recognized by the immune system, which leads to incompatibility in blood types.



ABO Blood types. In this figure, the membrane carbohydrate is represented by the "lollipops". They are termed "antigens". Photo credit: InvictaHOG, 2006. Wikimedia.

Membrane Fluidity

The mosaic characteristic of the membrane, described in the fluid mosaic model, helps to illustrate its nature. The proteins and other components that exist in the membrane can move with respect to each other, rather like boats floating on a lake. The membrane is not like a balloon, however, that can expand and contract; rather, it is fairly rigid and can burst if penetrated or if a cell takes in too much water. However, because of its mosaic nature, a very fine needle can easily penetrate a plasma membrane without causing it to burst, and the membrane will flow and self-seal when the needle is extracted.

The mosaic characteristics of the membrane explain some but not

all of its fluidity. There are two other factors that help maintain this fluid characteristic. One factor is the nature of the phospholipids themselves. The structure of the fatty acid tails in each phospholipid can make the membrane more dense and rigid, or less dense and flexible. The relative fluidity of the membrane is particularly important in a cold environment. A cold environment tends to make membranes less fluid and more susceptible to rupturing. Many organisms (fish are one example) are capable of adapting to cold environments by changing the proportion of different types of fatty acids in their membranes in response to the lowering of the temperature.

Animals have an additional membrane constituent that assists in maintaining fluidity. **Cholesterol,** which lies alongside the phospholipids in the membrane, tends to dampen the effects of temperature on the membrane. Thus, this lipid functions as a buffer, preventing lower temperatures from inhibiting fluidity and preventing increased temperatures from increasing fluidity too much. Thus, cholesterol extends, in both directions, the range of temperature in which the membrane is appropriately fluid and consequently functional. Cholesterol also serves other functions, such as organizing clusters of proteins into lipid rafts.

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71. Membranes are Selectively Permeable

Plasma membranes act not only as a barrier, but also as a gatekeeper. It must allow needed substances to enter and cell products to leave the cell, while preventing entrance of harmful material and exit of essential material. In other words, plasma membranes are **selectively permeable**—they allow some substances through but not others (Figure 1). If the membrane were to lose this selectivity, the cell would no longer be able to maintain homeostasis, or to sustain itself, and it would be destroyed. Some cells require larger amounts of specific substances than other cells; they must have a way of obtaining these materials from the extracellular fluids.

This may happen passively, as certain materials move back and forth, or the cell may have special mechanisms that ensure transport. Most cells expend most of their energy, in the form of adenosine triphosphate (ATP), to create and maintain an uneven distribution of ions on the opposite sides of their membranes. The structure of the plasma membrane contributes to these functions.

Figure 1 The selective permeable cell membrane is like a window screen – it keeps some things from passing through (like bugs), while allowing some things to pass (like air). Photo from: Jonas Bergsten; Wikimedia Commons; Public Domain

Selective Permeability

Plasma membranes are asymmetric, meaning that despite the mirror image formed by the phospholipids, the side of the membrane facing the inside of the cell is not identical to the exterior of the membrane. Proteins that act as channels or pumps work in one direction. Carbohydrates, attached to lipids or proteins, are also found on the exterior surface of the plasma membrane.

These carbohydrate complexes help the cell bind substances in the extracellular fluid that the cell needs. This adds considerably to the selective nature of plasma membranes.

Recall that plasma membranes have hydrophilic and hydrophobic regions. This characteristic helps the movement of certain materials through the membrane and hinders the movement of others. Lipid-soluble material can easily slip through the hydrophobic lipid core

of the membrane. Substances such as the fat-soluble vitamins A, D, E, and K readily pass through the plasma membranes in the digestive tract and other tissues. Fat-soluble drugs also gain easy entry into cells and are readily transported into the body's tissues and organs. Molecules of oxygen and carbon dioxide have no charge and pass through by simple diffusion.

Polar substances, with the exception of water, present problems for the membrane. While some polar molecules connect easily with the outside of a cell, they cannot readily pass through the lipid core of the plasma membrane. Additionally, whereas small ions could easily slip through the spaces in the mosaic of the membrane, their charge prevents them from doing so. Ions such as sodium, potassium, calcium, and chloride must have a special means of penetrating plasma membranes. Simple sugars and amino acids also need help with transport across plasma membranes.

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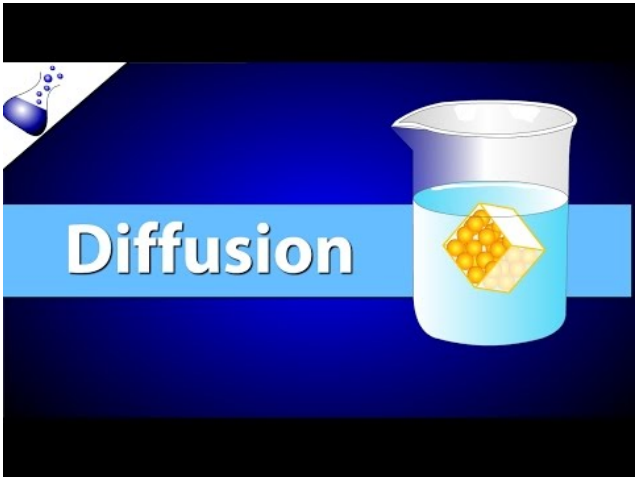
72. Passive Transport: Diffusion

The most direct forms of membrane transport are passive. **Passive transport** is a naturally occurring phenomenon and does not require the cell to expend energy to accomplish the movement. In passive transport, substances move from an area of higher concentration to an area of lower concentration in a process called **diffusion**. A physical space in which there is a different concentration of a single substance is said to have a **concentration gradient**.

Diffusion



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Diffusion is a passive process of transport. A single substance tends to move from an area of high concentration to an area of low concentration until the concentration is equal across the space. You are familiar with diffusion of substances through the air. For example, think about someone opening a bottle of perfume in a room filled with people. The perfume is at its highest concentration in the bottle and is at its lowest at the edges of the room. The perfume vapor will diffuse, or spread away, from the bottle, and gradually, more and more people will smell the perfume as it spreads. Materials move within the cell's cytosol by diffusion, and certain materials move through the plasma membrane by diffusion (**Figure 1**). Diffusion expends no energy. Rather the different

concentrations of materials in different areas are a form of potential energy, and diffusion is the dissipation of that potential energy as materials move down their concentration gradients, from high to low.

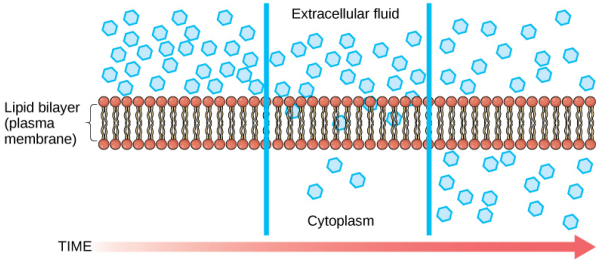

Figure 1 *Diffusion through a permeable membrane follows the concentration gradient of a substance, moving the substance from an area of high concentration to one of low concentration. (credit: modification of work by Mariana Ruiz Villarreal)*

Each separate substance in a medium, such as the extracellular fluid, has its own concentration gradient, independent of the concentration gradients of other materials. Additionally, each substance will diffuse according to that gradient.

Several factors affect the rate of diffusion:

- Extent of the concentration gradient: The greater the difference in concentration, the more rapid the diffusion. The closer the distribution of the material gets to equilibrium, the slower the rate of diffusion becomes.
- Mass of the molecules diffusing: More massive molecules move more slowly, because it is more difficult for them to move

between the molecules of the substance they are moving through; therefore, they diffuse more slowly.
- Temperature: Higher temperatures increase the energy and therefore the movement of the molecules, increasing the rate of diffusion.
- Solvent density: As the density of the solvent increases, the rate of diffusion decreases. The molecules slow down because they have a more difficult time getting through the denser medium.

Gas Exchange

Our bodies need to bring in oxygen and get rid of excess carbon dioxide. This process is called gas exchange. Gas exchange occurs at two sites in the body:

- In the lungs, where oxygen is picked up and carbon dioxide is released at the respiratory membrane. This is called external respiration.
- At the tissues, where oxygen is released and carbon dioxide is picked up. This is called internal respiration.

The actual exchange of gases occurs due to simple diffusion, which means that energy is not required to move oxygen or carbon dioxide across membranes. Instead, these gases follow pressure gradients that allow them to diffuse. You'll learn more about partial pressure and pressure gradients in A&P. Pressure is proportional to concentration, so we will discuss this process by

talking about the concentration of gas, rather than its pressure. The anatomy of the lung maximizes the diffusion of gases: The respiratory membrane is highly permeable to gases; the respiratory and blood capillary membranes are very thin; and there is a large surface area throughout the lungs.

External Respiration

As blood is pumped through small blood vessels (capillaries) in the lungs, gas exchange occurs from the air in the alveoli into the blood. Although a small amount of the oxygen is able to dissolve directly into plasma from the alveoli, most of the oxygen is picked up by erythrocytes (red blood cells) and binds to a protein called hemoglobin. Oxygenated hemoglobin is red, causing the overall appearance of bright red oxygenated blood, which returns to the heart through the pulmonary veins. Carbon dioxide is released in the opposite direction of oxygen, from the blood to the alveoli.

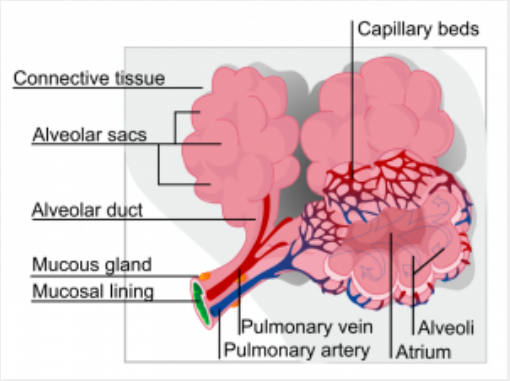

Figure 2 *A zoomed-in view of the alveolar sacs and capillaries inside the lung. Picture by: LadyofHats; Wikimedia Commons; Public Domain.*

Oxygen is diffusing from the air inside the alveoli within the lungs into the erythrocytes and blood plasma. Diffusion is a type of passive transport, where molecules move from high concentration to low concentration. This means that the concentration of oxygen in the air must be higher than it is in the blood.

The concentration of carbon dioxide is also different between the alveolar air and the blood of the capillary. Carbon dioxide diffuses out of the blood into the air spaces because the concentration of carbon dioxide is higher in the air spaces than in the blood.

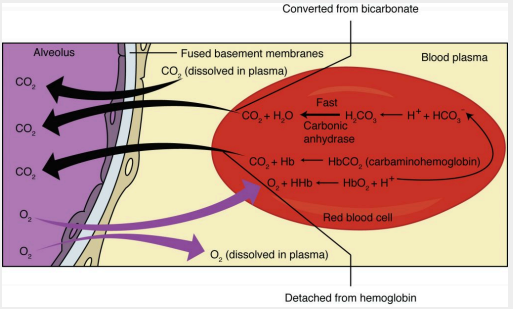

Figure 3 *In external respiration, oxygen diffuses across the respiratory membrane from the alveolus to the capillary, whereas carbon dioxide diffuses out of the capillary into the alveolus. From OpenStax Anatomy and Physiology.*

Internal Respiration

Internal respiration is gas exchange that occurs at the level of body tissues (Figure 2). Similar to external respiration, internal respiration also occurs as simple diffusion due to a concentration gradient. However, the concentrations are opposite of those present at the respiratory membrane. Oxygen diffuses into tissues

because its concentration is higher in the blood than inside the tissue (where oxygen is always being used up during cellular respiration). Carbon dioxide, which is always being produced during cellular respiration, diffuses out for the opposite reason. Hemoglobin that has little oxygen bound to it loses much of its brightness, so that blood returning to the heart is more burgundy in color. The blood is then pumped back to the lungs to be oxygenated once again during external respiration.

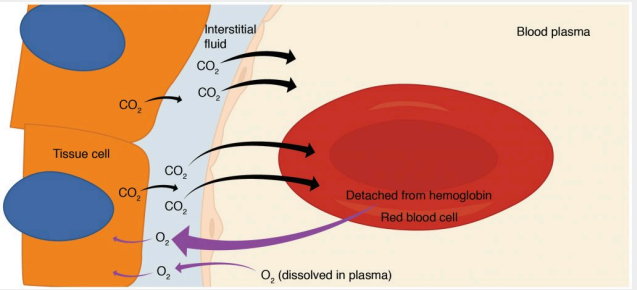

Figure 4 *During internal respiration, oxygen diffuses out of the capillary and into cells, whereas carbon dioxide diffuses out of cells and into the capillary. From OpenStax Anatomy and Physiology.*

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Gas Exchange Textbook from: OpenStax, Anatomy and Physiology. OpenStax CNX. August 13, 2019. https://cnx.org/contents/FPtK1zmh@16.1:mFGdwqYB@12/22-4-Gas-Exchange

73. Passive Transport: Facilitated Transport

In **facilitated transport**, also called facilitated diffusion, material moves across the plasma membrane with the assistance of transmembrane proteins down a concentration gradient (from high to low concentration) *without* the expenditure of cellular energy. However, the substances that undergo facilitated transport would otherwise not diffuse easily or quickly across the plasma membrane. The solution to moving polar substances and other substances across the plasma membrane rests in the proteins that span its surface. The material being transported is first attached to protein or glycoprotein receptors on the exterior surface of the plasma membrane. This allows the material that is needed by the cell to be removed from the extracellular fluid. The substances are then passed to specific integral proteins that facilitate their passage, because they form channels or pores that allow certain substances to pass through the membrane. The integral proteins involved in facilitated transport are collectively referred to as transport proteins, and they function as either channels for the material or carriers.

Channels

The integral proteins involved in facilitated transport are collectively referred to as transport proteins, and they function as either channels for the material or carriers. In both cases, they are transmembrane proteins (they span across the membrane). Channels are specific for the substance that is being transported. Channel proteins have hydrophilic domains exposed to the

intracellular and extracellular fluids; they additionally have a hydrophilic channel through their core that provides a hydrated opening through the membrane layers (**Figure 1**). Passage through the channel allows polar compounds to avoid the nonpolar central layer of the plasma membrane that would otherwise slow or prevent their entry into the cell. Aquaporins are channel proteins that allow water to pass through the membrane at a very high rate.

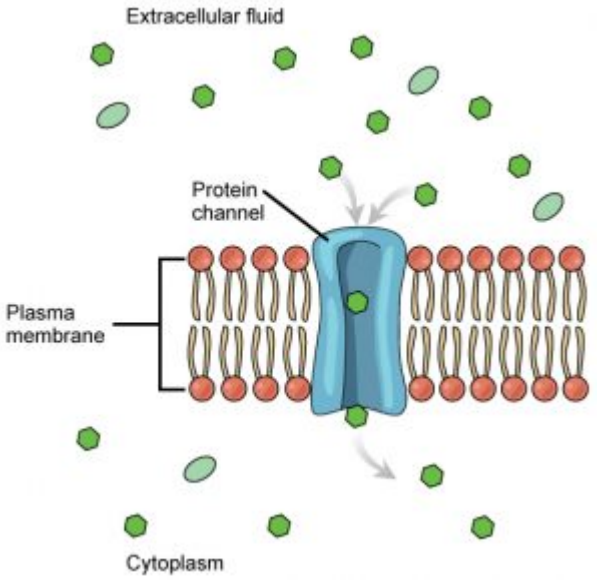
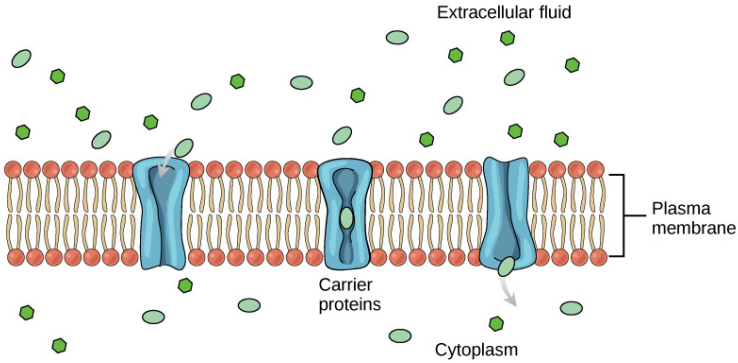


Figure 1*Facilitated transport moves substances down their concentration gradients. They may cross the plasma membrane with the aid of channel proteins. (credit: modification of work by Mariana Ruiz Villareal)*

Carrier Proteins

Another type of protein embedded in the plasma membrane is a carrier protein. This aptly named protein binds a substance and, in doing so, triggers a change of its own shape, moving the bound molecule from the outside of the cell to its interior (**Figure 2**); depending on the gradient, the material may move in the opposite direction. Carrier proteins are typically specific for a single

substance. This selectivity adds to the overall selectivity of the plasma membrane. The exact mechanism for the change of shape is poorly understood. Proteins can change shape when their hydrogen bonds are affected, but this may not fully explain this mechanism. Each carrier protein is specific to one substance, and there are a finite number of these proteins in any membrane. This can cause problems in transporting enough of the material for the cell to function properly. When all of the proteins are bound to their ligands, they are saturated and the rate of transport is at its maximum. Increasing the concentration gradient at this point will not result in an increased rate of transport.



An example of this process occurs in the kidney. Glucose, water, salts, ions, and amino acids needed by the body are filtered in one part of the kidney. This filtrate, which includes glucose, is then reabsorbed in another part of the kidney. Because there are only a finite number of carrier proteins for glucose, if more glucose is present than the proteins can handle, the excess is not transported and it is excreted from the body in the urine. In a diabetic individual, this is described as "spilling glucose into the urine." A different group of carrier proteins called glucose transport proteins, or GLUTs, are involved in transporting glucose and other hexose sugars through plasma membranes within the body.

Channel and carrier proteins transport material at different rates. Channel proteins transport much more quickly than do carrier proteins. Channel proteins facilitate diffusion at a rate of tens of millions of molecules per second, whereas carrier proteins work at a rate of a thousand to a million molecules per second.

Transport of Glucose

Glucose is a carbohydrate, which is polar (you know this – you've dissolved sugar in water before). Because glucose is polar, it can not diffuse freely across cell membranes. This is a good thing – if glucose could diffuse freely into cells, it could also diffuse freely *out* of cells and your cells would never be able to store any glucose inside themselves.

Cells in your body, such as red blood cells, use facilitated diffusion to bring glucose inside the cell. The body maintains a concentration of glucose in the blood that is higher than that inside most cells (cells are constantly breaking down glucose during cellular respiration, which makes the concentration of glucose inside the cell relatively low). This means that glucose will diffuse down its concentration gradient from higher concentration in the blood to a lower concentration inside the cell. However, since glucose is polar and can't freely pass through the membrane, it must travel through a protein channel – facilitated diffusion.

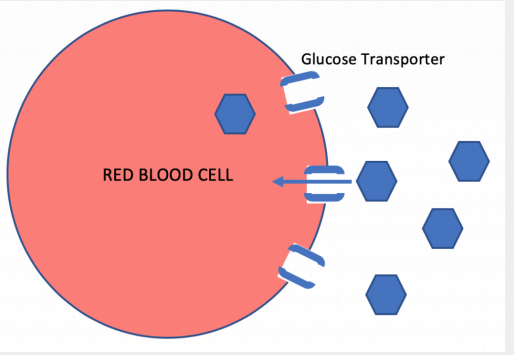


Figure 2 Facilitated diffusion of glucose into a red blood cell through a protein channel. Picture from: Lisa Bartee; 2019; Public Domain.

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74. Passive Transport: Osmosis

Osmosis is the diffusion of water through a semipermeable membrane according to the concentration gradient of water across the membrane. Whereas diffusion transports material across membranes and within cells, osmosis transports *only water* across a membrane and the membrane limits the diffusion of solutes in the water. Osmosis is a special case of diffusion. Water, like other substances, moves from an area of higher concentration to one of lower concentration. Imagine a beaker with a semipermeable membrane, separating the two sides or halves **(Figure 3**). On both sides of the membrane, the water level is the same, but there are different concentrations on each side of a dissolved substance, or **solute**, that cannot cross the membrane. If the volume of the water is the same, but the concentrations of solute are different, then there are also different concentrations of water, the **solvent,** on either side of the membrane.

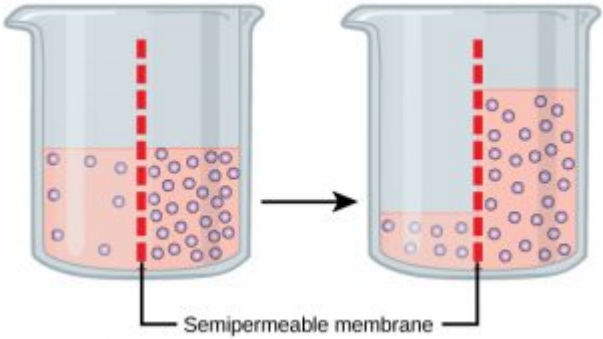

Figure 3*In osmosis, water always moves from an area of higher concentration (of water) to one of lower concentration (of water). In this system, the solute cannot pass through the selectively permeable membrane.*

A principle of diffusion is that the molecules move around and will spread evenly throughout the medium if they can. However, only the material capable of getting through the membrane will diffuse through it. In this example, the solute cannot diffuse through the membrane, but the water can. Water has a concentration gradient in this system. Therefore, water will diffuse down its concentration gradient, crossing the membrane to the side where it is less concentrated. This diffusion of water through the membrane– **osmosis** –will continue until the concentration gradient of water goes to zero. Osmosis proceeds constantly in living systems.

Tonicity

Tonicity describes the amount of solute in a solution. The measure of the tonicity of a solution, or the total amount of solutes dissolved in a specific amount of solution, is called its **osmolarity**. Three terms–hypotonic, isotonic, and hypertonic–are used to relate the osmolarity of a cell to the osmolarity of the extracellular fluid that contains the cells. All three of these terms are a *comparison*between two different solutions (for example, inside a cell compared to outside the cell).

In a **hypotonic**solution, such as tap water, the extracellular fluid has a lower concentration of solutes than the fluid inside the cell, and water enters the cell. (In living systems, the point of reference is always the cytoplasm, so the prefix *hypo–* means that the extracellular fluid has a lower concentration of solutes, or a lower osmolarity, than the cell cytoplasm.) It also means that the extracellular fluid has a higher concentration of water than does the cell. In this situation, water will follow its concentration gradient and enter the cell. This may cause an animal cell to burst, or **lyse.**

In a **hypertonic** solution (the prefix *hyper–* refers to the

extracellular fluid having a higher concentration of solutes than the cell's cytoplasm), the fluid contains less water than the cell does, such as seawater. Because the cell has a lower concentration of solutes, the water will leave the cell. In effect, the solute is drawing the water out of the cell. This may cause an animal cell to shrivel, or **crenate.**

In an **isotonic** solution, the extracellular fluid has the same osmolarity as the cell. If the concentration of solutes of the cell matches that of the extracellular fluid, there will be no net movement of water into or out of the cell. The cell will retain its "normal" appearance. Blood cells in hypertonic, isotonic, and hypotonic solutions take on characteristic appearances (**Figure 4**).

Remember that all three of these terms are *comparisons*between two solutions (i.e. inside and outside the cell). A solution can't be hypotonic, that would be like saying that Bob is taller. That doesn't make sense – you need to say that Bob is taller than Mike. You can say that the solution inside the cell is hypotonic to the solution outside the cell. That also means that the solution outside is hypertonic to the solution inside (just like Mike would be shorter than Bob).

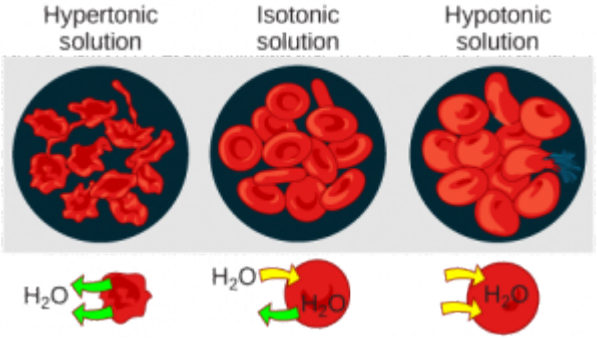

Figure 4*Osmotic pressure changes the shape of red blood cells in hypertonic, isotonic, and hypotonic solutions. (credit: modification of work by Mariana Ruiz Villarreal)*

Some organisms, such as plants, fungi, bacteria, and some protists,

have **cell walls**that surround the plasma membrane and prevent cell lysis. The plasma membrane can only expand to the limit of the cell wall, so the cell will not lyse. In fact, the cytoplasm in plants is always slightly hypertonic compared to the cellular environment, and water will always enter the plant cell if water is available. This influx of water produces **turgor pressure**, which stiffens the cell walls of the plant (**Figure 5**). In nonwoody plants, turgor pressure supports the plant. If the plant cells become hypertonic, as occurs in drought or if a plant is not watered adequately, water will leave the cell. Plants lose turgor pressure in this condition and wilt.

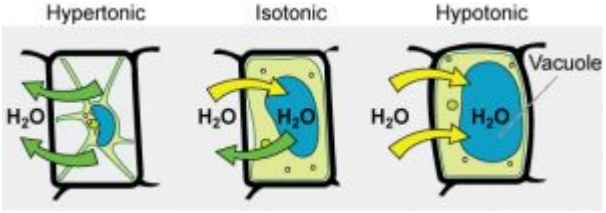

Figure 5*The turgor pressure within a plant cell depends on the tonicity of the solution that it is bathed in. (credit: modification of work by Mariana Ruiz Villarreal)*

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75. Active Transport

Active transport mechanisms require the use of the cell's energy, usually in the form of adenosine triphosphate (ATP). Active transport moves materials against their concentration gradient (from low to high concentration).

Electrochemical Gradient

We have discussed simple concentration gradients—differential concentrations of a substance across a space or a membrane. However, in living systems gradients are more complex. Cells contain many proteins, most of which are negatively charged. Due to these negatively charged proteins, coupled with the movement of ions into and out of cells, there is an electrical gradient (a difference of charge) across the plasma membrane. The interior of living cells is electrically negative as compared to the extracellular fluid in which cells are bathed; at the same time, cells contain higher concentrations of potassium (K+) and lower concentrations of sodium (Na+) than does the extracellular fluid. Thus, in a living cell, the concentration gradient and electrical gradient of Na+ promotes diffusion of the ion into the cell, and the electrical gradient of Na+ (a positive ion) tends to drive it inward to the negatively charged interior. The situation is more complex, however, for other elements such as potassium. The electrical gradient of K+ promotes diffusion of the ion *into* the cell, but the concentration gradient of K+ promotes diffusion *out* of the cell (**Figure 5**). The combined gradient that affects an ion is called its **electrochemical gradient**, and it is especially important to muscle and nerve cells.

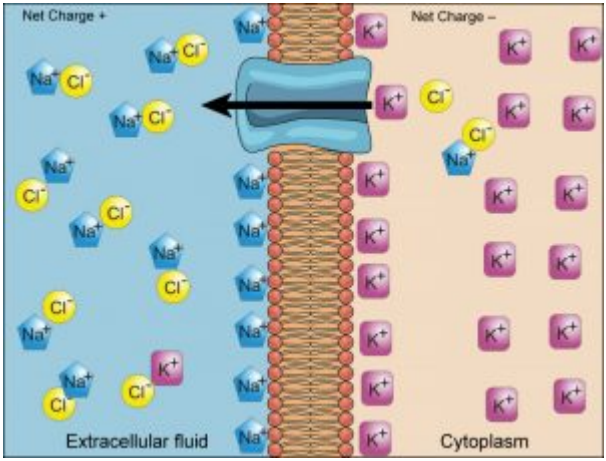

Figure 5 *Electrochemical gradients arise from the combined effects of concentration gradients and electrical gradients. (credit: modification of work by "Synaptitude"/Wikimedia Commons)*

Moving Against a Gradient

To move substances against a concentration or an electrochemical gradient, the cell must use energy. This energy is harvested from ATP that is generated through cellular metabolism. Active transport mechanisms, collectively called pumps or carrier proteins, work against electrochemical gradients. With the exception of ions, small substances constantly pass through plasma membranes. Active transport maintains concentrations of ions and other substances needed by living cells in the face of these passive changes. Much of a cell's supply of metabolic energy may be spent maintaining these processes. As active transport mechanisms depend on cellular metabolism for energy, they are sensitive to many metabolic poisons that interfere with the supply of ATP.

Two mechanisms exist for the transport of small-molecular weight material and macromolecules. **Primary active transport** moves ions across a membrane and creates a difference in charge across that membrane. The primary active transport system uses ATP to move a substance, such as an ion, into the cell, and often

at the same time, a second substance is moved out of the cell. The sodium-potassium pump, an important pump in animal cells, expends energy to move potassium ions into the cell and a different number of sodium ions out of the cell (**Figure 6**). The action of this pump results in a concentration and charge difference across the membrane.

Secondary active transport describes the movement of material using the energy of the electrochemical gradient established by primary active transport. Using the energy of the electrochemical gradient created by the primary active transport system, other substances such as amino acids and glucose can be brought into the cell through membrane channels. ATP itself is formed through secondary active transport using a hydrogen ion gradient in the mitochondrion.

Endocytosis

In addition to moving small ions and molecules through the membrane against their concentration gradients, cells also need to remove and take in larger molecules and particles. Some cells are even capable of engulfing entire unicellular microorganisms. You might have correctly hypothesized that the uptake and release of large particles by the cell requires energy. A very large particle, however, cannot pass directly through the membrane, even with energy supplied by the cell.

Endocytosis is a type of active transport that moves particles, such as large molecules, parts of cells, and even whole cells, into a cell. There are different variations of endocytosis, but all share a common characteristic: The plasma membrane of the cell invaginates, forming a pocket around the target particle. The pocket pinches off, resulting in the particle being contained in a newly created vacuole that is formed from the plasma membrane.

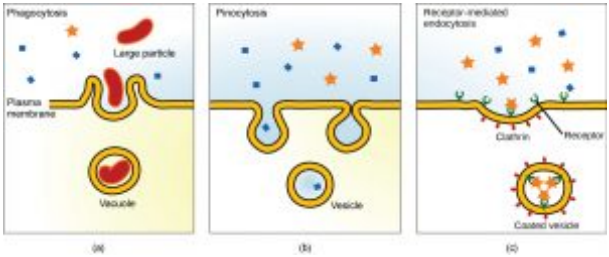

Figure 7 *Three variations of endocytosis are shown. (a) In one form of endocytosis, phagocytosis, the cell membrane surrounds the particle and pinches off to form an intracellular vacuole. (b) In another type of endocytosis, pinocytosis, the cell membrane surrounds a small volume of fluid and pinches off, forming a vesicle. (c) In receptor-mediated endocytosis, uptake of substances by the cell is targeted to a single type of substance that binds at the receptor on the external cell membrane. (credit: modification of work by Mariana Ruiz Villarreal)*

Phagocytosis is the process by which large particles, such as cells, are taken in by a cell. For example, when microorganisms invade the human body, a type of white blood cell called a neutrophil removes the invader through this process, surrounding and engulfing the microorganism, which is then destroyed by the neutrophil (**Figure 7**a).

A variation of endocytosis is called **pinocytosis**. This literally means "cell drinking" and was named at a time when the assumption was that the cell was purposefully taking in extracellular fluid. In reality, this process takes in solutes that the cell needs from the extracellular fluid (**Figure 7**b).

A targeted variation of endocytosis employs binding proteins in the plasma membrane that are specific for certain substances (**Figure 7**c). The particles bind to the proteins and the plasma membrane invaginates, bringing the substance and the proteins into the cell. If passage across the membrane of the target of **receptor-mediated endocytosis** is ineffective, it will not be removed from the tissue fluids or blood. Instead, it will stay in those fluids and increase in concentration.

Some human diseases are caused by a failure of receptor-mediated endocytosis. For example, the form of cholesterol termed low-density lipoprotein or LDL (also referred to as "bad" cholesterol) is removed from the blood by receptor mediated endocytosis. In the human genetic disease familial hypercholesterolemia, the LDL receptors are defective or missing entirely. People with this condition have life-threatening levels of cholesterol in their blood, because their cells cannot clear the chemical from their blood.

Exocytosis

In contrast to these methods of moving material into a cell is the

process of exocytosis. **Exocytosis** is the opposite of the processes discussed above in that its purpose is to expel material from the cell into the extracellular fluid. A particle enveloped in membrane fuses with the interior of the plasma membrane. This fusion opens the membranous envelope to the exterior of the cell, and the particle is expelled into the extracellular space (**Figure 8**).

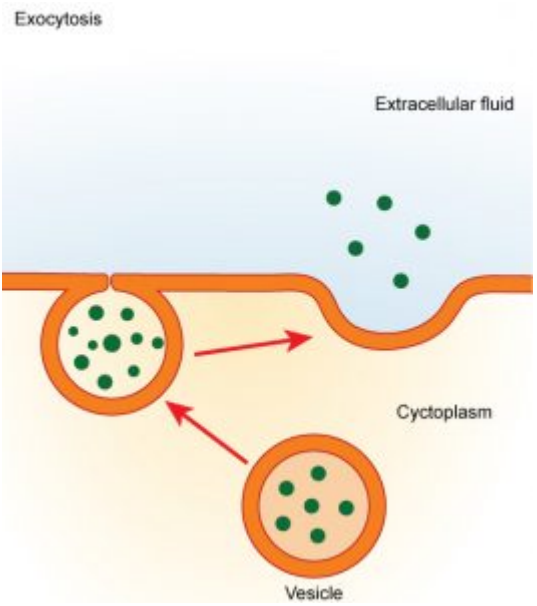

Figure 8*In exocytosis, a vesicle migrates to the plasma membrane, binds, and releases its contents to the outside of the cell. (credit: modification of work by Mariana Ruiz Villarreal)*

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76. Cell Communication

Imagine what life would be like if you and the people around you could not communicate. You would not be able to express your wishes to others, nor could you ask questions to find out more about your environment. Social organization is dependent on communication between the individuals that comprise that society; without communication, society would fall apart.

As with people, it is vital for individual cells to be able to interact with their environment. This is true whether a cell is growing by itself in a pond or is one of many cells that form a larger organism. In order to properly respond to external stimuli, cells have developed complex mechanisms of communication that can receive a message, transfer the information across the plasma membrane, and then produce changes within the cell in response to the message.

In multicellular organisms, cells send and receive chemical messages constantly to coordinate the actions of distant organs, tissues, and cells. The ability to send messages quickly and efficiently enables cells to coordinate and fine-tune their functions.

While the necessity for cellular communication in larger organisms seems obvious, even single-celled organisms communicate with each other. Yeast cells signal each other to aid mating. Some forms of bacteria coordinate their actions in order to form large complexes called biofilms or to organize the production of toxins to remove competing organisms. The ability of cells to communicate through chemical signals originated in single cells and was essential for the evolution of multicellular organisms. The efficient and error-free function of communication systems is vital for all life as we know it.

Receptors are protein molecules inside the target cell or on its surface that receive a chemical signal. Chemical signals are released by signaling cells in the form of small, usually volatile or soluble molecules called **ligands.** A ligand is a molecule that binds another

specific molecule, in some cases, delivering a signal in the process. Ligands can thus be thought of as signaling molecules. Ligands and receptors exist in several varieties; however, a specific ligand will have a specific receptor that typically binds only that ligand.

There are two basic types of **receptors:** internal receptors and cell surface receptors.

- **Internal receptors** are found in the cytoplasm of the cell and respond to ligands that cross the cell membrane into the cell. These receptors can have a direct effect on protein production by binding directly to the DNA.
- **Cell-surface receptors** are found on the cell membrane. They bind to ligands that do not cross the cell membrane. After the ligand binds, the receptor responds in some way. One response is to open a channel to allow ions to pass through the membrane. A second response is to activate an enzyme that sets off a response inside the cell. A third response is to activate a protein which is not an enzyme, but which can affect other cell components.

There are several different types of **ligands.**

- Small hydrophobic ligands can pass directly through the cell membrane. They typically interact with internal receptors. Steroid hormones are an example.
- Water soluble hydrophilic ligands can not pass directly through the cell membrane. They typically interact with cell-surface receptors. Peptide (protein) hormones are an example.
- There are a variety of other ligands such as nitric oxide (NO) gas. Nitroglycerin and Viagra affect the NO pathway.

Once a ligand binds to a receptor, the signal is transmitted through the membrane and into the cytoplasm. Continuation of a signal in this manner is called **signal transduction**. Signal transduction only occurs with cell-surface receptors because internal receptors are

able to interact directly with DNA in the nucleus to initiate protein synthesis.

Signal transduction pathways can be extremely complicated and involve large numbers of enzymes and other proteins. These pathways can help amplify a signal received by one receptor. There can also be different effects from the same ligand in different cell types due to different proteins present in different types of cells.

- **Kinases** are a type of enzyme that adds a phosphate group to another molecule (including other proteins). This is called **phosphorylation.** Phosphorylation can activate or deactivate other proteins.
- **Second messengers** are small molecules that help to spread a signal through the cytoplasm after a ligand binds to a receptor. They do this by altering the behavior of certain cellular proteins. Some examples of second messengers are cAMP (a modified version of AMP, which is related to ATP but only contains one phosphate) and calcium ions.

There are several categories of cellular responses to signals.

- **Changes in gene expression**: an increase or decrease in the production of a protein produced by a specific gene.
- **An increase in cellular metabolism**: the conversion of glucose to glycogen (and back) can be regulated depending on the energy needs of the cell.
- **Cell growth**: cells do not normally divide unless they are stimulated by signals from other cells.
- **Cell death**: apoptosis is controlled cell death; cells can be stimulated die if they are abnormal, infected with a bacteria or virus, or during specific parts of development (for example, to separate the fingers).

Stopping cell signaling pathways at the right time is just as

important as starting them correctly. Tumors often display abnormal responses to cell signaling pathways.

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PART XII

MEIOSIS - SEXUAL REPRODUCTION

Learning Objectives

Course Outcomes for this section:

1. Compare the process and consequences of mitosis and meiosis and how they are important in the lifecycle of an animal (such as a human).
    1. Describe circumstances in which mitosis and meiosis would occur and the results of those processes.
    2. Explain what can happen when there are errors in the processes of mitosis and meiosis.

The ability to reproduce *in kind* is a basic characteristic of all living things. *In kind* means that the offspring of any organism closely resembles its parent or parents. Hippopotamuses give birth to hippopotamus calves; Monterey pine trees produce seeds from which Monterey pine seedlings emerge; and adult flamingos lay eggs that hatch into flamingo chicks. *In kind* does not generally mean *exactly the same*. While many single-celled organisms and a few multicellular organisms can produce genetically identical clones of themselves through mitotic cell division, many single-celled organisms and most multicellular organisms reproduce regularly using another method.

Figure 1: Each of us, like these other large multicellular organisms, begins life as a fertilized egg. After trillions of cell divisions, each of us develops into a complex, multicellular organism. (credit a: modification of work by Frank Wouters; credit b: modification of work by Ken Cole, USGS; credit c: modification of work by Martin Pettitt)

Sexual reproduction is the production by parents of sex cells and the fusion of two sex cells to form a single, unique cell. In multicellular organisms, this new cell will then undergo mitotic cell divisions to develop into an adult organism. A type of cell division called **meiosis** leads to the cells that are part of the sexual reproductive cycle. Sexual reproduction, specifically meiosis and fertilization, introduces variation into offspring that may account for the evolutionary success of sexual reproduction. The vast majority of eukaryotic organisms can or must employ some form of meiosis and fertilization to reproduce.

Sexual reproduction was an early evolutionary innovation after

the appearance of eukaryotic cells. The fact that most eukaryotes reproduce sexually is evidence of its evolutionary success. In many animals, it is the only mode of reproduction. And yet, scientists recognize some real disadvantages to sexual reproduction. On the surface, offspring that are genetically identical to the parent may appear to be more advantageous. If the parent organism is successfully occupying a habitat, offspring with the same traits would be similarly successful. There is also the obvious benefit to an organism that can produce offspring by **asexual reproduction,** budding, fragmentation, or asexual production of eggs. These methods of reproduction do not require another organism of the opposite sex. There is no need to expend energy finding or attracting a mate. That energy can be spent on producing more offspring. Indeed, some organisms that lead a solitary lifestyle have retained the ability to reproduce asexually. In addition, asexual populations only have female individuals, so every individual is capable of reproduction. In contrast, the males in sexual populations (half the population) are not producing offspring themselves. Because of this, an asexual population can grow twice as fast as a sexual population in theory. This means that in competition, the asexual population would have the advantage. All of these advantages to asexual reproduction, which are also disadvantages to sexual reproduction, should mean that the number of species with asexual reproduction should be more common.

However, multicellular organisms that exclusively depend on asexual reproduction are exceedingly rare. Why is sexual reproduction so common? This is one of the important questions in biology and has been the focus of much research from the latter half of the twentieth century until now. A likely explanation is that the variation that sexual reproduction creates among offspring is very important to the survival and reproduction of those offspring. The only source of variation in asexual organisms is mutation. This is the ultimate source of variation in sexual organisms. In addition, those different mutations are continually reshuffled from one generation to the next when different parents combine their unique genomes,

and the genes are mixed into different combinations by the process of **meiosis**. Meiosis is the division of the contents of the nucleus that divides the chromosomes among gametes. Variation is introduced during meiosis, as well as when the gametes combine in fertilization.

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77. Overview of Meiosis

Sexual reproduction requires **fertilization**, a union of two cells from two individual organisms. If those two cells each contain one set of chromosomes, then the resulting cell contains two sets of chromosomes. The number of sets of chromosomes in a cell is called its ploidy level (Figure 1). **Haploid** cells contain one set of chromosomes. Cells containing two sets of chromosomes are called **diploid**. If the reproductive cycle is to continue, the diploid cell must somehow reduce its number of chromosome sets before fertilization can occur again, or there will be a continual doubling in the number of chromosome sets in every generation. So, in addition to fertilization, sexual reproduction includes a nuclear division, known as meiosis, that reduces the number of chromosome sets.

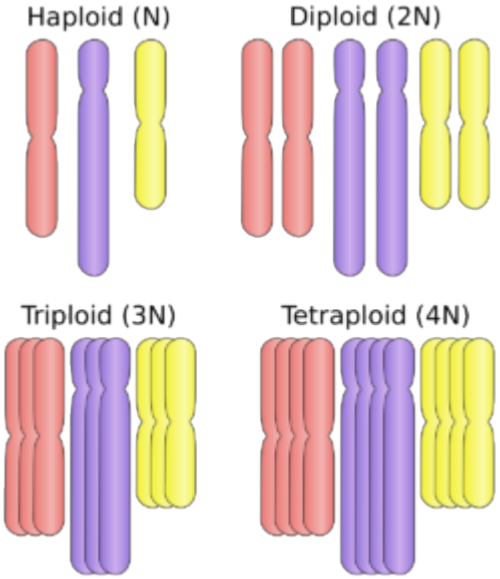

Figure 1 Number of chromosomes in a haploid and diploid cell. Note that triploid and tetraploid are not normal numbers of chromosomes in humans.

Most animals and plants are diploid, containing two sets of chromosomes; in each **somatic cell** (the non-reproductive cells of a multicellular organism), the nucleus contains two copies of each chromosome that are referred to as homologous chromosomes. Somatic cells are sometimes referred to as "body" cells. **Homologous chromosomes** are matched pairs containing genes for the same traits in identical locations along their length (Figure 2). Diploid organisms inherit one copy of each homologous chromosome from each parent; all together, they are considered a full set of chromosomes. In animals, haploid cells containing a single copy of each homologous chromosome are found only within gametes. One haploid gamete fuses with another haploid gamete to produce a diploid cell that will develop into the organism.

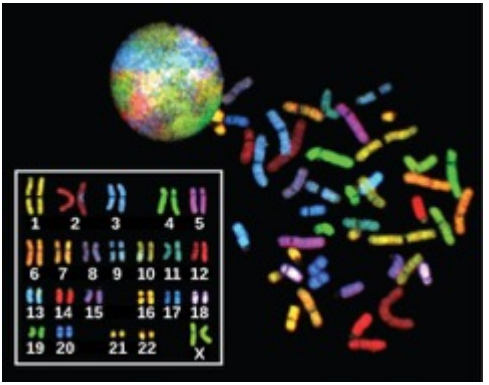

Figure 2 A karyotype displaying all of the chromosomes in the human genome. Note that there are two copies of each chromosome. These are the homologous chromosomes (one from each parent).

Nearly all animals employ a life-cycle strategy in which the only haploid cells produced by the organism are the gametes. Early in the development of the embryo, specialized diploid cells, called germ cells, are produced within the gonads, such as the testes and ovaries. **Germ cells** are capable of mitosis to perpetuate the cell line and meiosis to produce gametes. Once the haploid gametes are

formed, they lose the ability to divide again. There is no multicellular haploid life stage. Fertilization occurs with the fusion of two gametes, usually from different individuals, restoring the diploid state (Figure 3).

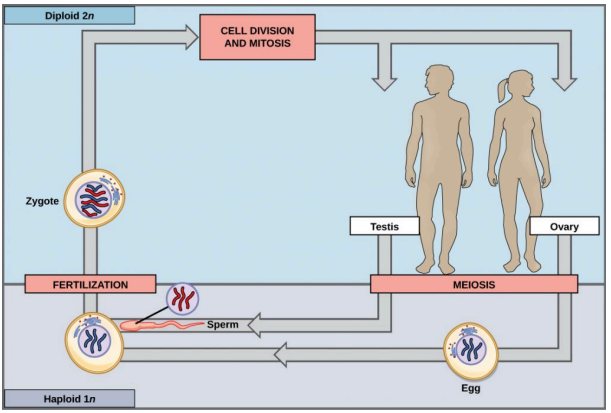

Figure 3 In animals, sexually reproducing adults form haploid gametes from diploid germ cells. Fusion of the gametes gives rise to a fertilized egg cell, or zygote. The zygote will undergo multiple rounds of mitosis to produce a multicellular offspring. The germ cells are generated early in the development of the zygote.

The nuclear division that forms haploid cells, which is called meiosis, is related to mitosis. As you have learned, mitosis is part of a cell reproduction cycle that results in identical daughter nuclei that are also genetically identical to the original parent nucleus. In mitosis, both the parent and the daughter nuclei contain the same number of chromosome sets—diploid for most plants and animals. Meiosis employs many of the same mechanisms as mitosis. However, the starting nucleus is always diploid and the nuclei that

result at the end of a meiotic cell division are haploid. To achieve the reduction in chromosome number, meiosis consists of one round of chromosome duplication and two rounds of nuclear division.

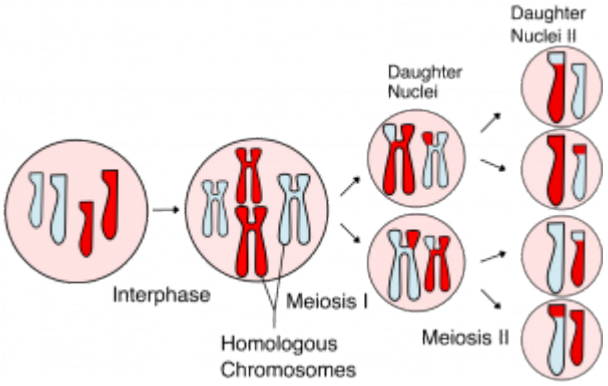

Figure 4 An overview of meiosis. Two sets of homologous chromosomes are shown. One set is comprised of a long red and a long blue chromosome. The second set is the two shorter chromosomes. During interphase, the chromosomes are duplicated so that in the second cell the look like X's. These two connected copies are called sister chromatids. Photo credit Rdbickel; Wikimedia.

Because the events that occur during each of the division stages are analogous to the events of mitosis, the same stage names are assigned. However, because there are two rounds of division, the stages are designated with a "I" or "II." Thus, **meiosis I** is the first round of meiotic division and reduces the number of chromosome

sets from two to one by separating the homologous pairs of chromosomes (Figure 4). The genetic information is also mixed at the beginning of meiosis I to create unique recombinant chromosomes that have different combinations of genes compared to the original chromosomes from the organism. **Meiosis II**, in which the second round of meiotic division takes place in a way that is similar to mitosis, separates the sister chromatids (the identical copies of each chromosome produced during DNA replication that are attached at the centromere).

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78. Meiosis I

Interphase

Meiosis is preceded by an interphase which is nearly identical to the interphase preceding mitosis. During interphase, the DNA of the chromosomes is replicated (during S phase). After DNA replication, each chromosome becomes composed of two identical copies (called sister chromatids) that are held together at the centromere.

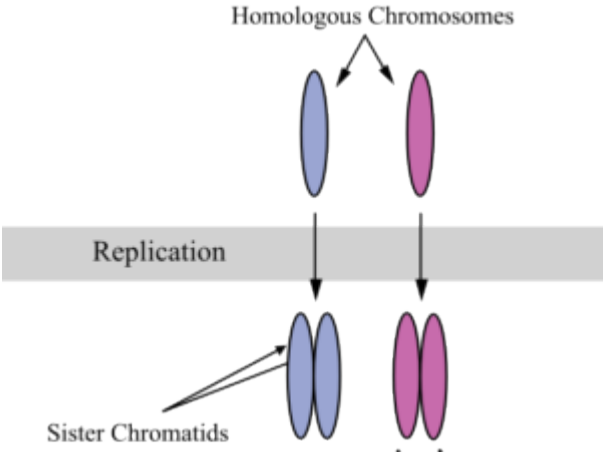

Figure 1: Sister chromatids are identical copies of a chromosome that are held together at the centromere. They are produced during DNA replication. (Credit: User:Syntax Error55, from Wikimedia)

Meiosis I

Meiosis is preceded by an interphase which is nearly identical to the interphase preceding mitosis. During interphase, the cell grows, ensures it has enough energy and other required molecules for division, and replicates its DNA.

During DNA replication, each chromosome is replicated to produce two identical copies, called sister chromatids, that are held together at the centromere. The centrosomes, which are the

structures that organize the microtubules of the meiotic spindle, also replicate. This prepares the cell to enter meiosis I.

Early in meiosis I, the chromosomes condense (wind up tightly). As the nuclear envelope begins to break down, the proteins associated with homologous chromosomes bring the pair close to each other. After the homologous chromosomes are aligned tightly with each other, the genes on each of the chromatids are precisely aligned with each other. This process does NOT occur during mitosis.

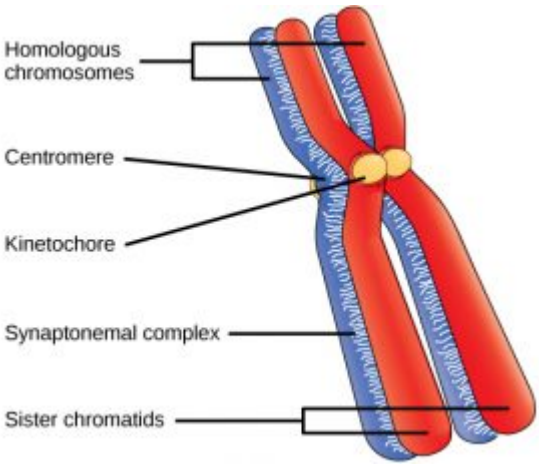

Figure 2 Early in prophase I, homologous chromosomes come together. The chromosomes are bound tightly together and in perfect alignment by proteins that connect the sister chromatids and the centromeres.

After the genes on the chromatids of the homologous chromosomes are aligned precisely with each other, an exchange of chromosome segments between non-sister homologous chromatids occurs. This is called **crossing over (Figure 3)**. The crossover events are the first source of genetic variation produced by meiosis. A single crossover event between homologous non-sister chromatids leads to a reciprocal exchange of equivalent DNA between a maternal chromosome and a paternal chromosome. Now, when that sister chromatid is moved into a gamete, it will carry some DNA from the mother of the person who made the gamete and some DNA from the

father of the person who made the gamete. The recombinant sister chromatid has a combination of maternal and paternal genes that did not exist before the crossover.

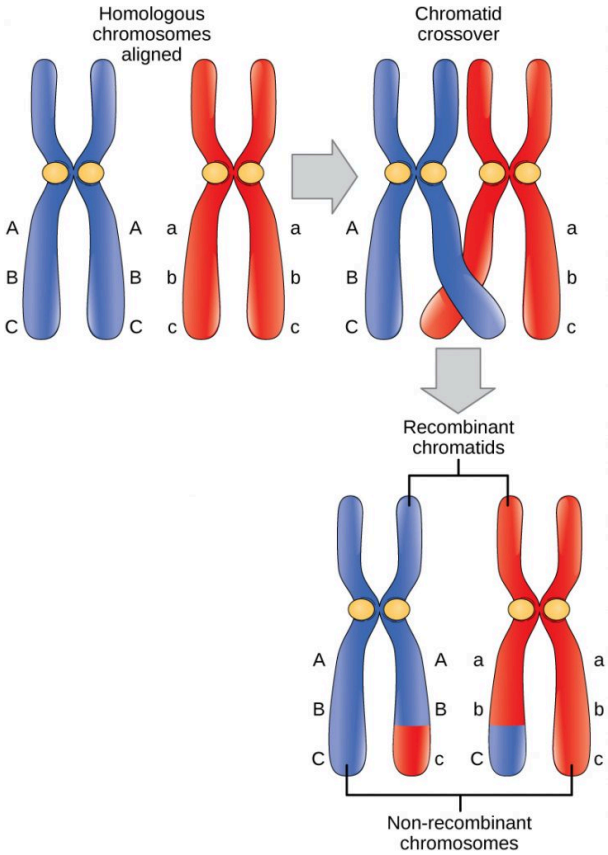

Figure 3: In this illustration of the effects of crossing over, the blue chromosome came from the individual's father and the red chromosome came from the individual's mother. Crossover occurs between non-sister chromatids of homologous chromosomes. The result is an exchange of genetic material between homologous chromosomes. The chromosomes that have a mixture of maternal and paternal sequence are called recombinant and the chromosomes that are completely paternal or maternal are called non-recombinant.

After crossing-over, microtubules grow from centrosomes placed at opposite poles of the cell and attach to one of the two fused homologous chromosomes. The microtubules attach at each chromosomes' centromeres. With each member of the homologous pair attached to opposite ends of the cell, the microtubules can pull now the homologous chromosomes apart. The cell undergoes cytokinesis to divide into two new cells. The end result of meiosis I is that the homologous pairs of chromosomes have been separated so each new cell only contains one copy of each homologous chromosome.

The orientation of each pair of homologous chromosomes at the center of the cell is random. This randomness, called **independent assortment**, is the physical basis for the generation of the second form of genetic variation in offspring (Figure 5). Consider that the homologous chromosomes of a sexually reproducing organism are originally inherited as two separate sets, one from each parent in the egg and the sperm. Using humans as an example, one set of 23 chromosomes is present in the egg donated by the mother. The father provides the other set of 23 chromosomes in the sperm that fertilizes the egg. These pairs line up at the midway point between the two poles of the cell. Because there is an equal chance that a microtubule fiber will encounter a maternally or paternally inherited chromosome, the arrangement of the chromosomes at the metaphase plate is random. Any maternally inherited chromosome may face either pole. Any paternally inherited chromosome may also face either pole. The orientation of each tetrad is independent of the orientation of the other 22 tetrads.

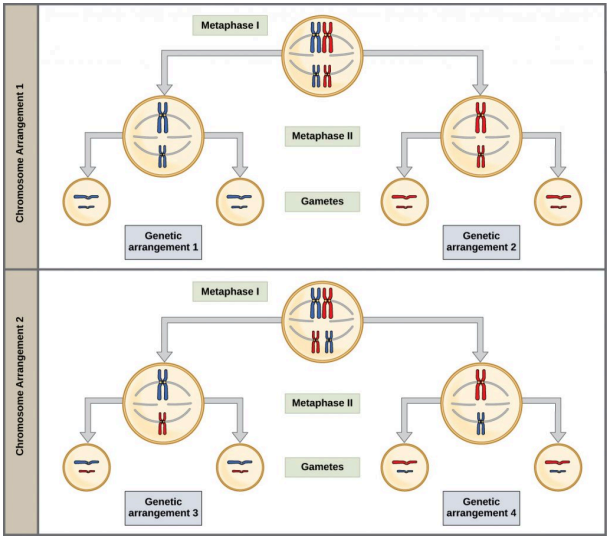

Figure 5 Random, independent assortment during metaphase I can be demonstrated by considering a cell with a set of two chromosomes ($n = 2$). In this case, there are two possible arrangements at the equatorial plane in metaphase I. The total possible number of different gametes is $2n$, where n equals the number of chromosomes in a set. In this example, there are four possible genetic combinations for the gametes. With $n = 23$ in human cells, there are over 8 million possible combinations of paternal and maternal chromosomes.

In each cell that undergoes meiosis, the arrangement of the chromosomes is different. The number of variations depends on the number of chromosomes making up a set. There are two possibilities for orientation (for each homologous pair); thus, the possible number of alignments equals $2n$ where n is the number of chromosomes per set. Humans have 23 chromosome pairs, which results in over eight million (223) possibilities. This number does not include the variability previously created in the sister chromatids by crossover. Given these two mechanisms, it is highly unlikely that any two haploid cells resulting from meiosis will have the same genetic composition (**Figure 5**).

To summarize the genetic consequences of meiosis I: the maternal and paternal genes are recombined by crossover events occurring on each homologous pair during prophase I; in addition, the random assortment of tetrads at metaphase produces a unique combination of maternal and paternal chromosomes that will make their way into the gametes.

Summary of Meiosis I

The chromosomes are copied during interphase (prior to meiosis I). This forms two identical sister chromatids that are attached together at the centromere. Crossing-over introduces genetic variation by swapping pieces of homologous chromosomes. Additional genetic variation is introduced by independent assortment, which takes into account how the homologous chromosomes line up in the middle of the cell. At the end of meiosis I, two haploid cells (where each chromosome still consists of two sister chromatids) are produced.

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79. Meiosis II

In some species, cells enter a brief interphase, or interkinesis, before entering meiosis II. Interkinesis lacks an S phase, so chromosomes are **not** duplicated. The two cells produced in meiosis I go through the events of meiosis II at the same time. During meiosis II, the sister chromatids within the two daughter cells separate, forming four new haploid gametes, each with one copy of each chromosome. The mechanics of meiosis II is similar to mitosis, except that each dividing cell has only one set of homologous chromosomes. Therefore, each cell has half the number of sister chromatids to separate out as a diploid cell undergoing mitosis.

During meiosis II, each sister chromatid is attached to spindle fiber microtubules from opposite poles. The sister chromatids are pulled apart by the spindle fiber microtubules and move toward opposite poles (Figure 1).

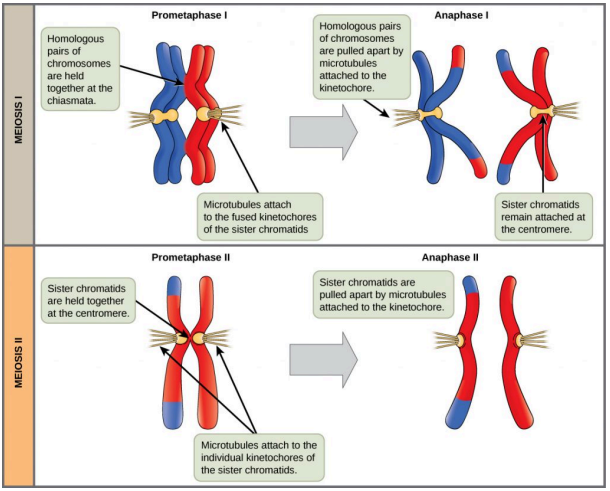

Figure 1 In prometaphase I, microtubules attach to the fused kinetochores of homologous chromosomes. In anaphase I, the homologous chromosomes are separated. In prometaphase II, microtubules attach to individual kinetochores of sister chromatids. In anaphase II, the sister chromatids are separated.

The chromosomes arrive at opposite ends of the cells and begin to decondense (unwind). Nuclear envelopes form around the chromosomes. Cytokinesis separates the two cells into four unique haploid cells. At this point, the newly formed nuclei are both haploid and have only one copy of the single set of chromosomes. The cells produced are genetically unique because of the random assortment of paternal and maternal homologs and because of the recombining of maternal and paternal segments of chromosomes (with their sets of genes) that occurs during crossover.

The entire process of meiosis is outlined in Figure 2 (you do not need to know the names of the phases or what happens during each phase, only what happens overall during meiosis I and II).

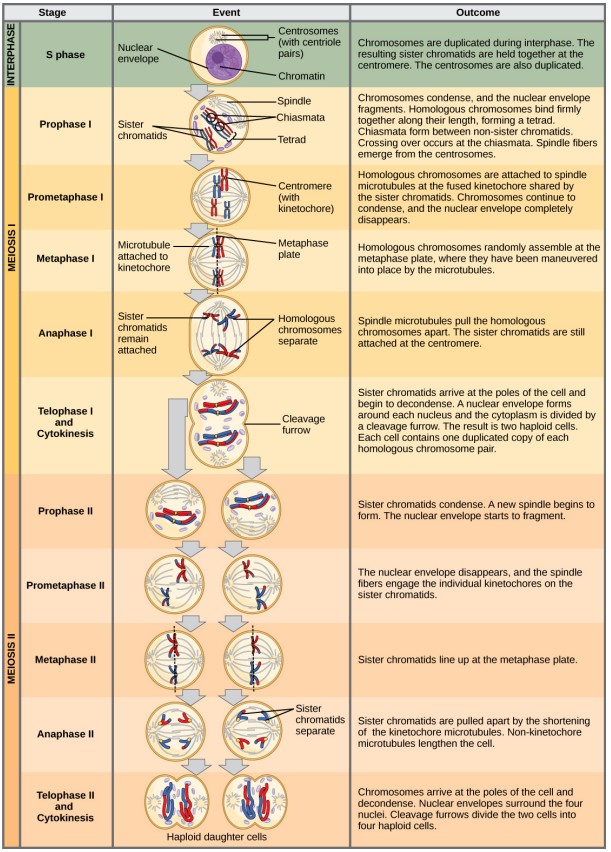

Figure 2 An animal cell with a diploid number of four (2n = 4) proceeds through the stages of meiosis to form four haploid daughter cells.

Summary of Meiosis II

Meiosis II begins with the 2 haploid cells where each chromosome is made up of two connected sister chromatids. DNA replication does

NOT occur at the beginning of meiosis II. The sister chromatids are separated, producing 4 genetically different haploid cells.

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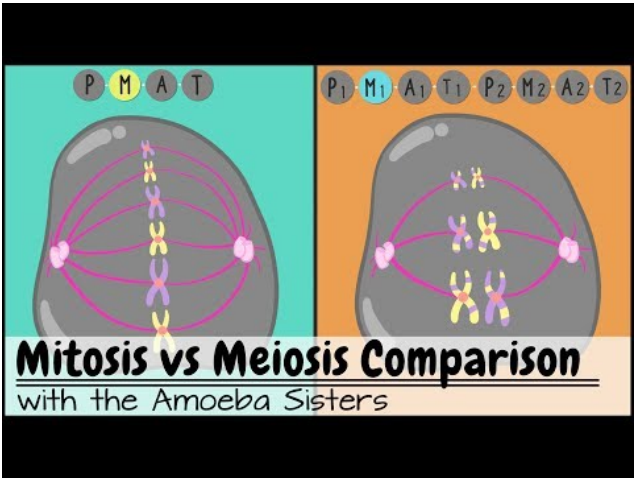
80. Comparing Meiosis and Mitosis



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Mitosis and meiosis, which are both forms of division of the nucleus in eukaryotic cells, share some similarities, but also exhibit distinct differences that lead to their very different outcomes. Mitosis is a single nuclear division that results in two nuclei, usually partitioned into two new cells. The nuclei resulting from a mitotic division are genetically identical to the original. They have the same number of sets of chromosomes: one in the case of haploid cells, and two in the case of diploid cells. On the other hand, meiosis is two nuclear divisions that result in four nuclei, usually partitioned into four

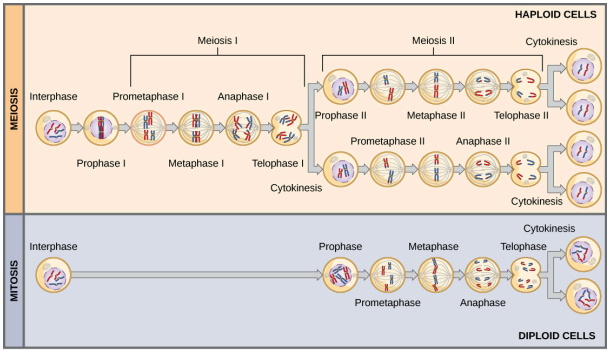
new cells. The nuclei resulting from meiosis are never genetically identical, and they contain one chromosome set only—this is half the number of the original cell, which was diploid.

The differences in the outcomes of meiosis and mitosis occur because of differences in the behavior of the chromosomes during each process. Most of these differences in the processes occur in meiosis I, which is a very different nuclear division than mitosis. In meiosis I, the homologous chromosome pairs become associated with each other, are bound together, experience crossover between homologous chromosomes, and line up in the center of the cell with spindle fibers from opposite spindle poles attached to each centromere. All of these events occur only in meiosis I, never in mitosis.

Homologous chromosomes move to opposite poles during meiosis I so the number of sets of chromosomes in each nucleus-to-be is reduced from two to one. For this reason, meiosis I is referred to as a **reduction division**. There is no such reduction in mitosis.

Meiosis II is much more similar to a mitotic division. In this case, duplicated chromosomes line up at the center of the cell. One sister chromatid is pulled to one pole and the other sister chromatid is pulled to the other pole. If it were not for the fact that there had been crossovers, the two products of each meiosis II division would be identical as in mitosis; instead, they are different because there has always been at least one crossover per chromosome. Meiosis II is not a reduction division because, although there are fewer copies of the genome in the resulting cells, there is still one set of chromosomes, as there was at the end of meiosis I.

Cells produced by mitosis will function in different parts of the body as a part of growth or replacing dead or damaged cells. Mitosis typically occurs in somatic cells, but they may be involved in asexual reproduction in some organisms. Cells produced by meiosis will only participate in sexual reproduction.



						OUTCOME
PROCESS	DNA synthesis	Synapsis of homologous chromosomes	Crossover	Homologous chromosomes line up at metaphase plate	Sister chromatids line up at metaphase plate	Number and genetic composition of daughter cells
MEIOSIS	Occurs in S phase of interphase	During prophase I	During prophase I	During metaphase I	During metaphase II	Four haploid cells at the end of meiosis II
MITOSIS	Occurs in S phase of interphase	Does not occur in mitosis	Does not occur in mitosis	Does not occur in mitosis	During metaphase	Two diploid cells at the end of mitosis

Figure 1 Meiosis and mitosis are both preceded by one round of DNA replication; however, meiosis includes two nuclear divisions. The four daughter cells resulting from meiosis are haploid and genetically distinct. The daughter cells resulting from mitosis are diploid and identical to the parent cell.

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81. Errors in Meiosis

Inherited disorders can arise when chromosomes behave abnormally during meiosis. Chromosome disorders can be divided into two categories: abnormalities in chromosome number and chromosome structural rearrangements. Because even small segments of chromosomes can span many genes, chromosomal disorders are characteristically dramatic and often fatal.

Disorders in Chromosome Number

The isolation and microscopic observation of chromosomes forms the basis of cytogenetics and is the primary method by which clinicians detect chromosomal abnormalities in humans. A **karyotype** is the number and appearance of chromosomes, including their length, banding pattern, and centromere position. To obtain a view of an individual's karyotype, cytologists photograph the chromosomes and then cut and paste each chromosome into a chart, or **karyogram** (**Figure 1**).

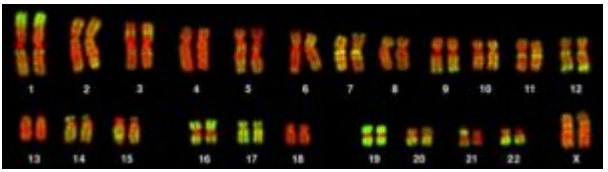

Figure 1 This karyogram shows the chromosomes of a normal female human immune cell during mitosis. (Credit: Andreas Bolzer, et al)

By observing a karyogram, geneticists can actually visualize the chromosomal composition of an individual to confirm or predict genetic abnormalities in offspring even before birth.

Geneticists Use Karyograms to Identify Chromosomal Aberrations

Although Mendel is referred to as the "father of modern genetics," he performed his experiments with none of the tools that the geneticists of today routinely employ. One such powerful cytological technique is karyotyping, a method in which traits characterized by chromosomal abnormalities can be identified from a single cell. To observe an individual's karyotype, a person's cells (like white blood cells) are first collected from a blood sample or other tissue. In the laboratory, the isolated cells are stimulated to begin actively dividing. A chemical called colchicine is then applied to cells to arrest condensed chromosomes in metaphase. Cells are then made to swell using a hypotonic solution so the chromosomes spread apart. Finally, the sample is preserved in a fixative and applied to a slide.

The geneticist then stains chromosomes with one of several dyes to better visualize the distinct and reproducible banding patterns of each chromosome pair. Following staining, the chromosomes are viewed using bright-field microscopy. A common stain choice is the Giemsa stain. Giemsa staining results in approximately 400–800 bands (of tightly coiled DNA and condensed proteins) arranged along all of the 23 chromosome pairs; an experienced geneticist can identify each band. In addition

to the banding patterns, chromosomes are further identified on the basis of size and centromere location. To obtain the classic depiction of the karyotype in which homologous pairs of chromosomes are aligned in numerical order from longest to shortest, the geneticist obtains a digital image, identifies each chromosome, and manually arranges the chromosomes into this pattern (Figure 1).

At its most basic, the karyogram may reveal genetic abnormalities in which an individual has too many or too few chromosomes per cell. Examples of this are Down Syndrome, which is identified by a third copy of chromosome 21, and Turner Syndrome, which is characterized by the presence of only one X chromosome in women instead of the normal two. Geneticists can also identify large deletions or insertions of DNA. For instance, Jacobsen Syndrome—which involves distinctive facial features as well as heart and bleeding defects—is identified by a deletion on chromosome 11. Finally, the karyotype can pinpoint translocations, which occur when a segment of genetic material breaks from one chromosome and reattaches to another chromosome or to a different part of the same chromosome. Translocations are implicated in certain cancers, including chronic myelogenous leukemia.

During Mendel's lifetime, inheritance was an abstract concept that could only be inferred by performing crosses and observing the traits expressed by offspring. By observing a karyogram, today's geneticists can actually visualize the chromosomal composition of an individual to confirm or predict genetic abnormalities in offspring, even before birth.

Of all the chromosomal disorders, abnormalities in chromosome

number are the most easily identifiable from a karyogram. Disorders of chromosome number include the duplication or loss of entire chromosomes, as well as changes in the number of complete sets of chromosomes. They are caused by **nondisjunction**, which occurs when pairs of homologous chromosomes or sister chromatids fail to separate during meiosis. The risk of nondisjunction increases with the age of the parents.

Nondisjunction can occur during either meiosis I or II, with different results (**Figure 2**). If homologous chromosomes fail to separate during meiosis I, the result is two gametes that lack that chromosome and two gametes with two copies of the chromosome. If sister chromatids fail to separate during meiosis II, the result is one gamete that lacks that chromosome, two normal gametes with one copy of the chromosome, and one gamete with two copies of the chromosome.

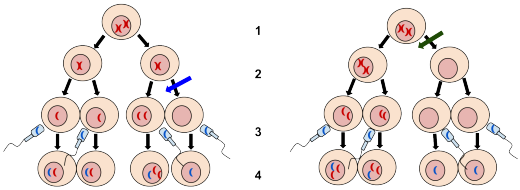

Figure 2 Nondisjunction occurs when homologous chromosomes or sister chromatids fail to separate during meiosis, resulting in an abnormal chromosome number. Nondisjunction may occur during meiosis I or meiosis II. Photo credit Tweety207; Wikimedia.

In humans, an individual with the typical number of chromosomes has 22 pairs of autosomes (non-sex chromosomes) and one pair of sex chromosomes (X and Y; such as is seen in the karyotype in Figure 1). An individual with an error in chromosome number is described as aneuploid, a term that includes **monosomy** (loss of one chromosome) or **trisomy** (gain of an extraneous chromosome). Monosomic human zygotes missing any one copy of an autosomal chromosome will not develop to birth because they have only one copy of essential genes. Most autosomal trisomies also fail to develop to birth; however, duplications of some of the smaller chromosomes (13, 15, 18, 21, or 22) can result in offspring that survive for several weeks to many years. Trisomic individuals suffer from a different type of genetic imbalance: an excess in gene dose. Cell functions are calibrated to the amount of gene product produced by two copies (doses) of each gene; adding a third copy (dose) disrupts this balance. The most common trisomy is that of chromosome 21, which leads to Down syndrome. Individuals with this inherited disorder have characteristic physical features and developmental delays in growth and cognition.

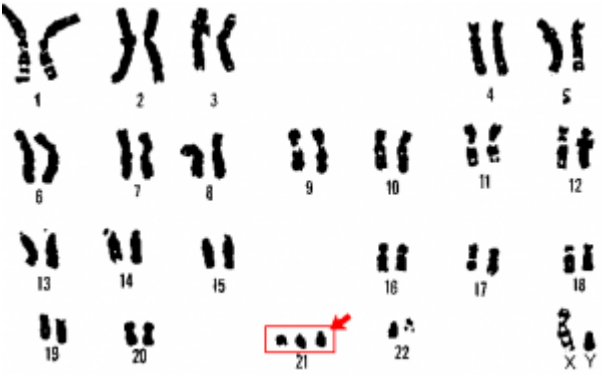

Figure 3 Karyotype of an individual with Down Syndrome. Photo credit U.S. Department of Energy Human Genome Program. Wikimedia.

The incidence of Down syndrome is correlated with maternal age, such that older women are more likely to give birth to children with Down syndrome (Figure 4).

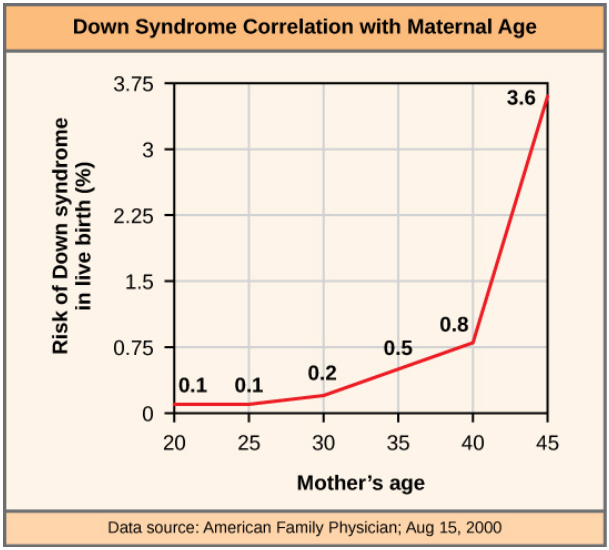

Figure 4: The incidence of having a fetus with trisomy 21 increases dramatically with maternal age.

An individual with more than the correct number of chromosome sets (two for diploid species) is called **polyploid**. For instance, fertilization of an abnormal diploid egg with a normal haploid sperm would yield a triploid zygote. Polyploid animals are extremely rare, with only a few examples among the flatworms, crustaceans, amphibians, fish, and lizards. Triploid animals are sterile (if they develop at all) because meiosis cannot proceed normally with an odd number of chromosome sets. In contrast, polyploidy is very common in the plant kingdom, and polyploid plants tend to be larger and more robust than euploids of their species (Figure 5).

Figure 5 As with many polyploid plants, this triploid orange daylily (Hemerocallis fulva) is particularly large and robust, and grows flowers with triple the number of petals of its diploid counterparts. (credit: Steve Karg)

Sex Chromosome Nondisjunction

Humans display dramatic deleterious effects with autosomal trisomies and monosomies. Therefore, it may seem counterintuitive that human females and males can function normally, despite carrying different numbers of the X chromosome. In part, this occurs because of a process called **X inactivation**. Early in development, when female mammalian embryos consist of just a few thousand cells, one X chromosome in each cell inactivates by condensing into a structure called a Barr body. The genes on the inactive X chromosome are not expressed. The particular X chromosome (maternally or paternally derived) that is inactivated in each cell is random, but once the inactivation occurs, all cells descended from that cell will have the same inactive X chromosome. By this process, females compensate for their double genetic dose of X chromosome.

In so-called "tortoiseshell" cats, X inactivation is observed as

coat-color variegation (**Figure 6**). Females heterozygous for an X-linked coat color gene will express one of two different coat colors over different regions of their body, corresponding to whichever X chromosome is inactivated in the embryonic cell progenitor of that region. When you see a tortoiseshell cat, you will know that it has to genetically be a female.

Figure 6 Embryonic inactivation of one of two different X chromosome s encoding different coat colors gives rise to the tortoiseshell phenotype in cats. (credit: Michael Bodega)

In an individual carrying an abnormal number of X chromosomes, cellular mechanisms will inactivate all but one X in each of her cells. As a result, X-chromosomal abnormalities are typically associated with mild mental and physical defects, as well as sterility. If the X chromosome is absent altogether, the individual will not develop.

Several errors in sex chromosome number have been characterized. Individuals with three X chromosomes, called triplo-X, appear female but express developmental delays and reduced fertility. The XXY chromosome complement, corresponding to one type of Klinefelter syndrome, corresponds to male individuals with small testes, enlarged breasts, and reduced body hair. The extra X chromosome undergoes inactivation to compensate for the excess

genetic dosage. Turner syndrome, characterized as an X0 chromosome complement (i.e., only a single sex chromosome), corresponds to a female individual with short stature, webbed skin in the neck region, hearing and cardiac impairments, and sterility.

Chromosome Structural Rearrangements

Cytologists have characterized numerous structural rearrangements in chromosomes, including partial duplications, deletions, inversions, and translocations. Duplications and deletions often produce offspring that survive but exhibit physical and mental abnormalities. Cri-du-chat (from the French for "cry of the cat") is a syndrome associated with nervous system abnormalities and identifiable physical features that results from a deletion of most of the small arm of chromosome 5 (**Figure 7**). Infants with this genotype emit a characteristic high-pitched cry upon which the disorder's name is based.

Figure 7 This individual with cri-du-chat syndrome is shown at various ages: (A) age two, (B) age four, (C) age nine, and (D) age 12. (credit: Paola Cerruti Mainardi)

Chromosome inversions and translocations can be identified by observing cells during meiosis because homologous chromosomes with a rearrangement in one of the pair must contort to maintain appropriate gene alignment and pair effectively during prophase I.

A **chromosome inversion** is the detachment, 180° rotation, and reinsertion of part of a chromosome (**Figure 8**). Unless they disrupt a gene sequence, inversions only change the orientation of genes and are likely to have more mild effects than aneuploid errors.

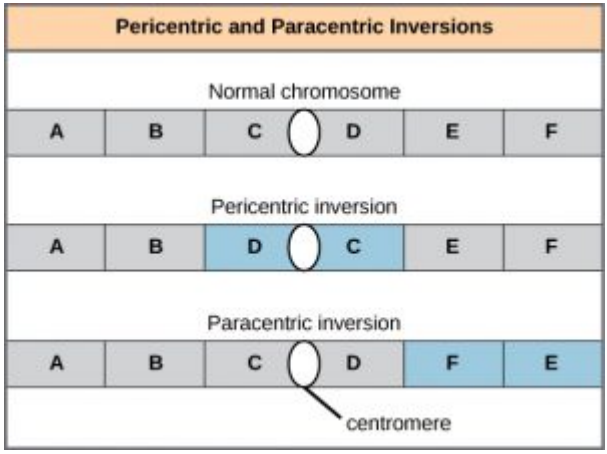

Figure 8 An inversion occurs when a chromosome segment breaks from the chromosome, reverses its orientation, and then reattaches in the original position.

A translocation occurs when a segment of a chromosome dissociates and reattaches to a different, nonhomologous chromosome. Translocations can be benign or have devastating effects, depending on how the positions of genes are altered with respect to regulatory sequences. Notably, specific translocations have been associated with several cancers and with schizophrenia. Reciprocal translocations result from the exchange of chromosome segments between two nonhomologous chromosomes such that there is no gain or loss of genetic information (**Figure 9**).

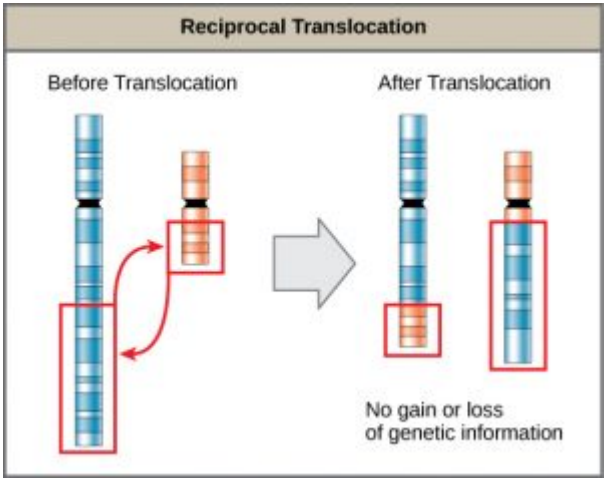

Figure 9 A reciprocal translocation occurs when a segment of DNA is transferred from one chromosome to another, nonhomologous chromosome. (credit: modification of work by National Human Genome Research/ USA)

One specific example of a chromosomal translocation is the "Philadelphia chromosome" that is found in people who suffer from chronic myeloid leukemia (CML). In this translocation, a piece of chromosome 9 is swapped with a section of chromosome 22. This connects two genes on chromosome 22 – one that was originally from chromosome 9 and one that was from chromosome 22. This translocation produces the BCR-ABL fusion protein, which causes white blood cells to divide out of

control. BCR-ABL positive cancers can be treated with the drug Gleevac.

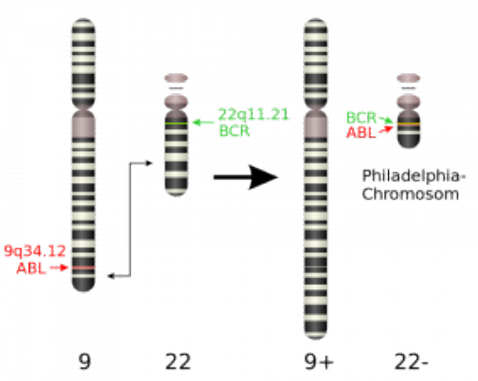

Figure 9 "Philadelphia chromosome" showing the location of the BCR-ABL fusion protein. Photo credit A Obeidat; Wikimedia.

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PART XIII

GENETICS: DOG COAT COLOR

Learning Objectives

By the end of this section, you will be able to:

- Describe the molecular basis of inheritance.
- Determine the outcome in crosses involving complete dominance.
- Present and decipher information about inheritance using a pedigree.

Figure 1: Experimenting with thousands of garden peas, Johann Gregor Mendel uncovered the fundamentals of genetics. (credit: modification of work by Jerry Kirkhart)

Remember that a trait is an aspect of the physical appearance of an organism that can vary. Organisms get their traits from proteins; proteins are produced using the information found in the organism's DNA. Variation in the DNA between different organisms causes the production of proteins that contain differing orders of amino acids. These proteins can have different shapes and therefore different functions. When proteins function differently, this leads to differences in traits.

Recall that **diploid** organisms have two copies of each chromosome: a pair of homologous chromosomes. The reason that they have two copies is because they inherited one copy of each chromosome from each parent. Each parent donates one **haploid gamete** (egg or sperm) to the reproductive process. A haploid gamete contains one copy of each chromosome because during meiosis the number of chromosomes is cut in half: the DNA is copied once and then divided twice. This separation of the homologous chromosomes means that only one of the copies of the gene gets moved into a gamete. The offspring are formed when that gamete unites with one from another parent and the two copies of each gene (and chromosome) are restored in the diploid offspring.

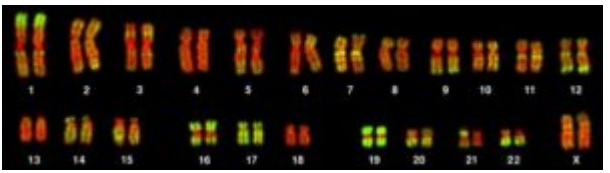


Figure 2: A karyogram is a picture of all the chromosomes in a cell, organized into homologous pairs. This is a human karyogram which shows the 46 chromosomes present in diploid human somatic cells.

A diploid organism has two copies of a given gene. The two copies may or may not encode the same version of that characteristic. For example, one individual pea plant (such as those studied by Mendel) would have two copies of the gene that controls flower color. That individual could carry one version of the gene that leads to white flower color and a second different version of that same gene that leads to violet flower color. The interaction between these two different versions of the same gene will lead to the visible flower color in the pea plant. Gene variations that arise by mutation and exist at the same relative locations on homologous chromosomes are called **alleles**. Mendel examined the inheritance of genes with just two allele forms, but it is common to encounter more than two alleles for many genes in a natural population.

Each individual (assuming it is a diploid organism) will have two alleles for a specific gene: one from each of its two parents. These two alleles are expressed and interact to produce physical characteristics. The observable traits expressed by an organism are referred to as its **phenotype**. An organism's underlying genetic makeup, consisting of both the physically visible and the non-expressed alleles, is called its **genotype**.

Diploid organisms that are **homozygous** for a gene have two identical alleles, one on each of their homologous chromosomes. If the organism has two different alleles, this is referred to as **heterozygous.**

This chapter will address a simple type of inheritance: complete dominance. In this type of inheritance, there are two alleles: dominant and recessive. A **dominant** allele will completely cover up a recessive allele. This means that if one dominant allele is present, the organism will have the trait conferred by that allele. In order for the recessive phenotype to be seen, the organism must have two **recessive** alleles. Just because an allele is dominant does not automatically make it better than a recessive trait. It also does not make it more common than the recessive trait. All it means for an allele to be dominant is that it is able to cover up the recessive allele.

We typically abbreviate the genotype of an organism by using

single letters. The letter chosen is often the first letter of the dominant trait. A homozygous dominant genotype would be written AA, a heterozygous genotype as Aa, and a homozygous recessive genotype as aa.

82. Introduction to Genetics

"Genetics" is the study of how traits are inherited.A **trait** is defined as a variation in the physical appearance of a heritable characteristic. It seeks to understand how traits are passed from generation to generation. Before you start learning about the details of inheritance, let's review some topics that are important in order to understand genetics.

Recall that genes are segments of DNA that are typically several hundred or thousand bases long. Each gene directs the production of a protein through the process of protein synthesis: DNA gets transcribed to produce an mRNA; mRNA provides to code for a ribosome to produce a chain of amino acids. Read this section of the book if you need to review this topic: How do genes direct the production of proteins?

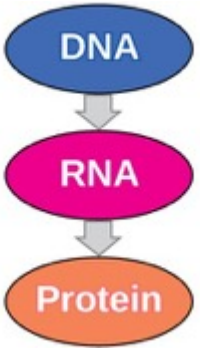
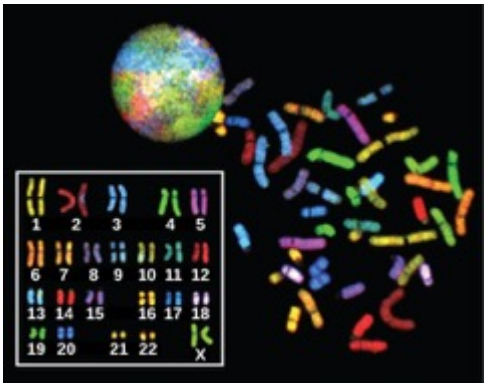


Figure 1 The Central Dogma – DNA is used to make RNA is used to make protein

Recall that genes are found on chromosomes and that each chromosome typically contains hundreds or thousands of genes. In humans and other animals, each cell contains two copies of each

chromosome. The reason we have two copies of each gene is that we inherit one from each parent. In fact, it is the chromosomes we inherit and the two copies of each gene are located on paired chromosomes.Read this section of the book if you need to review this topic: How DNA is arranged in the cell

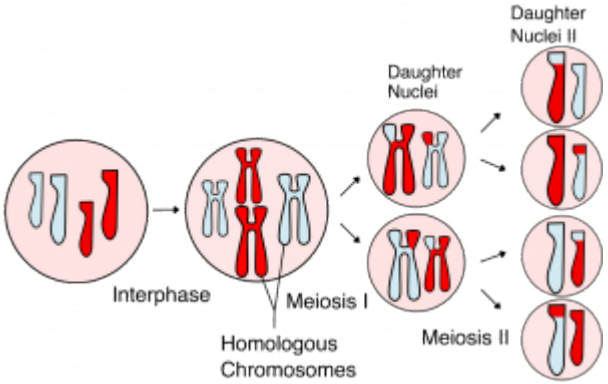


There are 23 pairs of chromosomes in a female human body cell. These chromosomes are viewed within the nucleus (top), removed from a cell during cell division (right), and arranged according to length (left) in an arrangement called a karyotype. In this image, the chromosomes were exposed to fluorescent stains to distinguish them. (credit: "718 Bot"/Wikimedia Commons, National Human Genome Research)

Chromosomes are inherited by the offspring from the parents via the egg or sperm. Inside one egg or one sperm is one copy of each chronometer (so 23 total in humans). When an egg is fertilized by a sperm, the resulting **zygote** (fertilized egg) will contain two copies of each chromosome, just like each of its parents.

Meiosis is the process that produces eggs and sperm. Eggs and sperm are also known as **gametes**. During meiosis, one copy of each paired chromosome is moved into the gamete. Cells with one copy of each chromosome are known as "**haploid**". This separation, or segregation, of the **homologous** (paired) chromosomes means also that only one of the copies of the gene gets moved into a gamete.

The offspring are formed when that gamete unites with one from another parent and the two copies of each gene (and chromosome) are restored. Read this section of the book if you need more information on this topic: Overview of Meiosis



During meiosis, the DNA is copied once, then the cell divides twice. This produces cells with half as much genetic information as the original cell (1 copy of each chromosome). These cells become the sex cells (eggs or sperm). When two sex cells unite during fertilization, the original number of chromosomes (2 copies of each one) is restored.

The offspring will receive two copies of each gene (one from each parent), but the copies are not necessarily identical. You already knew this – you don't get identical information from your mother and your father because they have different DNA (which gives them different traits). The different versions of one specific gene are known as **alleles.** As you learn about genetics, you will learn about how the information from both alleles of a specific gene interact

to give an individual their trait. The genetic information that an individual has is called their **genotype.** The genotype of an individual produces the individual's **phenotype,** or physical traits.

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83. Pedigrees and Punnett Squares

Pedigrees

Inheritance of a trait through generations can be shown visually using a pedigree, such as is pictured in **Figure 3**. Square shapes represent males; circles represent females. Filled-in shapes are individuals that have whatever trait is being shown in the pedigree. Two individuals connected together with a horizontal line between them are the parents of the individuals that are connected by vertical lines below them. Siblings are typically shown in birth order with the oldest sibling to the left.

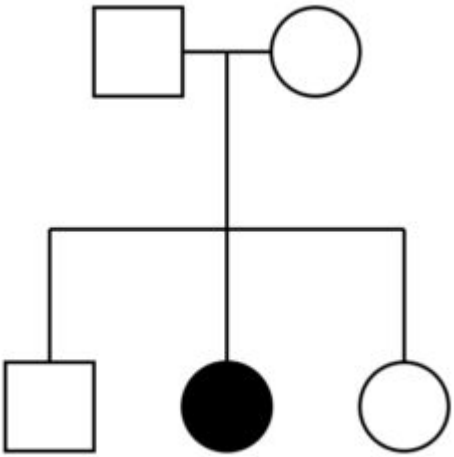

Figure 3: A simple pedigree. In this pedigree, the parents (at the top) have produced three children: a male and two females. The first female has the condition being shown in the pedigree.

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As discussed above, diploid individuals have two copies of each chromosome: one from their male parent, one from their female parent. This means they have two copies of each gene. They can have two of the same alleles (homozygous) or two different alleles (heterozygous). Regardless of their genotype, they will pass one copy of each chromosome to their offspring. This is because meiosis produces haploid gametes that contain one copy of each chromosome. Since genes are present on chromosomes, this means they will pass one copy of each gene to their offspring. That means that an offspring inherits one allele of each gene from each of its two parents. This is illustrated in Figure 4.

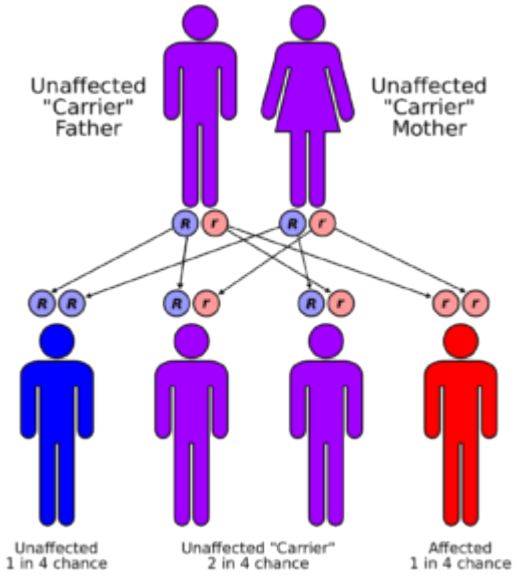

Figure 4: Two parents who are heterozygous each pass one chromosome / gene / allele to each offspring. Each resulting offspring has two of each chromosome / gene. The individual can have two of the same or two different alleles.

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An easy, organized way of illustrating the offspring that can result from two specific parents is to use a Punnett square. The gametes that can be generated by each parent are represented above the rows and next to the columns of the square. Each gamete is haploid for the "A gene", meaning it only contains one copy of that gene. In the Punnett square seen in Figure 5, haploid eggs are above each column and haploid sperm are next to each row. When a haploid sperm and a haploid egg (each with 1 copy of the "A gene") combine

during the process of fertilization, a diploid offspring (with 2 copies of the A gene) is the result.

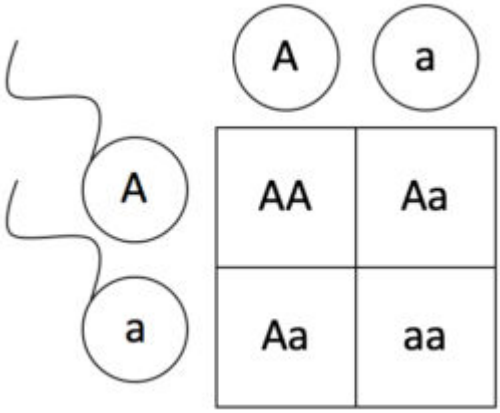

Figure 5: A Punnett square showing a cross between two individuals who are both heterozygous for A.

A Punnett square shows the probability of an offspring with a given genotype resulting from a cross. It does not show actual offspring. For example, the Punnett square in Figure 5 shows that there is a 25% chance that a homozygous recessive offspring will result from the cross Aa x Aa. It does *not* mean that these parents must have 4 offspring and that they will have the ratio 1 AA : 2 Aa : 1 aa. It's just like flipping a coin: you expect 50% heads, but you wouldn't be too surprised to see 7 heads out of 10 coin flips. Additionally, the probability does not change for successive offspring. The probability that the first offspring will have the genotype "aa" is 25% and the probability of the second offspring having the genotype "aa" is still 25%. Again, it's just like flipping a coin: if you flip heads the first time, that doesn't change the probability of getting heads on the next flip.

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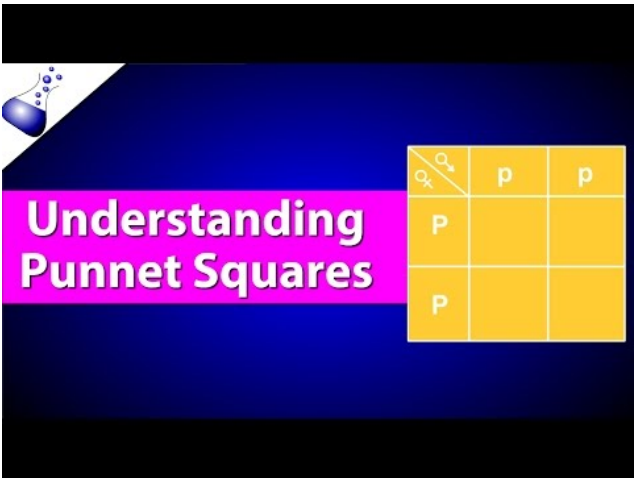

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Organisms don't just inherit one trait at a time, though. They inherit all their traits at once. Sometimes, we want to determine the probability of an individual inheriting two different traits. The easiest way to do this is to determine the probability of the individual inheriting each trait separately, then multiply those probabilities together. An example of this can be seen in **Figure 6**.

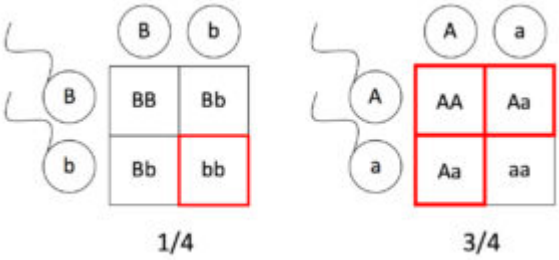


Figure 6: These two Punnett square show the cross between two individuals who are both heterozygous for two different genes: BbAa x BbAa. We can determine the probability of an offspring having the recessive trait for "B" and the dominant trait for "A". The probability of the offspring having the recessive phenotype for "B" is 1/4. The probability of the offspring having the dominant phenotype for "A" is 3/4. 1/4 x 3/4 = 3/16.

Another way of determining the probability of getting two different traits is to use a dihybrid Punnett square. **Figure 7** shows three generations of the inheritance of pea seed color and shape. Peas can be either yellow or green, and they can be either round or wrinkled. These are two of the traits that Mendel studied in his work

with peas. In the first generation (the "P" generation), two true-breeding (homozygous) individuals are crossed. Their offspring will get one allele of the Y gene and one allele of the R gene from each parent. This means that all their offspring (the "F1" generation) will be heterozygous for both genes. The results (the "F2" generation) from crossing two heterozygous individuals can be seen in the 4×4 Punnett square in **Figure 7**.

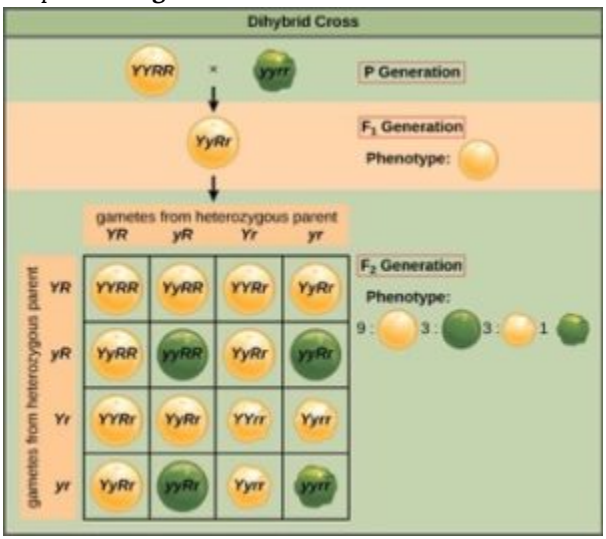
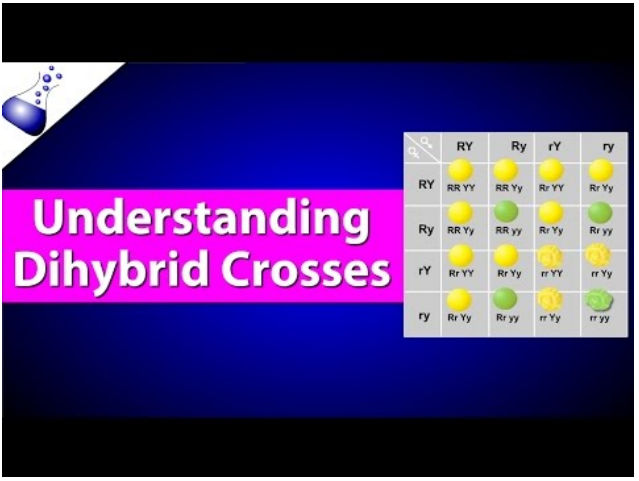


Figure 7: This dihybrid cross shows the expected offspring from the F2 generation after crossing YYRR x yyrr. Compare the results from this Punnett square to the results seen in the previous figure. They match!

The gametes produced by the F1 individuals must have one allele from each of the two genes. For example, a gamete could get an *R* allele for the seed shape gene and either a Y or a *y* allele for the seed color gene. It cannot get both an *R* and an *r* allele; each gamete can have only one allele per gene. The law of independent assortment states that a gamete into which an *r* allele is sorted would be equally likely to contain either a Y or a *y* allele. Thus, there are four equally likely gametes that can be formed when the *RrYy* heterozygote is self-crossed, as follows: *RY*, *rY*, *Ry*, and *ry*. Arranging

these gametes along the top and left of a 4 × 4 Punnett square (**Figure 7**) gives us 16 equally likely genotypic combinations. From these genotypes, we find a phenotypic ratio of 9 round–yellow:3 round–green:3 wrinkled–yellow:1 wrinkled–green (**Figure 7**). These are the offspring ratios we would expect, assuming we performed the crosses with a large enough sample size.

We can look for individuals who have the recessive phenotype for Y and the dominant phenotype for R. These individuals must have two little y's and at least one big R. The possible genotypes are yyRR or yyRr. Examining the Punnett square in **Figure 7**, we can find 3 individuals with these genotypes (they are round and green). If you compare the results from **Figure 6** and **Figure 7**, you'll see that we have arrived at the same value: 3/16!



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84. Black fur color: a dominant trait

Black fur color is dominant over brown

Figure 8: This chocolate lab has two recessive alleles of the TYRP1 gene. (Credit: Rob Hanson; photo from Wikimedia.)

Most of us are familiar with the labrador retriever dog breed, such as the chocolate lab seen in **Figure 8**. But have you ever thought about what makes this dog brown? The difference between brown and black coat color in dogs is caused by a mutation in the TYRP1 gene. The TYRP1 gene provides instructions for making an enzyme called tyrosinase-related protein 1. This enzyme is required to produce a pigment called eumelanin. Eumelanin is a dark colored pigment.

The TYRP1 gene is located on chromosome 11 in dogs (Parker, 2001).

A group of scientists who were interested in determining what

caused the difference between black and brown coats sequenced the DNA within the protein-coding region of the TYRP1 gene (Schmutz, 2002). They identified three variations in the DNA making up the TYRP1 gene between brown dogs and black dogs. These variations in DNA sequence are examples of different **alleles** of the TYRP1 gene.

Table 1: Variations in the TYRP1 allele that lead to brown color in dogs. Data from Schmutz, 2002.

Location	Black DNA sequence	Brown DNA sequence	Effect on protein
exon 2	TGT	CGT	changes a cysteine amino acid to a serine
exon 5	CAG	TAG	introduces a premature stop codon which results acids instead of 512 amino acids in the protein
exon 5	CCT	– (deleted)	deletion of a proline amino acid

All of these variations in the DNA sequence are predicted to cause a change in the amino acid sequence of the TYRP1 protein. These changes affect the production of eumelanin pigment, which is black in color. When eumelanin is not being produced correctly, the dog appears brown instead of black.

Like other diploid organisms, dogs all have two copies of the TYRP1 gene (one from their male parent, one from their female parent). Dogs that are homozygous for the black allele (dogs that have two copies of the black allele) are obviously going to be black in color. Dogs that are homozygous for the brown allele are obviously going to be brown. Dogs that are heterozygous (dogs that have one black allele and one brown allele) appear black. The black and brown colors do not blend together: the black allele covers up the brown allele. This means that the black allele is **dominant** over the brown allele. Remember that dominant alleles cover up **recessive** alleles. If there is one dominant allele present, the dog will appear black. The brown allele is recessive to the black allele. There must be two copies of the recessive brown allele present in order for the dog to appear brown.

Figure 9: Black and brown phenotypes in labrador retrievers. (Credit: demealiffe; from Wikimedia)

Remember that genotypes can be abbreviated with a single letter and that the letter which is chosen is typically the first letter of the dominant trait. In this case, the letter "B" is used to represent the dominant black allele, while "b" represents a recessive brown allele.

The reason that the black allele is dominant over the brown allele in this specific situation is because the black allele produces functional TYRP1 protein, while the brown allele does not. The presence of one functional allele produces enough TYRP1 protein allows the cells to produce eumelanin and appear black.

Remember: dominant does not mean "better" or "more normal". Black color does not confer any special advantages on dogs compared to brown color. It's just a difference.

Figure 10: What alleles of TYRP1 does this black lab puppy have? We can't tell by looking at it. The puppy could be homozygous (BB) or heterozygous (Bb). Since black is completely dominant over brown, both options would be black. (Credit: Alice Birkin)

Let's visualize the inheritance of black and brown using a pedigree. The pedigree in **Figure 11** shows a litter of puppies. The shaded symbol shows a brown puppy, while open symbols are black individuals.

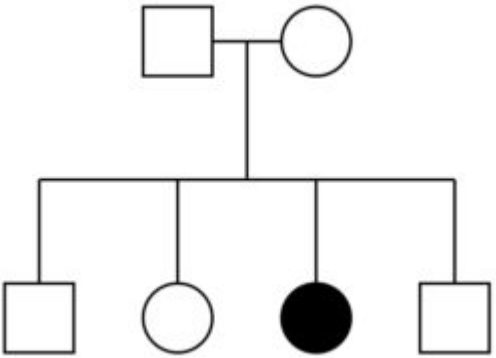

Figure 11: An example litter of puppies. The filled-in symbol shows a brown individual.

To interpret this pedigree, let's start with information that we already know:

- Brown is recessive, which means brown individuals must have the genotype bb. In this pedigree, brown individuals are filled in.
- Black is dominant, which means black individuals must have at least one B allele. Their genotype could be either BB or Bb. In this pedigree, black individuals are not filled in.

Figure 12 shows the same pedigree, but with information about the individual's genotypes filled in.

1. The shaded individual, who is a brown female puppy, must have the genotype bb. If she had any B alleles, she would be black because the black allele is dominant over the brown allele.
2. In order for the brown puppy to have the genotype bb, she must have gotten two "b" alleles: one from each of her parents. We know that her parents are both black (because they are unshaded), which means they must have a least one "B" allele. This means that both parents must be heterozygous: Bb.
3. The three black puppies must have at least one "B" allele in order for them to be black in color. However, we can't tell whether they are homozygous dominant (BB) or heterozygous (Bb) since both of those genotypes would result in black color. One way to represent this on a pedigree is B-, meaning that the second allele could be either B or b.

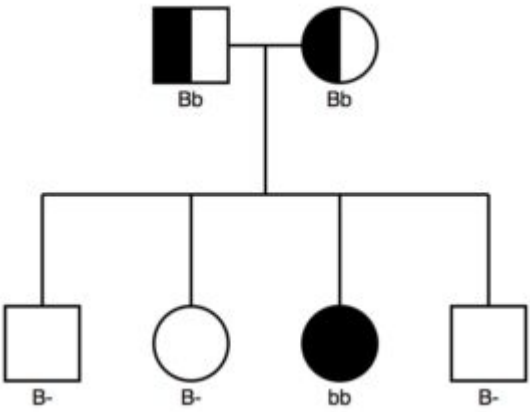

Figure 12: Genotypes of the individuals in this pedigree.

We can also show the cross between these parents as a Punnett square (**Figure 13**). We would expect 1/4 of the offspring to have the genotype bb, and that is what we see in the pedigree above.

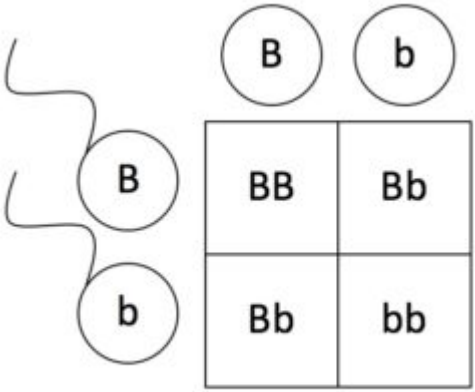

Figure 13: The information from the pedigree shown in Figure can also be shown as a Punnett square.

Human Connection

A small number of mutations in the TYRP1 gene have been found to cause oculocutaneous albinism type 3. This condition includes a form of albinism called rufous oculocutaneous albinism, which has been described primarily in dark-skinned people from southern Africa. Affected individuals have reddish-brown skin, ginger or red hair, and hazel or brown irises. Two TYRP1 mutations are known to cause this form of albinism in individuals from Africa. One mutation replaces a protein building block (amino acid) in tyrosine-related protein 1 with a signal that prematurely stops protein production. This mutation, written as Ser166Ter or S166X, affects the amino acid serine at protein position 166. The other mutation, written as 368delA, deletes a single DNA building block from the TYRP1 gene. Other alterations in this gene have been reported in a few affected people of non-African heritage. Most TYRP1 mutations lead to the production of an abnormally short, nonfunctional version of tyrosinase-related protein 1. Because this enzyme plays a role in normal pigmentation, its loss leads to the changes in skin, hair, and eye coloration that are characteristic of oculocutaneous albinism.

Photo credit: Mu ntuwandi; from Wikipedia.

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Information about TYRP1 and oculocutaneous albinism type 3:

"Tyrp1" by Genetics Home Reference: Your Guide to Understanding Genetic Conditions, National Institutes of Health; U.S> National Library of Medicine is in the Public Domain

85. Yellow fur color: a recessive trait

Yellow color in dogs

Labrador retrievers don't only come in brown and black, they also come in yellow. Yellow color in labs is caused by variations in a different gene: MC1R. This gene controls the production of the melanocortin 1 receptor protein. MC1R is located on chromosome 5 in dogs (Schmutz, 2001).

Figure 14: This yellow lab is producing light-colored pheomelanin instead of dark-colored eumelanin. (Credit: Djmirko; from Wikimedia)

Melanocytes make two forms of melanin, eumelanin and pheomelanin. The relative amounts of these two pigments help determine the color of an individual's hair and skin. Individuals who produce mostly eumelanin tend to have brown or black hair and

dark skin that tans easily (in humans). Eumelanin also protects skin from damage caused by ultraviolet (UV) radiation in sunlight. Individuals who produce mostly pheomelanin tend to have red or blond hair, freckles, and light-colored skin that tans poorly. Because pheomelanin does not protect skin from UV radiation, people with more pheomelanin have an increased risk of skin damage caused by sun exposure.

The melanocortin 1 receptor controls which type of melanin is produced by melanocytes. When the receptor is activated, it triggers a series of chemical reactions inside melanocytes that stimulate these cells to make eumelanin. If the receptor is not activated or is blocked, melanocytes make pheomelanin instead of eumelanin. This means that if the receptor is working correctly and is turned on, dark pigment will be produced. If the receptor is not functional or is not turned on, light pigment will be produced.

Figure 14: The three recognized colors of labs are due to black eumelanin, brown eumelanin, or pheomelanin. (Credit: Erikeltic, from Wikimedia)

Schmutz et. al. (2002) determined the DNA sequence for the MC1R

gene from dogs of various colors. They determined that black and brown dogs all have one allele of MC1R, while yellow and red dogs have a different allele. The allele that leads to yellow or red color has a premature stop codon which results in a shorter-than-normal protein. This protein would be predicted to not function correctly. Remember that when the melanocortin 1 receptor is not functioning correctly, light pheomelanin pigment is produced and not dark eumelanin.

Dogs that are homozygous for the functioning allele of MC1R (which would cause eumelanin to be produced) are dark in color. Dogs that are homozygous for the non-functioning allele (which would cause pheomelanin to be produced) are light in color. Dogs that are heterozygous are dark in color. What does this tell you about which allele is dominant? If you said "the dark allele is dominant because it covers up the light allele", you're correct. We will use "E" to represent the genotype at MC1R because the dominant phenotype in this case is the production of eumelanin. Dogs that have the genotype EE or Ee will produce eumelanin and be dark. Dogs that have the genotype "ee" will produce pheomelanin and be light.

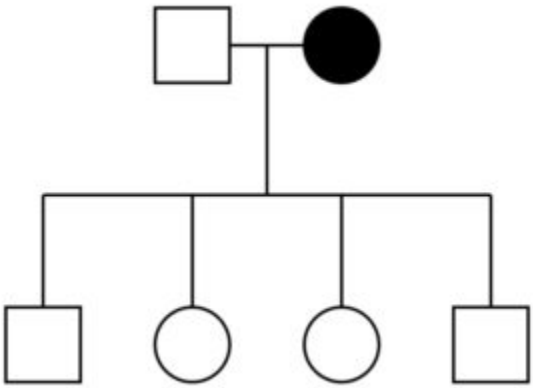

Figure 15: In this pedigree, the shaded individual is yellow. She therefore has the genotype ee and produces pheomelanin. We can't

tell the genotype of her mate by looking (he could be Ee or EE), but since all of their puppies were dark in color, we would predict that his genotype was EE. In this cross: EE x ee, 100% of the puppies would have the genotype Ee, so 100% of the puppies would produce eumelanin instead of pheomelanin.

The cross shown in **Figure 15** can also be shown as a Punnett square. Since we are unsure whether the male dog has the genotype "EE" or "Ee", we have to make two Punnett squares. Since all of the puppies resulting from this cross were black, we would predict that the first Punnett square shows the cross. However, it is possible that the second Punnett square is correct. There are only 4 puppies, so it's not hard to imagine that they could all be black even though the Punnett square predicts only 50% black. It would be comparable to flipping a coin 4 times and getting 4 heads in a row. Getting 4 heads in a row is less likely, but definitely possible.

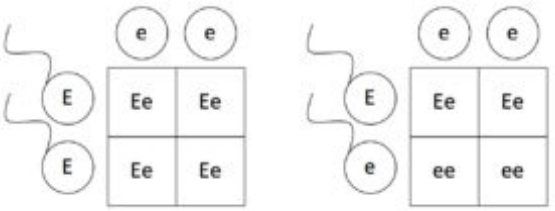

Figure 16: Cross from Figure 15 shown as Punnett squares

It is very important to note here that yellow dogs still have the TYRP1 gene, even though they are not black or brown!

Human Connection

Common variations (polymorphisms) in the MC1R gene are associated with normal differences in skin and hair

color. Certain genetic variations are most common in people with red hair, fair skin, freckles, and an increased sensitivity to sun exposure. These MC1R polymorphisms reduce the ability of the melanocortin 1 receptor to stimulate eumelanin production, causing melanocytes to make mostly pheomelanin. Although MC1R is a key gene in normal human pigmentation, researchers believe that the effects of other genes also contribute to a person's hair and skin coloring.

The melanocortin 1 receptor is also active in cells other than melanocytes, including cells involved in the body's immune and inflammatory responses. The receptor's function in these cells is unknown.

Photo credit: dusdin on flickr; from Wikipedia.

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86. Epistasis: the relationship between black, brown, and yellow fur

Epistasis

Dogs don't have either the TYRP1 gene *or* the MC1R gene – they have both. In fact, every dog will have two copies of the TYRP1 gene and two copies of the MC1R gene. Since both genes control aspects of coat color, it makes sense that they interact. In fact, TYRP1 and MC1R have what is called an epistatic relationship: the action of one gene controls the expression of a second gene. Another way to phrase this relationship is that the effect of one gene is dependent on another gene.

Remember that TYRP1 is required for the production of eumelanin. The dominant allele of TYRP1 (B) produces black eumelanin, while the recessive allele (b) produces brown eumelanin. However, if a dog is homozygous recessive for MC1R (ee), they lack the ability to produce eumelanin at all. If no eumelanin is being produced, it doesn't matter whether it would have been black or brown: there is none. This means that any dog that is homozygous recessive for MC1R will appear yellow regardless of its genotype at TYRP1. These two genes are epistatic: the action of MC1R controls the expression of TYRP1. The effect of TYRP1 is dependent on MC1R.

If a dog has at least one dominant functioning allele of MC1R, then its genotype at TYRP1 can be seen. If the dog has at least one dominant allele of TYRP1, it will appear black. If it has two recessive alleles, it will appear brown.

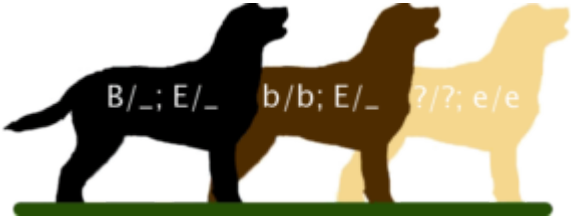

Figure 17: Genotypes for TYRP1 (B) and MC1R (E) that lead to the three recognized colors of labs. (Credit EArellano, from Wikimedia)

A pedigree can be used to show the inheritance of two different genes such as TYRP1 and MC1R.

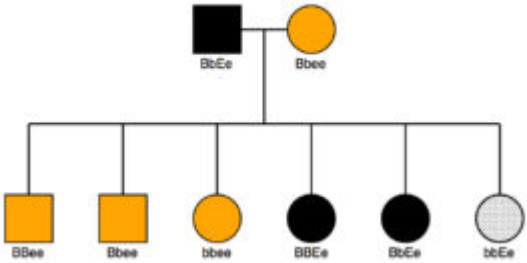

Figure 18: In this pedigree, a cross between an individual who is heterozygous for both MC1R and TYRP1 and an individual who has the genotype "Bbee"is shown. Black individuals are shaded black, yellow individuals are shaded yellow, and brown individuals are shaded grey. The 6 different possible genotypes are each shown as one offspring. This does not give you any information about the probability of getting a certain genotype of offspring – it gives you the actual number of offspring observed and their traits.

Punnett squares can also be used to show this cross. If the probability of inheriting one trait is multiplied by the probability of inheriting the second trait, the overall probability of getting any given offspring can be determined.

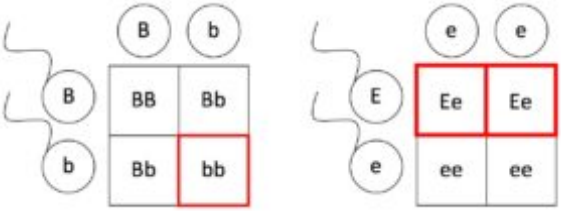

Figure 19: These two Punnett squares can be used to determine the results of a cross between these individuals: Bbee x BbEe. If you wanted to determine the probability of getting a brown dog, you would multiply the probability of getting bb by the probability of having at least one dominant E. That would equal 1/4 x 1/2 = 1/8. This gives you the probability of getting a brown dog, but doesn't tell you anything about the number of brown dogs actually observed.

Human Connection

Individuals who have albinism lack the ability to produce any pigment. If no pigment is being produced, the color that the pigment would have been is unimportant. The effect of the pigment genes is controlled by the gene that allows pigment to be produced. This is an example of epistasis.

Albinism can occur in humans (see the section on TYRP1) as well as other animals, such as the squirrel seen below.

Photo credit: Stephenkniatt from Wikipedia.

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87. Brindle color: partial dominance and epistasis

Brindle coloration is caused by different alleles at the "K locus", which is probably a gene called ASIP that controls pigment switching (Ciampolini, 2013). There are three alleles of the K locus: K^B, k^{br}, and k^y (Kerns, 2007). Any individual dog can only have two of these three alleles (one from each parent), but the dog can have any combination of two the three alleles. The combination of the alleles produces different phenotypes.

The K^B allele is dominant over the other two alleles and produces solid black color. k^{br} produces the brindle color pattern and is dominant over the k^y allele. This means that dogs with the genotype $k^{br}k^{br}$ or $k^{br}k^y$ will have the brindle color pattern. Dogs with the genotype k^yk^y are yellow in color.

Figure : This boxer shows the brindle color pattern, which looks sort of like tiger stripes. (Credit: Steve Henderson Location: Memphis, TN)

The K locus and MC1R (which controls the difference between dark

eumelanin and light pheomelanin production) have an epistatic relationship. If a dog has two recessive alleles for MC1R and is therefore unable to make eumelanin, the dog will appear yellow regardless of its genotype at the K locus.

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88. Incomplete dominance: when traits blend

Flower color in snapdragons

Mendel's results in crossing peas, black vs brown fur color, and eumelanin production vs pheomelanin production all demonstrate traits are inherited as dominant and recessive. This contradicts the historical view that offspring always exhibited a blend of their parents' traits. However, sometimes heterozygote phenotype is intermediate between the two parents. For example, in the snapdragon, *Antirrhinum majus* (**Figure 20**), a cross between a homozygous parent with white flowers (C^WC^W) and a homozygous parent with red flowers (C^RC^R) will produce offspring with pink flowers (C^RC^W) (**Figure 21**).

Figure 20: These pink flowers of a heterozygote snapdragon result from incomplete dominance. (credit: "storebukkeb ruse"/Flickr)

Note that different genotypic abbreviations are used to distinguish these patterns from simple dominance and recessiveness. The abbreviation C^W can be read as "at the flower color gene (C), the white allele is present."

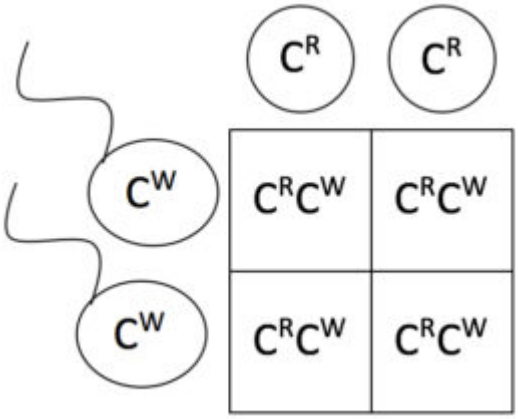

Figure 21: A cross between a red and white snapdragon will yield 100% pink offspring.

This pattern of inheritance is described as **incomplete dominance**, meaning that neither of the alleles is completely dominant over the other: both alleles can be seen at the same time. The allele for red flowers is incompletely dominant over the allele for white flowers. Red + white = pink. The results of a cross where the alleles are incompletely dominant can still be predicted, just as with complete dominant and recessive crosses. **Figure 22** shows the results from a cross between two heterozygous individuals: C^RC^W x C^RC^W . The expected offspring would have the genotypic ratio 1 C^RC^R:2 C^RC^W:1 C^WC^W, and the phenotypic ratio would be 1:2:1 for red:pink:white. The basis for the intermediate color in the heterozygote is simply that the pigment produced by the red allele (anthocyanin) is diluted in the heterozygote and therefore appears pink because of the white background of the flower petals.

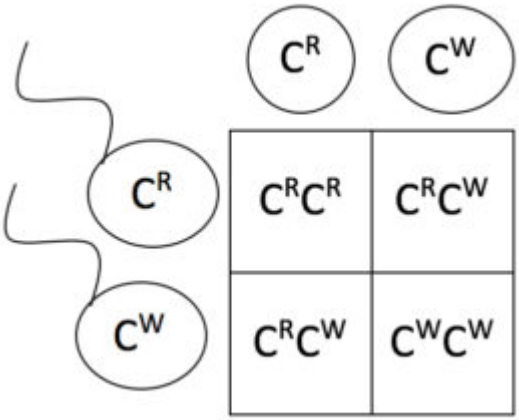

Figure 22: The results of crossing two pink snapdragons.

STRAIGHT, CURLY, AND WAVY HAIR IN DOGS

Another example of incomplete dominance is the inheritance of straight, wavy, and curly hair in dogs. The KRT71 gene is used to synthesize the keratin 71 protein. Genes in the KRT family provide instructions for making proteins called keratins. Keratins are a group of tough, fibrous proteins that form the structural framework of epithelial cells, which are cells that line the surfaces and cavities of the body. Epithelial cells make up tissues such as the hair, skin, and nails. These cells also line the internal organs and are an important part of many glands.

Figure 23: The wavy hair on this labradoodle is caused by incomplete dominance. (Credit: Localpups, Flickr)

Keratins are best known for providing strength and resilience to cells that form the hair, skin, and nails. These proteins allow tissues to resist damage from friction and minor trauma, such as rubbing and scratching. Keratins are also involved in several other critical cell functions, including cell movement (migration), regulation of cell size, cell growth and division (proliferation), wound healing, and transport of materials within cells. Different combinations of keratin proteins are found in different tissues.

The mutation which causes curly hair in dogs, such as the labradoodle seen in Figure 23, is in exon 2 of the gene and is predicted to substantially disrupt the structure of the keratin 71 protein (Cadieu, 2009). This change in protein shape prevents the keratin proteins from interacting together correctly within the hair, altering the structure of the hair and resulting in a curly coat (Runkel, 2006).

When a dog has two curly alleles (K^CK^C), it has a very curly coat, such as on the poodle in **Figure 24**. A dog with two straight alleles (K^+K^+) has a straight coat. Dogs that are heterozygous (K^+K^C) have an intermediate or wavy coat like the labradoodle in **Figure 23**.

Figure 24: This poodle has two copies of the curly allele of the KRT71 gene (KCKC). Compare his curly hair to the wavy hair of the labradoodle in Figure 23. The labradoodle is heterozygous (K+KC). (Credit B. Schoener; From Wikimedia)

Human Connection – Blood Type

Blood is classified into different groups according to the presence or absence of molecules called antigens on the surface of every red blood cell in a person's body. Antigens determine blood type and can either be proteins or complexes of sugar molecules (polysaccharides). The genes in the blood group antigen family provide instructions for making antigen proteins. Blood group antigen proteins serve a variety of functions within the cell membrane of red blood cells. These protein functions include transporting other proteins and molecules into and out of the cell,

maintaining cell structure, attaching to other cells and molecules, and participating in chemical reactions.

There are 29 recognized blood groups, most involving only one gene. Variations (polymorphisms) within the genes that determine blood group give rise to the different antigens for a particular blood group protein. For example, changes in a few DNA building blocks (nucleotides) in the ABO gene give rise to the A, B, and O blood types of the ABO blood group. The changes that occur in the genes that determine blood group typically affect only blood type and are not associated with adverse health conditions, although exceptions do occur.

The A and B alleles are codominant, which is similar to incomplete dominance in that heterozygotes have an intermediate phenotype (instead of a blend). If both the A and B alleles are present, both will be seen in the phenotype. The O allele is recessive to both A and B.

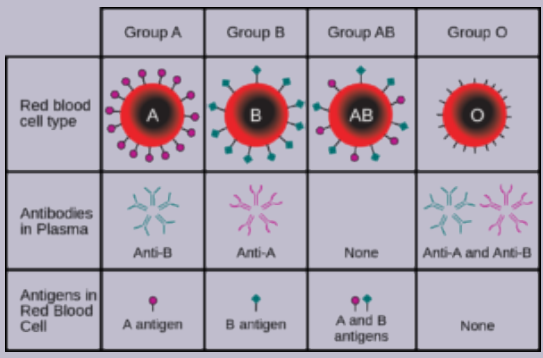

Photo credit: InvictaHOG, from Wikipedia.

Human Connection

Curly hair and straight hair are incompletely dominant alleles of one gene. A person with two curly alleles will have very curly hair. A person with two straight alleles will have straight hair. A person with one curly and one straight allele will have wavy hair!

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"Keratins" by Genetics Home Reference: Your Guide to Understanding Genetic Conditions, National Institutes of Health: U.S> National Library of Medicine is in the Public Domain

89. White spotting: When there's more than two alleles

So far, we have discussed genes which have only two alleles. However, that is not always the case: there can be more than two alleles for a given gene. One example is the MITF gene, which is the major gene that controls white spotting in dogs. This protein is required for the migration and survival of melanocytes into the skin during development. If it is not functional, it impairs the ability of the skin to make pigment, thus "covering up" the effect of other color genes. There are thought to be at least four alleles that can contribute (Karlsson, 2007). Depending on which alleles are present in a dog, the amount of white can vary from none (a solid-colored dog) to mostly white (**Table 2** and **Figure 24**).

Table 2: Combinations of different alleles for MITF result in different amounts of white present in the coat.

Alleles	Amount of white
SS	None (solid colored)
Ss^{i}	Small amounts of white possible on chin, chest, feet, and tail tip
Ss^{p}	Pied markings where the coat is more than 50% colored, with white on the face, chest, feet, collar, underbelly, and tail tip
$s^{i}s^{p}$	Approximately even amounts of color and white
$s^{i}s^{e}$	More than 50% white with irregular splashes of color
$s^{e}s^{e}$	Mostly white with only minimal areas of color, perhaps on one or both ears, an eye patch, or a spot near the tail

Figure 24: These dogs have different combinations of alleles of the MITF gene. The first dog probably has the genotype "SS"; the dog in the center is likely "Ssp"; the dog on the right is likely "sese". (Credits: Funny black dog by X posid from Publicdomainpictures. A black and white dog by Petr Kratochvil from Free stock photos. White dog with black ears by RetyiRetyi from Pixabay.)

Human Connection – Blood Type

Human blood type was discussed in the previous section.

You may remember that there are three alleles for the ABO gene: A, B, and O. A and B are codominant, meaning that if both alleles are present, both will be seen in the phenotype. A person with type AB blood has one A allele and one B allele.

O is recessive to A and B. A person with the genotype AO will have Type A blood. A person with the genotype BO will have type B blood. Type O blood results from two O alleles.

	A	B	O
A	AA	AB	AO
B	AB	BB	BO
O	AO	BO	OO

Photo credit: Kalaiarasy, from Wikipedia.

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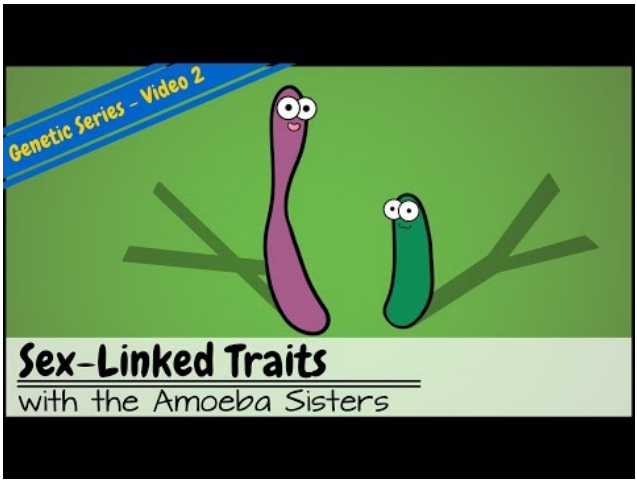
90. Hemophilia: a sex-linked disorder

So far, all the genes we have discussed have had two copies present in all individuals. This is because the individual inherited one from the male parent's haploid gamete and one from the female parent's haploid gamete. The two gametes came together during fertilization to produce a diploid individual. There is, however, one exception to this: genes which are present on the sex chromosomes.



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In humans, as well as in many other animals and some plants, the sex of the individual is determined by **sex chromosomes –** one pair of non-homologous chromosomes. Until now, we have only

considered inheritance patterns among non-sex chromosomes, or **autosomes.** In addition to 22 homologous pairs of autosomes, human females have a homologous pair of X chromosomes, whereas human males have an XY chromosome pair. Although the Y chromosome contains a small region of similarity to the X chromosome so that they can pair during meiosis, the Y chromosome is much shorter and contains fewer genes. When a gene being examined is present on the X, but not the Y, chromosome, it is **X-linked**.

The X chromosome is one of two sex chromosomes. Humans and most mammals have two sex chromosomes, the X and Y. Females have two X chromosomes in their cells, while males have X and Y chromosomes in their cells. Egg cells all contain an X chromosome, while sperm cells contain an X or a Y chromosome. This arrangement means that during fertilization, it is the male that determines the sex of the offspring since the female can only give an X chromosome to the offspring.

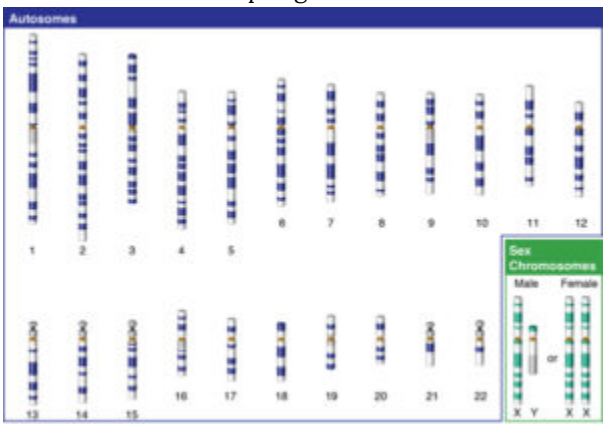

Figure 24: A diagram showing the autosomal and sex chromosomes. Remember that in a diploid cell, there would be two copies of each autosomal chromosome present. (Credit: Darryl Lega, NHGRI)

Most sex-linked genes are present on the X chromosome simply because it is much larger than the Y chromosome. The X chromosome spans about 155 million DNA base pairs and represents

approximately 5 percent of the total DNA in cells. The X chromosome likely contains 800 to 900 genes. In contrast, the Y chromosome has approximately 59 million base pairs and only 50-60 genes. Sex is determined by the SRY gene, which is located on the Y chromosome and is responsible for the development of a fetus into a male. This means that the presence of a Y chromosome is what causes a fetus to develop as male. Other genes on the Y chromosome are important for male fertility.

Hemophilia is a bleeding disorder that slows the blood clotting process. People with this condition experience prolonged bleeding or oozing following an injury, surgery, or having a tooth pulled. In severe cases of hemophilia, continuous bleeding occurs after minor trauma or even in the absence of injury (spontaneous bleeding). Serious complications can result from bleeding into the joints, muscles, brain, or other internal organs. Milder forms of hemophilia do not necessarily involve spontaneous bleeding, and the condition may not become apparent until abnormal bleeding occurs following surgery or a serious injury.

The major types of this condition are hemophilia A (also known as classic hemophilia or factor VIII deficiency) and hemophilia B (also known as Christmas disease or factor IX deficiency). Although the two types have very similar signs and symptoms, they are caused by mutations in different genes.

Hemophilia A and hemophilia B are inherited in an X-linked recessive pattern. The genes associated with these conditions are located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would have to occur in both copies of the gene to cause the disorder. Because it is unlikely that females will have two altered copies of this gene, it is very rare for females to have hemophilia. A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

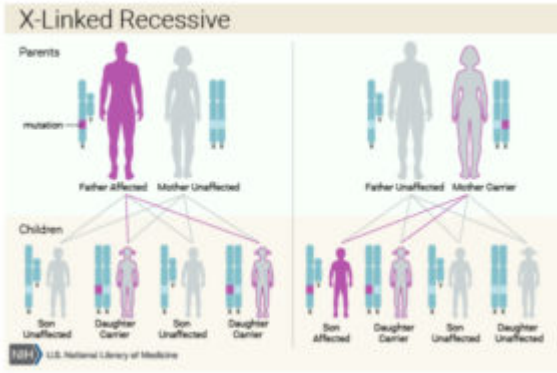

Figure 25: X-linked recessive inheritance. (Credit: U.S. National Library of Medicine)

In X-linked recessive inheritance, a female with one altered copy of the gene in each cell is called a carrier. Carrier females have about half the usual amount of coagulation factor VIII or coagulation factor IX, which is generally enough for normal blood clotting. However, about 10 percent of carrier females have less than half the normal amount of one of these coagulation factors; these individuals are at risk for abnormal bleeding, particularly after an injury, surgery, or tooth extraction.

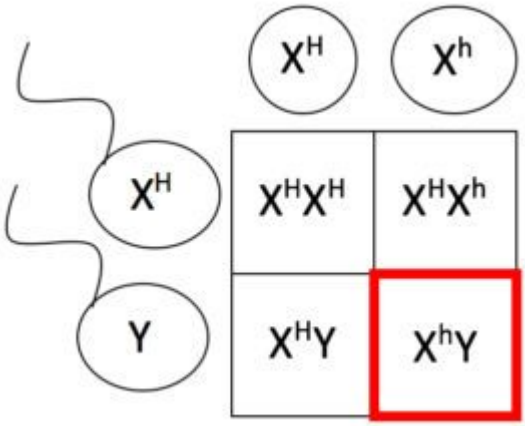

Figure 25: If a carrier female and a normal male produce offspring, there is a 25% total chance that they will have a child with hemophilia. None of their daughters will have the disease (although all will be carriers). Half their sons will be hemophiliacs .

Colorblindness is another example of a sex-linked trait in humans. The genes that produce the photopigments necessary for color vision are located on the X chromosome. If one of these genes is not functional because it contains a harmful mutation, the individual will be colorblind. Men are much more likely than women to be colorblind: up to 100 times more men than women have various types of colorblindness (http://www.colour-blindness.com/general/prevalence/).

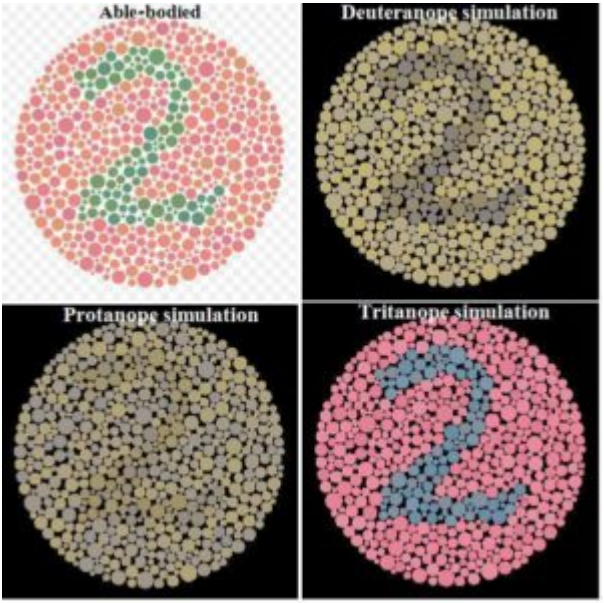

Figure 26: A test image for color-blindness as seen by someone with normal color vision and several types of colorblindness. (Credit: Sakurambo)

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Determining Sex Isn't That Simple

For the purposes of solving Punnett Square problems, we will assume that males are XY and females are XX. However, it is not nearly that simple in real life. You will not be tested on the material in this video, but I highly recommend it because it's fascinating.

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This topic is also discussed in this article in Scientific American: https://www.scientificamerican.com/article/sex-redefined-the-idea-of-2-sexes-is-overly-simplistic1/

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"Hemophilia" by Genetics Home Reference: Your Guide to Understanding Genetic Conditions, National Institutes of Health: U.S> National Library of Medicine is in the Public Domain

91. Overall phenotypes: putting it all together

None of the genes discussed in these sections occur in isolation: one individual dog would have all the genes for color, hair structure, and hemoglobin (dogs can get hemophilia too). Genes interact together to produce the overall phenotype of the individual.

Example 1: Sugar

For example, look at Sugar in **Figure 26**. She has short hair that is mostly white. The colored portion of her hair is the tiger-striped pattern termed "brindle."

Figure 26: Sugar has short hair with colored spots. (Credit: Lisa Bartee)

The difference between short and long hair in dogs is caused by different alleles of a gene called FGF5. This gene produces a protein that is important in regulating the hair growth cycle. When the protein doesn't function correctly, the growth phase of the hair cycle is longer, resulting in long hair. Short hair is the dominant trait. Since Sugar has short hair, we know she has at least one dominant allele of FGF5. We can use the letter "S" for short hair. Sugar's genotype for FGF5 is therefore "S-", meaning she has one dominant allele and we can't tell by looking at her what her second allele is.

Sugar's hair is also straight, which means that she has two straight alleles of KRT71. Her genotype would be $K^{+}K^{+}$.

Sugar is more than 50% white with irregular splashes of color, which means that her genotype for MITF (the gene that controls white spotting) is $s^{i}s^{e}$.

The brindle pattern is caused by the k^{br} allele at the K locus. Sugar can't have the K^{B} allele or she would have solid color instead of the brindle pattern because K^{B} is dominant over k^{br} and k^{y}. She could have either the genotype $k^{br}k^{br}$ or $k^{br}k^{y}$, since the k^{br} allele is dominant over the yellow allele (k^{y}).

Sugar has black eumelanin pigment in her hair and nose. This means she has the dominant phenotype for TYPR1, so her genotype would be "B-". Because she has eumelanin and not pheomelanin in her coat, she has the dominant phenotype for MC1R, so her genotype would be "E-".

Sugar is a female dog who does not have hemophilia. This means that her genotype would be either $X^{H}X^{H}$ or $X^{H}X^{h}$.

Putting all these together, we could say that Sugar's overall coat genotype is S- $K^{+}K^{+}$ $s^{i}s^{e}$ B- E- $X^{H}X$–

We could potentially determine some of the unknown alleles in her genotype if we knew anything about her parents, but Sugar was adopted from the Multnomah County Animal Shelter after being picked up as a stray. Therefore, her ancestry is unknown.

Example 2: Rags

Figure 27: Rags is similar in color to Sugar, but has a very different fur type. (Credit: Lisa Bartee)

Rags has "furnishings", a term used to describe his beard and mustache. Furnishings are caused by a mutation in the RSPO2 gene. This gene produces a protein that is involved in establishing hair follicles. The allele that leads to furnishings is dominant over the allele for no furnishings. Rags must therefore have the genotype "F-" at RSPO2. This allele also causes the long-ish hair on his legs and tail.

Gene	Genotype	Phenotype
RSPO2	FF or Ff	has furnishings
FGF5	SS or Ss	short fur (his longer fur is caused by the furnishings allele)
KRT71	$K^{+}K^{+}$	straight fur
MITF	$s^{i}s^{e}$	more than 50% white
K locus	$K^{B}K^{B}$, $K^{B}k^{br}$, or $K^{B}k^{y}$	Solid color, not brindle or yellow.
TYRP1	BB or Bb	Produces black eumelanin, not brown
MC1R	EE or Ee	Produces eumelanin instead of pheomelanin
F8	$X^{H}Y$	Male, no hemophilia

Example 3: Black poodle

Figure : Black poodle. (Credit: B. Schoener from Wikimedia)

Gene	Genotype	Phenotype
RSPO2	ff	no furnishings
FGF5	ss	long fur
KRT71	KcKc	curly fur
MITF	SS	entirely solid color
K locus	KBKB, KBkbr, or KBky	Solid color, not brindle or yellow.
TYRP1	BB or Bb	Produces black eumelanin, not brown
MC1R	EE or Ee	Produces eumelanin instead of pheomelanin

EXAMPLE 4: GOLDEN RETRIEVER

12.Golden_Retriever_Carlos_(10581910556)

Figure : Golden Retriever. (Credit: Dirk Vorderstraße)

Gene	Genotype	Phenotype
RSPO2	ff	no furnishings
FGF5	ss	long fur
KRT71	K+K+	straight fur
MITF	SS	entirely solid color
K locus	KBKB, KBkbr, or KBky	Solid color, not brindle or yellow.
TYRP1	BB or Bb	Produces black eumelanin, not brown (seen in the nose)
MC1R	ee	Produces pheomelanin instead of eumelanin, so appears yellow

References

92. Additional complexity

Figure 29: An English Cocker Spaniel. (Credit eNil)

We haven't exhaustively discussed all the genes that can affect dog appearance. For example, what gene (or genes) causes the English Springer Spaniel in **Figure 29** to be red? What gene(s) cause it to be speckled on it's back? Or lead to its freckles? There are estimated to be about 19,000 genes in the dog genome (Ostrander, 2005). The interactions of all these genes together lead to the overall phenotype of one individual dog.If you're interested in learning more about the genes that are involved in the appearance of dogs, check out the Dog Coat Color Genetics website at http://www.doggenetics.co.uk.

References

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93. It's not all in the genes

Not all traits are directly caused by DNA alone. The environment also plays a large role in shaping an individual's traits. Some examples can be seen below.

- **Height and weight:** A number of genes interact to determine the general height and weight that a person will have. But the environment has a major influence as well. If an individual is malnourished, their growth may be slowed and they may be smaller than they would have been if they had gotten enough food. In contrast, if a person consumes more calories than they need, their weight will likely increase regardless of their genetics.

- **Fingerprints:** the general characteristics of a person's fingerprints are determined by genetics, but the specific pattern is generated randomly during development. Identical twins typically have fingerprints that are similar, but not identical.

- **Intelligence:** Like most aspects of human behavior and cognition, intelligence is a complex trait that is influenced by both genetic and environmental factors. Roughly 50% of a person's IQ appears to be determined by genetic factors. Factors related to a child's home environment and parenting, education and availability of learning resources, and nutrition, among others, also contribute to intelligence. A person's environment and genes influence each other, and it can be challenging to tease apart the effects of the environment from those of genetics. For example, if a child's IQ is similar to that of his or her parents, is that similarity due to genetic factors passed down from parent to child, to shared environmental factors, or (most likely) to a combination of

both? It is clear that both environmental and genetic factors play a part in determining intelligence.

- **Cancer Risk:** For example, a person could inherit a mutation in the BRCA1 gene, which increases the risk of developing breast or ovarian cancer. Researchers have identified more than 1,800 mutations in the BRCA1 gene. Most BRCA1 gene mutations lead to the production of an abnormally short version of the BRCA1 protein or prevent any protein from being made from one copy of the gene. As a result, less of this protein is available to help repair damaged DNA or fix mutations that occur in other genes. As these defects accumulate, they can trigger cells to grow and divide uncontrollably to form a tumor. These mutations are present in every cell in the body and can be passed from one generation to the next. As a result, they are associated with cancers that cluster in families. However, not everyone who inherits a mutation in the BRCA1 gene will develop cancer. Other genetic, environmental, and lifestyle factors also contribute to a person's cancer risk.
- In contrast, cancer can be caused by purely environmental factors. According to the CDC, cigarette smoking is the number one risk factor for lung cancer. In the United States, cigarette smoking is linked to about 90% of lung cancers and people who smoke are 15 to 30 times more likely to get lung cancer or die from lung cancer than people who do not smoke. Radon exposure also increases the likelihood that a person will develop lung cancer.

Figure 30: The colors on the poodle seen in this figure have no relationship to his DNA: he was dyed for a parade. (Credit: skeeze)

References

"BRCA1" by Genetics Home Reference: Your Guide to Understanding Genetic Conditions, National Institutes of Health: U.S> National Library of Medicine is in the Public Domain

"Is intelligence determined by genetics?" by Genetics Home Reference: Your Guide to Understanding Genetic Conditions, National Institutes of Health: U.S> National Library of Medicine is in the Public Domain

PART XIV

PATTERNS OF INHERITANCE

PART

12. PATTERNS OF INHERITANCE

Learning Objectives

By the end of this section, you will be able to:

- Describe the molecular basis of inheritance.
- Determine the outcome in crosses involving various types of inheritance.
- Present and decipher information about trait inheritance using a pedigree.

References

OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/GFy_h8cu@10.57:O2lXSTlf@2/Introduction

PART XV

BIOTECHNOLOGY

The latter half of the twentieth century began with the discovery of the structure of DNA, then progressed to the development of the basic tools used to study and manipulate DNA. These advances, as well as advances in our understanding of and ability to manipulate cells, have led some to refer to the twenty-first century as the biotechnology century. The rate of discovery and of the development of new applications in medicine, agriculture, and energy is expected to accelerate, bringing huge benefits to humankind and perhaps also significant risks. Many of these developments are expected to raise significant ethical and social questions that human societies have not yet had to consider.

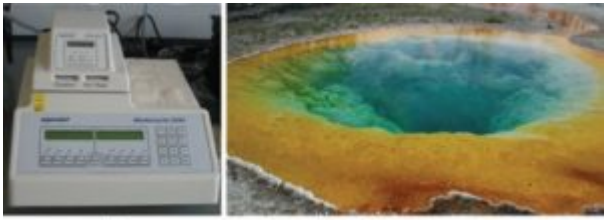

Figure 1: (a) A thermal cycler, such as the one shown here, is a basic tool used to study DNA in a process called the polymerase chain reaction (PCR). The polymerase enzyme most often used with PCR comes from a strain of bacteria that lives in (b) the hot springs of Yellowstone National Park. (credit a: modification of work by Magnus Manske; credit b: modification of work by Jon Sullivan)

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94. Manipulating Genetic Material

Biotechnology is the use of artificial methods to modify the genetic material of living organisms or cells to produce novel compounds or to perform new functions. Biotechnology has been used for improving livestock and crops since the beginning of agriculture through selective breeding. Since the discovery of the structure of DNA in 1953, and particularly since the development of tools and methods to manipulate DNA in the 1970s, biotechnology has become synonymous with the manipulation of organisms' DNA at the molecular level. The primary applications of this technology are in medicine (for the production of vaccines and antibiotics) and in agriculture (for the genetic modification of crops). Biotechnology also has many industrial applications, such as fermentation, the treatment of oil spills, and the production of biofuels, as well as many household applications such as the use of enzymes in laundry detergent.

To accomplish the applications described above, biotechnologists must be able to extract, manipulate, and analyze nucleic acids.

Review of Nucleic Acid Structure

To understand the basic techniques used to work with nucleic acids, remember that nucleic acids are macromolecules made of nucleotides (a sugar, a phosphate, and a nitrogenous base). The phosphate groups on these molecules each have a net negative charge. An entire set of DNA molecules in the nucleus of eukaryotic organisms is called the genome. DNA has two complementary strands linked by hydrogen bonds between the paired bases.

Unlike DNA in eukaryotic cells, RNA molecules leave the nucleus. Messenger RNA (mRNA) is analyzed most frequently because it represents the protein-coding genes that are being expressed in the cell.

Isolation of Nucleic Acids

To study or manipulate nucleic acids, the DNA must first be extracted from cells. Various techniques are used to extract different types of DNA (**Figure 10.2**). Most nucleic acid extraction techniques involve steps to break open the cell, and then the use of enzymatic reactions to destroy all undesired macromolecules. Cells are broken open using a detergent solution containing buffering compounds. To prevent degradation and contamination, macromolecules such as proteins and RNA are inactivated using enzymes. The DNA is then brought out of solution using alcohol. The resulting DNA, because it is made up of long polymers, forms a gelatinous mass.

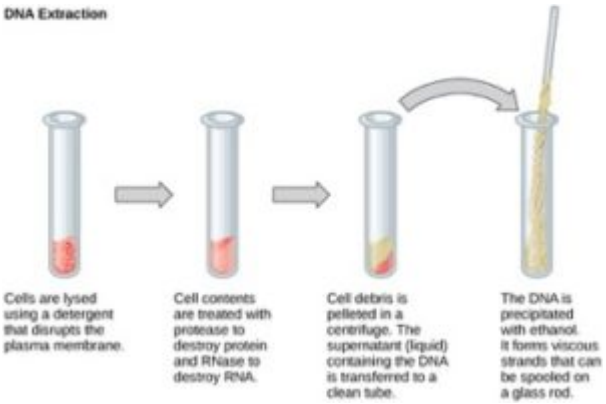

Figure 2: This diagram shows the basic method used for the extraction of DNA.

RNA is studied to understand gene expression patterns in cells.

RNA is naturally very unstable because enzymes that break down RNA are commonly present in nature. Some are even secreted by our own skin and are very difficult to inactivate. Similar to DNA extraction, RNA extraction involves the use of various buffers and enzymes to inactivate other macromolecules and preserve only the RNA.

Gel Electrophoresis

Because nucleic acids are negatively charged ions at neutral or alkaline pH in an aqueous environment, they can be moved by an electric field. **Gel electrophoresis** is a technique used to separate charged molecules on the basis of size and charge. The nucleic acids can be separated as whole chromosomes or as fragments. The nucleic acids are loaded into a slot at one end of a gel matrix, an electric current is applied, and negatively charged molecules are pulled toward the opposite end of the gel (the end with the positive electrode). Smaller molecules move through the pores in the gel faster than larger molecules; this difference in the rate of migration separates the fragments on the basis of size. The nucleic acids in a gel matrix are invisible until they are stained with a compound that allows them to be seen, such as a dye. Distinct fragments of nucleic acids appear as bands at specific distances from the top of the gel (the negative electrode end) that are based on their size (**Figure 10.3**). A mixture of many fragments of varying sizes appear as a long smear, whereas uncut genomic DNA is usually too large to run through the gel and forms a single large band at the top of the gel.

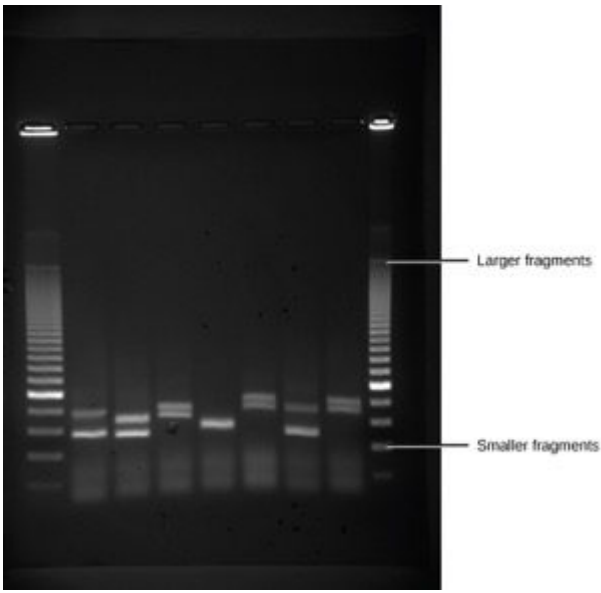

Figure 3: Shown are DNA fragments from six samples run on a gel, stained with a fluorescent dye and viewed under UV light. (credit: modification of work by James Jacob, Tompkins Cortland Community College)

DNA analysis often requires focusing on one or more specific regions of the genome. It also frequently involves situations in which only one or a few copies of a DNA molecule are available for further analysis. These amounts are insufficient for most procedures, such as gel electrophoresis. **Polymerase chain reaction (PCR)** is a technique used to rapidly increase the number of copies of specific regions of DNA for further analyses (**Figure 10.4**). PCR uses a special form of DNA polymerase, the enzyme that replicates DNA, and other short nucleotide sequences called primers that base pair to a specific portion of the DNA being replicated. PCR is used for many purposes in laboratories. These include: 1) the identification of the owner of a DNA sample left at a crime scene; 2) paternity analysis; 3) the comparison of small amounts of ancient DNA with modern organisms; and 4) determining the sequence of nucleotides in a specific region.

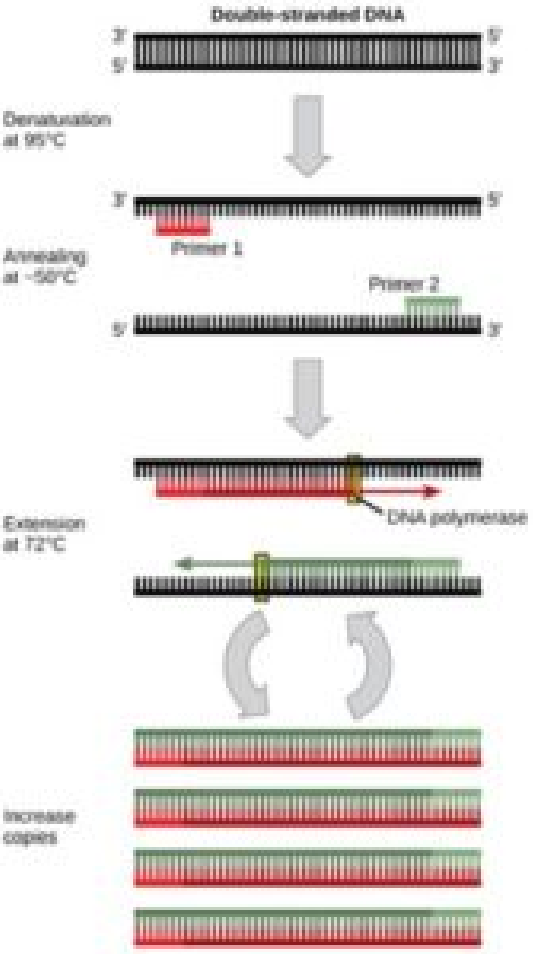

Figure 4: Polymerase chain reaction, or PCR, is used to produce many copies of a specific sequence of DNA using a special form of DNA polymerase.

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contents/s8Hh0oOc@9.10:8CA_YwJq@3/Cloning-and-Genetic-Engineerin

95. Cloning

In general, **cloning** means the creation of a perfect replica. Typically, the word is used to describe the creation of a genetically identical copy. In biology, the re-creation of a whole organism is referred to as "reproductive cloning." Long before attempts were made to clone an entire organism, researchers learned how to copy short stretches of DNA—a process that is referred to as molecular cloning.

Molecular Cloning

Cloning allows for the creation of multiple copies of genes, expression of genes, and study of specific genes. To get the DNA fragment into a bacterial cell in a form that will be copied or expressed, the fragment is first inserted into a plasmid. A **plasmid** (also called a vector in this context) is a small circular DNA molecule that replicates independently of the chromosomal DNA in bacteria. In cloning, the plasmid molecules can be used to provide a "vehicle" in which to insert a desired DNA fragment. Modified plasmids are usually reintroduced into a bacterial host for replication. As the bacteria divide, they copy their own DNA (including the plasmids). The inserted DNA fragment is copied along with the rest of the bacterial DNA. In a bacterial cell, the fragment of DNA from the human genome (or another organism that is being studied) is referred to as foreign DNA to differentiate it from the DNA of the bacterium (the host DNA).

Plasmids occur naturally in bacterial populations (such as *Escherichia coli*) and have genes that can contribute favorable traits to the organism, such as antibiotic resistance (the ability to be unaffected by antibiotics). Plasmids have been highly engineered as vectors for molecular cloning and for the subsequent large-scale

production of important molecules, such as insulin. A valuable characteristic of plasmid vectors is the ease with which a foreign DNA fragment can be introduced. These plasmid vectors contain many short DNA sequences that can be cut with different commonly available **restriction enzymes**. Restriction enzymes (also called restriction endonucleases) recognize specific DNA sequences and cut them in a predictable manner; they are naturally produced by bacteria as a defense mechanism against foreign DNA. Many restriction enzymes make staggered cuts in the two strands of DNA, such that the cut ends have a 2- to 4-nucleotide single-stranded overhang. The sequence that is recognized by the restriction enzyme is a four- to eight-nucleotide sequence that is a palindrome. Like with a word palindrome, this means the sequence reads the same forward and backward. In most cases, the sequence reads the same forward on one strand and backward on the complementary strand. When a staggered cut is made in a sequence like this, the overhangs are complementary (**Figure 10.5**).

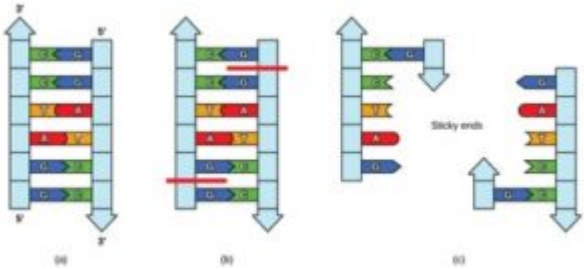

Figure 5: In this (a) six-nucleotide restriction enzyme recognition site, notice that the sequence of six nucleotides reads the same in the 5′ to 3′ direction on one strand as it does in the 5′ to 3′ direction on the complementary strand. This is known as a palindrome. (b) The restriction enzyme makes breaks in the DNA strands, and (c) the cut in the DNA results in "sticky ends". Another piece of DNA cut on either end by the same restriction enzyme could attach to these sticky ends and be inserted into the gap made by this cut.

Because these overhangs are capable of coming back together by hydrogen bonding with complementary overhangs on a piece of DNA cut with the same restriction enzyme, these are called "sticky ends." The process of forming hydrogen bonds between complementary sequences on single strands to form doublestranded DNA is called **annealing**. Addition of an enzyme called DNA ligase, which takes part in DNA replication in cells, permanently joins the DNA fragments when the sticky ends come together. In this way, any DNA fragment can be spliced between the two ends of a plasmid DNA that has been cut with the same restriction enzyme (**Figure 10.6**).

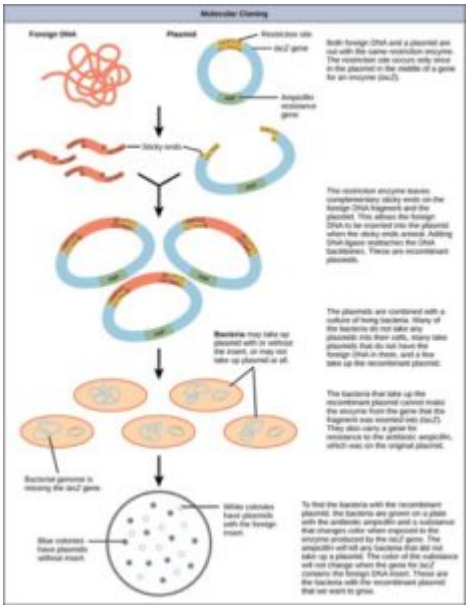

Figure 6: This diagram shows the steps involved in molecular cloning.

Plasmids with foreign DNA inserted into them are called **recombinant DNA** molecules because they contain new combinations of genetic material. Proteins that are produced from recombinant DNA molecules are called **recombinant proteins**. Not

all recombinant plasmids are capable of expressing genes. Plasmids may also be engineered to express proteins only when stimulated by certain environmental factors, so that scientists can control the expression of the recombinant proteins.

Reproductive Cloning

Reproductive cloning is a method used to make a clone or an identical copy of an entire multicellular organism. Most multicellular organisms undergo reproduction by sexual means, which involves the contribution of DNA from two individuals (parents), making it impossible to generate an identical copy or a clone of either parent. Recent advances in biotechnology have made it possible to reproductively clone mammals in the laboratory.

Natural sexual reproduction involves the union, during fertilization, of a sperm and an egg. Each of these gametes is haploid, meaning they contain one set of chromosomes in their nuclei. The resulting cell, or zygote, is then diploid and contains two sets of chromosomes. This cell divides mitotically to produce a multicellular organism. However, the union of just any two cells cannot produce a viable zygote; there are components in the cytoplasm of the egg cell that are essential for the early development of the embryo during its first few cell divisions. Without these provisions, there would be no subsequent development. Therefore, to produce a new individual, both a diploid genetic complement and an egg cytoplasm are required. The approach to producing an artificially cloned individual is to take the egg cell of one individual and to remove the haploid nucleus. Then a diploid nucleus from a body cell of a second individual, the donor, is put into the egg cell. The egg is then stimulated to divide so that development proceeds. This sounds simple, but in fact it takes many attempts before each of the steps is completed successfully.

The first cloned agricultural animal was Dolly, a sheep who was

born in 1996. The success rate of reproductive cloning at the time was very low. Dolly lived for six years and died of a lung tumor (**Figure 10.7**). There was speculation that because the cell DNA that gave rise to Dolly came from an older individual, the age of the DNA may have affected her life expectancy. Since Dolly, several species of animals (such as horses, bulls, and goats) have been successfully cloned.

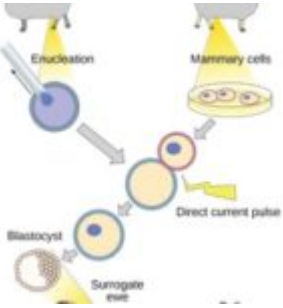

Figure 7: The creation of Dolly the sheep

There have been attempts at producing cloned human embryos as sources of embryonic stem cells. In the procedure, the DNA from an adult human is introduced into a human egg cell, which is then stimulated to divide. The technology is similar to the technology that was used to produce Dolly, but the embryo is never implanted into a surrogate mother. The cells produced are called embryonic stem cells because they have the capacity to develop into many different kinds of cells, such as muscle or nerve cells. The stem cells could be used to research and ultimately provide therapeutic applications, such as replacing damaged tissues. The benefit of cloning in this instance is that the cells used to regenerate new tissues would be a perfect match to the donor of the original DNA. For example, a leukemia patient would not require a sibling with a tissue match for a bone-marrow transplant.

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96. Genetic Engineering

Using recombinant DNA technology to modify an organism's DNA to achieve desirable traits is called **genetic engineering**. Addition of foreign DNA in the form of recombinant DNA vectors that are generated by molecular cloning is the most common method of genetic engineering. An organism that receives the recombinant DNA is called a **genetically modified organism** (GMO). If the foreign DNA that is introduced comes from a different species, the host organism is called **transgenic**. Bacteria, plants, and animals have been genetically modified since the early 1970s for academic, medical, agricultural, and industrial purposes. These applications will be examined in more detail in the next module.

Although the classic methods of studying the function of genes began with a given phenotype and determined the genetic basis of that phenotype, modern techniques allow researchers to start at the DNA sequence level and ask: "What does this gene or DNA element do?" This technique, called **reverse genetics**, has resulted in reversing the classical genetic methodology. One example of this method is analogous to damaging a body part to determine its function. An insect that loses a wing cannot fly, which means that the wing's function is flight. The classic genetic method compares insects that cannot fly with insects that can fly, and observes that the non-flying insects have lost wings. Similarly in a reverse genetics approach, mutating or deleting genes provides researchers with clues about gene function. Alternately, reverse genetics can be used to cause a gene to overexpress itself to determine what phenotypic effects may occur.

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97. Biotechnology in Medicine and Agriculture

It is easy to see how biotechnology can be used for medicinal purposes. Knowledge of the genetic makeup of our species, the genetic basis of heritable diseases, and the invention of technology to manipulate and fix mutant genes provides methods to treat diseases. Biotechnology in agriculture can enhance resistance to disease, pests, and environmental stress to improve both crop yield and quality.

Genetic Diagnosis and Gene Therapy

The process of testing for suspected genetic defects before administering treatment is called genetic diagnosis by genetic testing. In some cases in which a genetic disease is present in an individual's family, family members may be advised to undergo genetic testing. For example, mutations in the *BRCA* genes may increase the likelihood of developing breast and ovarian cancers in women and some other cancers in women and men. A woman with breast cancer can be screened for these mutations. If one of the highrisk mutations is found, her female relatives may also wish to be screened for that particular mutation, or simply be more vigilant for the occurrence of cancers. Genetic testing is also offered for fetuses (or embryos with in vitro fertilization) to determine the presence or absence of disease-causing genes in families with specific debilitating diseases.

Gene therapy is a genetic engineering technique that may one day be used to cure certain genetic diseases. In its simplest form, it involves the introduction of a non-mutated gene at a random

location in the genome to cure a disease by replacing a protein that may be absent in these individuals because of a genetic mutation. The non-mutated gene is usually introduced into diseased cells as part of a vector transmitted by a virus, such as an adenovirus, that can infect the host cell and deliver the foreign DNA into the genome of the targeted cell (**Figure 10.8**). To date, gene therapies have been primarily experimental procedures in humans. A few of these experimental treatments have been successful, but the methods may be important in the future as the factors limiting its success are resolved.

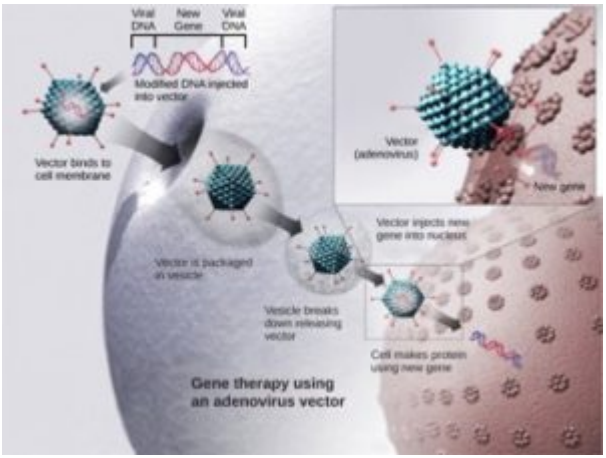

Figure 8: This diagram shows the steps involved in curing disease with gene therapy using an adenovirus vector. (credit: modification of work by NIH)

Traditional vaccination strategies use weakened or inactive forms of microorganisms or viruses to stimulate the immune system. Modern techniques use specific genes of microorganisms cloned into vectors and mass-produced in bacteria to make large quantities of specific substances to stimulate the immune system. The substance is then used as a vaccine. In some cases, such as the H1N1 flu vaccine, genes cloned from the virus have been used to combat the constantly changing strains of this virus.

Antibiotics kill bacteria and are naturally produced by microorganisms such as fungi; penicillin is perhaps the most well-

known example. Antibiotics are produced on a large scale by cultivating and manipulating fungal cells. The fungal cells have typically been genetically modified to improve the yields of the antibiotic compound.

Recombinant DNA technology was used to produce large-scale quantities of the human hormone insulin in *E. coli* as early as 1978. Previously, it was only possible to treat diabetes with pig insulin, which caused allergic reactions in many humans because of differences in the insulin molecule. In addition, human growth hormone (HGH) is used to treat growth disorders in children. The HGH gene was cloned from a cDNA (complementary DNA) library and inserted into *E. coli* cells by cloning it into a bacterial vector.

Transgenic Animals

Although several recombinant proteins used in medicine are successfully produced in bacteria, some proteins need a eukaryotic animal host for proper processing. For this reason, genes have been cloned and expressed in animals such as sheep, goats, chickens, and mice. Animals that have been modified to express recombinant DNA are called transgenic animals (**Figure 10.9**).

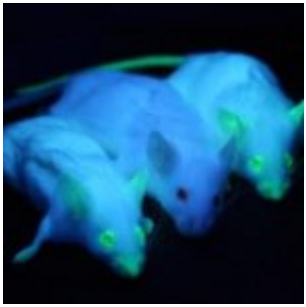

Figure 9: It can be seen that two of these mice are transgenic because they have a gene that causes them to fluoresce under a UV light. The non-transgenic mouse does not have the gene that causes fluorescence. (credit: Ingrid Moen et al.)

Several human proteins are expressed in the milk of transgenic sheep and goats. In one commercial example, the FDA has approved a blood anticoagulant protein that is produced in the milk of transgenic goats for use in humans. Mice have been used extensively for expressing and studying the effects of recombinant genes and mutations.

Transgenic Plants

Manipulating the DNA of plants (creating genetically modified organisms, or GMOs) has helped to create desirable traits such as disease resistance, herbicide, and pest resistance, better nutritional value, and better shelf life (**Figure 10.10**). Plants are the most important source of food for the human population. Farmers

developed ways to select for plant varieties with desirable traits long before modernday biotechnology practices were established.

Figure 10: Corn, a major agricultural crop used to create products for a variety of industries, is often modified through plant biotechnology. (credit: Keith Weller, USDA)

Transgenic plants have received DNA from other species. Because they contain unique combinations of genes and are not restricted to the laboratory, transgenic plants and other GMOs are closely monitored by government agencies to ensure that they are fit for human consumption and do not endanger other plant and animal life. Because foreign genes can spread to other species in the environment, particularly in the pollen and seeds of plants, extensive testing is required to ensure ecological stability. Staples like corn, potatoes, and tomatoes were the first crop plants to be genetically engineered.

Transformation of Plants Using Agrobacterium tumefaciens

In plants, tumors caused by the bacterium *Agrobacterium tumefaciens* occur by transfer of DNA from the bacterium to the

plant. The artificial introduction of DNA into plant cells is more challenging than in animal cells because of the thick plant cell wall. Researchers used the natural transfer of DNA from *Agrobacterium* to a plant host to introduce DNA fragments of their choice into plant hosts. In nature, the disease-causing *A. tumefaciens* have a set of plasmids that contain genes that integrate into the infected plant cell's genome. Researchers manipulate the plasmids to carry the desired DNA fragment and insert it into the plant genome.

The Organic Insecticide Bacillus thuringiensis

Bacillus thuringiensis (Bt) is a bacterium that produces protein crystals that are toxic to many insect species that feed on plants. Insects that have eaten Bt toxin stop feeding on the plants within a few hours. After the toxin is activated in the intestines of the insects, death occurs within a couple of days. The crystal toxin genes have been cloned from the bacterium and introduced into plants, therefore allowing plants to produce their own crystal Bt toxin that acts against insects. Bt toxin is safe for the environment and non-toxic to mammals (including humans). As a result, it has been approved for use by organic farmers as a natural insecticide. There is some concern, however, that insects may evolve resistance to the Bt toxin in the same way that bacteria evolve resistance to antibiotics.

FlavrSavr Tomato

The first GM crop to be introduced into the market was the FlavrSavr Tomato produced in 1994. Molecular genetic technology was used to slow down the process of softening and rotting caused by fungal infections, which led to increased shelf life of the GM

tomatoes. Additional genetic modification improved the flavor of this tomato. The FlavrSavr tomato did not successfully stay in the market because of problems maintaining and shipping the crop.

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98. Genomics and Proteomics

The study of nucleic acids began with the discovery of DNA, progressed to the study of genes and small fragments, and has now exploded to the field of **genomics**. Genomics is the study of entire genomes, including the complete set of genes, their nucleotide sequence and organization, and their interactions within a species and with other species. The advances in genomics have been made possible by DNA sequencing technology. Just as information technology has led to Google Maps that enable us to get detailed information about locations around the globe, genomic information is used to create similar maps of the DNA of different organisms.

Mapping Genomes

Genome mapping is the process of finding the location of genes on each chromosome. The maps that are created are comparable to the maps that we use to navigate streets. A **genetic map** is an illustration that lists genes and their location on a chromosome. Genetic maps provide the big picture (similar to a map of interstate highways) and use genetic markers (similar to landmarks). A genetic marker is a gene or sequence on a chromosome that shows genetic linkage with a trait of interest. The genetic marker tends to be inherited with the gene of interest, and one measure of distance between them is the recombination frequency during meiosis. Early geneticists called this linkage analysis.

Physical maps get into the intimate details of smaller regions of the chromosomes (similar to a detailed road map) (**Figure 10.11**). A physical map is a representation of the physical distance, in nucleotides, between genes or genetic markers. Both genetic linkage maps and physical maps are required to build a complete

picture of the genome. Having a complete map of the genome makes it easier for researchers to study individual genes. Human genome maps help researchers in their efforts to identify human disease-causing genes related to illnesses such as cancer, heart disease, and cystic fibrosis, to name a few. In addition, genome mapping can be used to help identify organisms with beneficial traits, such as microbes with the ability to clean up pollutants or even prevent pollution. Research involving plant genome mapping may lead to methods that produce higher crop yields or to the development of plants that adapt better to climate change.

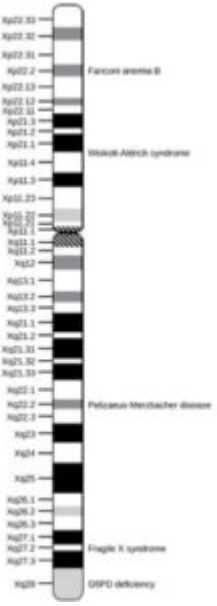

Figure 11: This is a physical map of the human X chromosome. (credit: modification of work by NCBI, NIH)

Genetic maps provide the outline, and physical maps provide the details. It is easy to understand why both types of genome-mapping techniques are important to show the big picture. Information obtained from each technique is used in combination to study the genome. Genomic mapping is used with different model organisms that are used for research. Genome mapping is still an ongoing

process, and as more advanced techniques are developed, more advances are expected. Genome mapping is similar to completing a complicated puzzle using every piece of available data. Mapping information generated in laboratories all over the world is entered into central databases, such as the National Center for Biotechnology Information (NCBI). Efforts are made to make the information more easily accessible to researchers and the general public. Just as we use global positioning systems instead of paper maps to navigate through roadways, NCBI allows us to use a genome viewer tool to simplify the data mining process.

Whole Genome Sequencing

Although there have been significant advances in the medical sciences in recent years, doctors are still confounded by many diseases and researchers are using whole genome sequencing to get to the bottom of the problem. **Whole genome sequencing** is a process that determines the DNA sequence of an entire genome. Whole genome sequencing is a brute-force approach to problem solving when there is a genetic basis at the core of a disease. Several laboratories now provide services to sequence, analyze, and interpret entire genomes.

In 2010, whole genome sequencing was used to save a young boy whose intestines had multiple mysterious abscesses. The child had several colon operations with no relief. Finally, a whole genome sequence revealed a defect in a pathway that controls apoptosis (programmed cell death). A bone marrow transplant was used to overcome this genetic disorder, leading to a cure for the boy. He was the first person to be successfully diagnosed using whole genome sequencing.

The first genomes to be sequenced, such as those belonging to viruses, bacteria, and yeast, were smaller in terms of the number of nucleotides than the genomes of multicellular organisms. The

genomes of other model organisms, such as the mouse (*Mus musculus*), the fruit fly (*Drosophila melanogaster*), and the nematode (*Caenorhabditis elegans*) are now known. A great deal of basic research is performed in **model organisms** because the information can be applied to other organisms. A model organism is a species that is studied as a model to understand the biological processes in other species that can be represented by the model organism. For example, fruit flies are able to metabolize alcohol like humans, so the genes affecting sensitivity to alcohol have been studied in fruit flies in an effort to understand the variation in sensitivity to alcohol in humans. Having entire genomes sequenced helps with the research efforts in these model organisms (**Figure 10.12**).

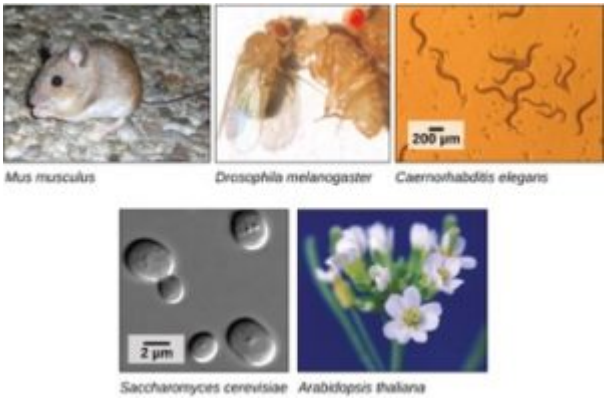

Figure 12: Much basic research is done with model organisms, such as the mouse, Mus musculus; the fruit fly, Drosophila melanogaster; the nematode Caenorhabditis elegans; the yeast Saccharomyces cerevisiae; and the common weed, Arabidopsis thaliana. (credit "mouse": modification of work by Florean Fortescue; credit "nematodes": modification of work by "snickclunk"/Flickr; credit "common weed": modification of work by Peggy Greb, USDA; scale-bar data from Matt Russell)

The first human genome sequence was published in 2003. The number of whole genomes that have been sequenced steadily increases and now includes hundreds of species and thousands of individual human genomes.

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99. Applying Genomics

The introduction of DNA sequencing and whole genome sequencing projects, particularly the Human Genome Project, has expanded the applicability of DNA sequence information. Genomics is now being used in a wide variety of fields, such as metagenomics, pharmacogenomics, and mitochondrial genomics. The most commonly known application of genomics is to understand and find cures for diseases.

Predicting Disease Risk at the Individual Level

Predicting the risk of disease involves screening and identifying currently healthy individuals by genome analysis at the individual level. Intervention with lifestyle changes and drugs can be recommended before disease onset. However, this approach is most applicable when the problem arises from a single gene mutation. Such defects only account for about 5 percent of diseases found in developed countries. Most of the common diseases, such as heart disease, are multifactorial or polygenic, which refers to a phenotypic characteristic that is determined by two or more genes, and also environmental factors such as diet. In April 2010, scientists at Stanford University published the genome analysis of a healthy individual (Stephen Quake, a scientist at Stanford University, who had his genome sequenced); the analysis predicted his propensity to acquire various diseases. A risk assessment was done to analyze Quake's percentage of risk for 55 different medical conditions. A rare genetic mutation was found that showed him to be at risk for sudden heart attack. He was also predicted to have a 23 percent risk of developing prostate cancer and a 1.4 percent risk of developing

Alzheimer's disease. The scientists used databases and several publications to analyze the genomic data. Even though genomic sequencing is becoming more affordable and analytical tools are becoming more reliable, ethical issues surrounding genomic analysis at a population level remain to be addressed. For example, could such data be legitimately used to charge more or less for insurance or to affect credit ratings?

Genome-wide Association Studies

Since 2005, it has been possible to conduct a type of study called a genome-wide association study, or GWAS. A GWAS is a method that identifies differences between individuals in single nucleotide polymorphisms (SNPs) that may be involved in causing diseases. The method is particularly suited to diseases that may be affected by one or many genetic changes throughout the genome. It is very difficult to identify the genes involved in such a disease using family history information. The GWAS method relies on a genetic database that has been in development since 2002 called the International HapMap Project. The HapMap Project sequenced the genomes of several hundred individuals from around the world and identified groups of SNPs. The groups include SNPs that are located near to each other on chromosomes so they tend to stay together through recombination. The fact that the group stays together means that identifying one marker SNP is all that is needed to identify all the SNPs in the group. There are several million SNPs identified, but identifying them in other individuals who have not had their complete genome sequenced is much easier because only the marker SNPs need to be identified.

In a common design for a GWAS, two groups of individuals are chosen; one group has the disease, and the other group does not. The individuals in each group are matched in other characteristics to reduce the effect of confounding variables causing differences

between the two groups. For example, the genotypes may differ because the two groups are mostly taken from different parts of the world. Once the individuals are chosen, and typically their numbers are a thousand or more for the study to work, samples of their DNA are obtained. The DNA is analyzed using automated systems to identify large differences in the percentage of particular SNPs between the two groups. Often the study examines a million or more SNPs in the DNA. The results of GWAS can be used in two ways: the genetic differences may be used as markers for susceptibility to the disease in undiagnosed individuals, and the particular genes identified can be targets for research into the molecular pathway of the disease and potential therapies. An offshoot of the discovery of gene associations with disease has been the formation of companies that provide socalled "personal genomics" that will identify risk levels for various diseases based on an individual's SNP complement. The science behind these services is controversial.

Because GWAS looks for associations between genes and disease, these studies provide data for other research into causes, rather than answering specific questions themselves. An association between a gene difference and a disease does not necessarily mean there is a cause-and-effect relationship. However, some studies have provided useful information about the genetic causes of diseases. For example, three different studies in 2005 identified a gene for a protein involved in regulating inflammation in the body that is associated with a disease-causing blindness called age-related macular degeneration. This opened up new possibilities for research into the cause of this disease. A large number of genes have been identified to be associated with Crohn's disease using GWAS, and some of these have suggested new hypothetical mechanisms for the cause of the disease.

Pharmacogenomics

Pharmacogenomics involves evaluating the effectiveness and safety of drugs on the basis of information from an individual's genomic sequence. Personal genome sequence information can be used to prescribe medications that will be most effective and least toxic on the basis of the individual patient's genotype. Studying changes in gene expression could provide information about the gene transcription profile in the presence of the drug, which can be used as an early indicator of the potential for toxic effects. For example, genes involved in cellular growth and controlled cell death, when disturbed, could lead to the growth of cancerous cells. Genome-wide studies can also help to find new genes involved in drug toxicity. The gene signatures may not be completely accurate, but can be tested further before pathologic symptoms arise.

Metagenomics

Traditionally, microbiology has been taught with the view that microorganisms are best studied under pure culture conditions, which involves isolating a single type of cell and culturing it in the laboratory. Because microorganisms can go through several generations in a matter of hours, their gene expression profiles adapt to the new laboratory environment very quickly. On the other hand, many species resist being cultured in isolation. Most microorganisms do not live as isolated entities, but in microbial communities known as biofilms. For all of these reasons, pure culture is not always the best way to study microorganisms. **Metagenomics** is the study of the collective genomes of multiple species that grow and interact in an environmental niche. Metagenomics can be used to identify new species more rapidly and

to analyze the effect of pollutants on the environment (**Figure 10.13**). Metagenomics techniques can now also be applied to communities of higher eukaryotes, such as fish.

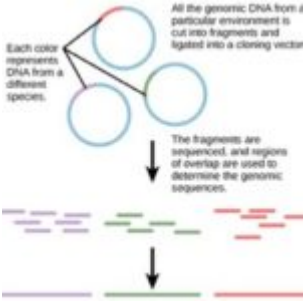

Figure 13: Metagenomics involves isolating DNA from multiple species within an environmental niche. The DNA is cut up and sequenced, allowing entire genome sequences of multiple species to be reconstructed from the sequences of overlapping pieces.

Knowledge of the genomics of microorganisms is being used to find better ways to harness biofuels from algae and cyanobacteria. The primary sources of fuel today are coal, oil, wood, and other plant products such as ethanol. Although plants are renewable resources, there is still a need to find more alternative renewable sources of energy to meet our population's energy demands. The microbial world is one of the largest resources for genes that encode new enzymes and produce new organic compounds, and it remains largely untapped. This vast genetic resource holds the potential to provide new sources of biofuels (**Figure 10.14**).

Figure 14: Renewable fuels were tested in Navy ships and aircraft at the first Naval Energy Forum. (credit: modification of work by John F Williams, US Navy)

Mitochondria are intracellular organelles that contain their own DNA. Mitochondrial DNA mutates at a rapid rate and is often used to study evolutionary relationships. Another feature that makes studying the mitochondrial genome interesting is that in most multicellular organisms, the mitochondrial DNA is passed on from the mother during the process of fertilization. For this reason, mitochondrial genomics is often used to trace genealogy.

Genomics in Forensic Analysis

Information and clues obtained from DNA samples found at crime scenes have been used as evidence in court cases, and genetic markers have been used in forensic analysis. Genomic analysis has also become useful in this field. In 2001, the first use of genomics in forensics was published. It was a collaborative effort between academic research institutions and the FBI to solve the mysterious cases of anthrax (**Figure 10.15**) that was transported by the US Postal Service. Anthrax bacteria were made into an infectious powder and

mailed to news media and two U.S. Senators. The powder infected the administrative staff and postal workers who opened or handled the letters. Five people died, and 17 were sickened from the bacteria. Using microbial genomics, researchers determined that a specific strain of anthrax was used in all the mailings; eventually, the source was traced to a scientist at a national biodefense laboratory in Maryland.

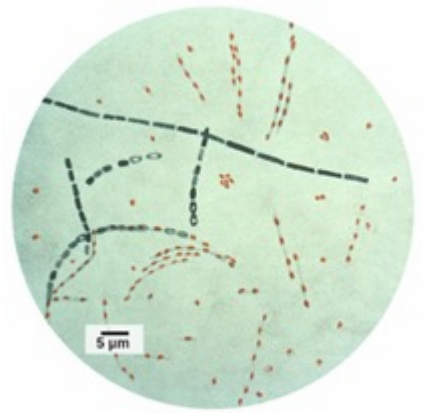

Figure 15: Bacillus anthracis is the organism that causes anthrax. (credit: modification of work by CDC; scale-bar data from Matt Russell)

Genomics can reduce the trials and failures involved in scientific research to a certain extent, which could improve the quality and quantity of crop yields in agriculture (**Figure 10.16**). Linking traits to genes or gene signatures helps to improve crop breeding to generate hybrids with the most desirable qualities. Scientists use genomic data to identify desirable traits, and then transfer those traits to a different organism to create a new genetically modified organism, as described in the previous module. Scientists are discovering how genomics can improve the quality and quantity of agricultural production. For example, scientists could use desirable traits to create a useful product or enhance an existing product, such as making a drought-sensitive crop more tolerant of the dry season.

Figure 16: Transgenic agricultural plants can be made to resist disease. These transgenic plums are resistant to the plum pox virus. (credit: Scott Bauer, USDA ARS)

References

OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:TE1njgbY@4/Genomics-and-Proteomics

100. Proteomics

Proteins are the final products of genes that perform the function encoded by the gene. Proteins are composed of amino acids and play important roles in the cell. All enzymes (except ribozymes) are proteins and act as catalysts that affect the rate of reactions. Proteins are also regulatory molecules, and some are hormones. Transport proteins, such as hemoglobin, help transport oxygen to various organs. Antibodies that defend against foreign particles are also proteins. In the diseased state, protein function can be impaired because of changes at the genetic level or because of direct impact on a specific protein.

A proteome is the entire set of proteins produced by a cell type. Proteomes can be studied using the knowledge of genomes because genes code for mRNAs, and the mRNAs encode proteins. The study of the function of proteomes is called **proteomics**. Proteomics complements genomics and is useful when scientists want to test their hypotheses that were based on genes. Even though all cells in a multicellular organism have the same set of genes, the set of proteins produced in different tissues is different and dependent on gene expression. Thus, the genome is constant, but the proteome varies and is dynamic within an organism. In addition, RNAs can be alternatively spliced (cut and pasted to create novel combinations and novel proteins), and many proteins are modified after translation. Although the genome provides a blueprint, the final architecture depends on several factors that can change the progression of events that generate the proteome.

Genomes and proteomes of patients suffering from specific diseases are being studied to understand the genetic basis of the disease. The most prominent disease being studied with proteomic approaches is cancer (**Figure 10.17**). Proteomic approaches are being used to improve the screening and early detection of cancer; this is achieved by identifying proteins whose expression is affected by

the disease process. An individual protein is called a **biomarker**, whereas a set of proteins with altered expression levels is called a **protein signature**. For a biomarker or protein signature to be useful as a candidate for early screening and detection of a cancer, it must be secreted in body fluids such as sweat, blood, or urine, so that large-scale screenings can be performed in a noninvasive fashion. The current problem with using biomarkers for the early detection of cancer is the high rate of false-negative results. A false-negative result is a negative test result that should have been positive. In other words, many cases of cancer go undetected, which makes biomarkers unreliable. Some examples of protein biomarkers used in cancer detection are CA-125 for ovarian cancer and PSA for prostate cancer. Protein signatures may be more reliable than biomarkers to detect cancer cells. Proteomics is also being used to develop individualized treatment plans, which involves the prediction of whether or not an individual will respond to specific drugs and the side effects that the individual may have. Proteomics is also being used to predict the possibility of disease recurrence.

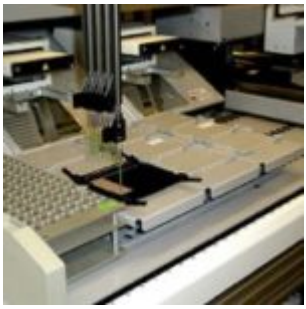

Figure 17: This machine is preparing to do a proteomic pattern analysis to identify specific cancers so that an accurate cancer prognosis can be made. (credit: Dorie Hightower, NCI, NIH)

The National Cancer Institute has developed programs to improve

the detection and treatment of cancer. The Clinical Proteomic Technologies for Cancer and the Early Detection Research Network are efforts to identify protein signatures specific to different types of cancers. The Biomedical Proteomics Program is designed to identify protein signatures and design effective therapies for cancer patients.

References

OpenStax, Biology. OpenStax CNX. May 27, 2016 http://cnx.org/contents/s8Hh0oOc@9.10:TE1njgbY@4/Genomics-and-Proteomics

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