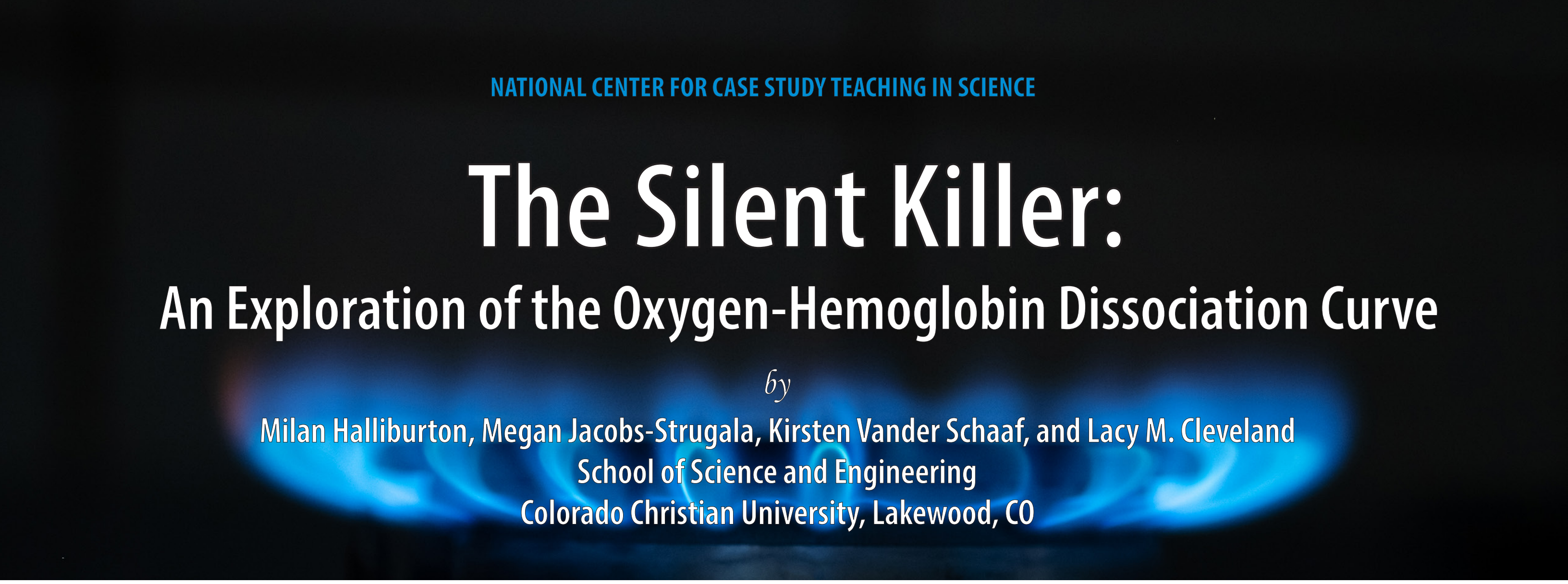


NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

The Silent Killer:

An Exploration of the Oxygen-Hemoglobin Dissociation Curve

by

Milan Halliburton, Megan Jacobs-Strugala, Kirsten Vander Schaaf, and Lacy M. Cleveland
School of Science and Engineering
Colorado Christian University, Lakewood, CO

Part I – A Hotel Tragedy

Mason Cooper had been vacationing in California when his family received news from a police officer informing them that their son was found dead in his hotel room. They had been told that although the cause of death was not known at that time, a forensic pathologist would be doing an autopsy.

Having completed the autopsy, the medical examiner, Dr. Pepyr, knew that the cause of death was hypoxia. The medical doctor reviewed her notes as the family would soon arrive to discuss the details of their son's death.

Questions

1. What is hypoxia?

2. What physiological or environmental conditions could lead to hypoxia?

Part II – The Autopsy

After welcoming Mr. and Mrs. Cooper into the office, Dr. Pepyr shared the results of the autopsy. "Mr. and Mrs. Cooper, I am truly sorry for your loss. The autopsy revealed that your son passed away from carbon monoxide poisoning. Carbon monoxide prevents oxygen from reaching body tissues, creating a condition known as hypoxia, a term to describe when the tissues do not have adequate oxygen and are unable to perform their life sustaining functions."

Mrs. Cooper was clearly overcome with emotion. Holding back tears she said, "I don't understand. Mason was a fit individual. He exercised often. His heart was strong. I don't understand why his heart and lungs didn't simply work harder."

Dr. Pepyr replied, "I know this is all difficult to hear and process. Unfortunately, no amount of exercise could have made Mason strong enough to overcome carbon monoxide poisoning." Dr. Pepyr proceeded to explain to the family the role of erythrocytes in transporting oxygen to the tissues and how carbon monoxide severely limits this activity.

Questions

3. Which of the following are functions of erythrocytes?
   a. Antibody production.
   b. Delivering CO_2 to the lungs.
   c. Transporting O_2 to systemic tissues.
   d. Stimulating the coagulation cascade.
   e. Providing immunity against foreign invaders.

4. List the various ways that oxygen is transported in the blood.

5. List the various ways that carbon dioxide is transported in the blood.

6. Both oxygen (O_2) and carbon dioxide (CO_2) are transported in the blood as dissolved gases and bound to hemoglobin. However, the ease with which they dissolve differs, and the location where they bind to hemoglobin is also different. Complete Figure 1 on the following page by choosing from among the following options (options may be used more than once): bicarbonate ion (HCO_3^-), carbon dioxide (CO_2), carbonic acid (H_2CO_3), iron (Fe^{2+}), heme, hydrogen ion (H^+), oxygen (O_2), oxyhemoglobin (HbO_2).

7. Using Figure 1 as a reference, determine if each of the following statements is true of carbon dioxide, oxygen or both.
   a. Which gas can hemoglobin bind four molecules of?
   b. Which gas binds to the N-termini of the polypeptide chains?
   c. Which gas binds to an Fe^{2+} within heme?
   d. Which gas more readily dissolves in plasma?

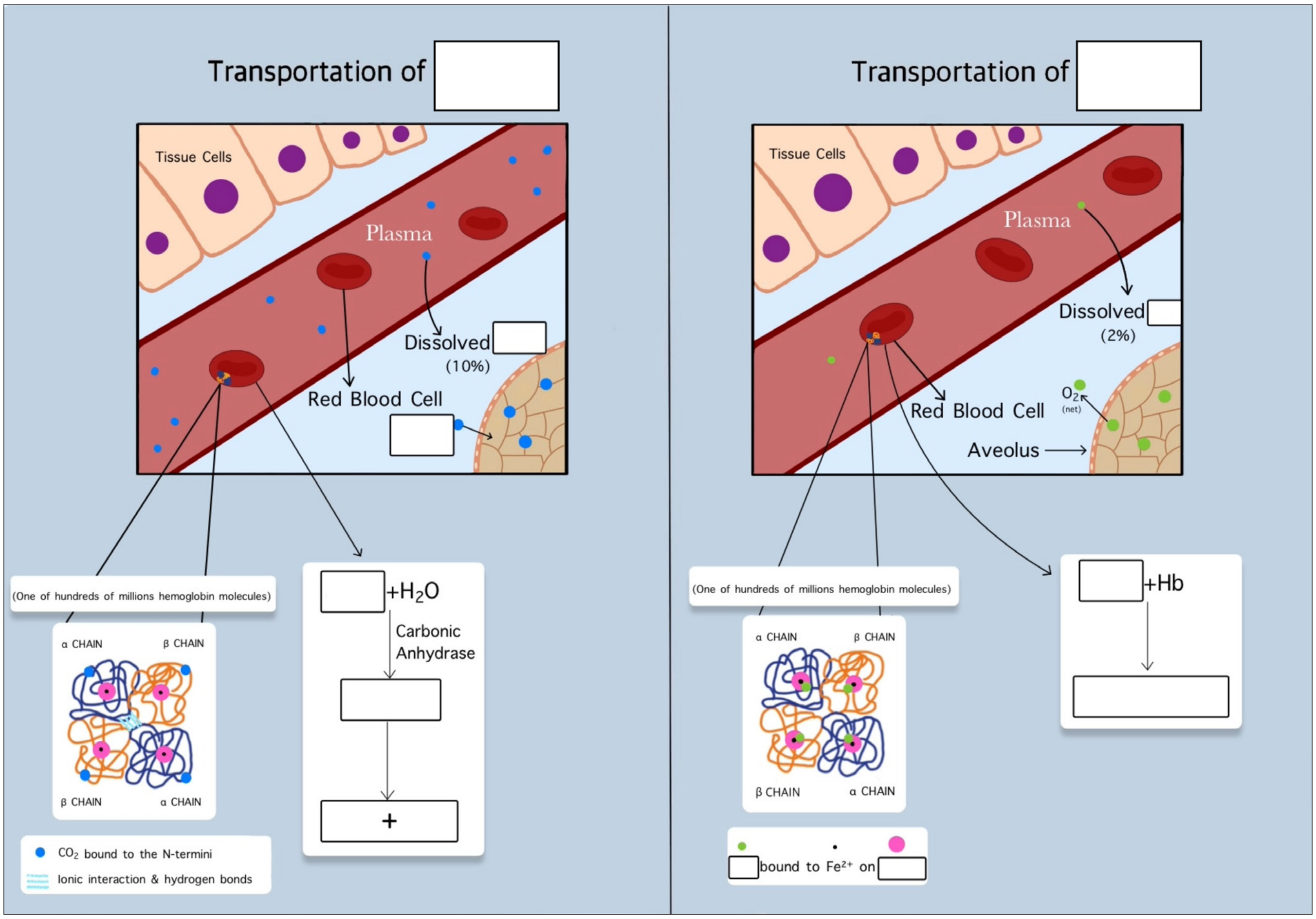


Figure 1. Transportation of blood gases. *Credit:* Milan N. Halliburton.

8. Tissues must receive adequate oxygen to perform cellular respiration. A variety of toxins and diseases can reduce oxygen availability in the blood. Common symptoms of decreased hemoglobin-oxygen saturation include fatigue, weakness, pale skin, and tachycardia (a rapid heart rate). Describe why a decrease in hemoglobin-oxygen saturation would lead to each of these symptoms.
   a. fatigue:

   b. weakness:

   c. pale skin:

   d. tachycardia:

Part III – Sources of Carbon Monoxide

After leaving the medical examiner's office, Mr. and Mrs. Cooper met with the lead detective, Sergeant Halloway. Halloway informed the Coopers that the hotel rooms contained gas stoves, which if not properly regulated or if left on can lead to elevated levels of carbon monoxide. Halloway also noted the hotel room was not equipped with a carbon monoxide sensor.

Still grappling with their grief and overwhelmed by a day of meetings, Mr. and Mrs. Cooper decide to seek legal counsel. In their years as a married couple, they had always had carbon monoxide sensors installed throughout their home and were struggling to understand why the hotel would fail to do the same. They believed their son's death was preventable.

The Cooper family hired Mr. Ricci to serve as their legal counsel.

Questions

Prior to answering the questions below, review the following article:

- New York State Department of Health. (2016). Carbon monoxide: the silent killer. <https://www.health.ny.gov/publications/2826.pdf>

9. Why is carbon monoxide referred to as the "silent killer"?

10. List at least three common sources of carbon monoxide.

11. Provide at least three symptoms of carbon monoxide poisoning.

12. How can individuals reduce their risk of carbon monoxide poisoning?

13. Read the following article and then answer the questions below:
    - Schultz, J. (2023). Carbon monoxide detector installation statutes. [Webpage]. <https://www.ncsl.org/environment-and-natural-resources/carbon-monoxide-detector-installation-statutes>

    a. Does California law require carbon monoxide detectors in hotels?

    b. Does your home state require carbon monoxide detectors in hotels?

Part IV – The Legal Battle Begins

The pivotal day had arrived for the judge and jury to determine the trial outcome of Cooper family versus the Clementine Hotel. Legal representatives for both parties had completed their opening statements, and it was now time to call witnesses to the stand.

Mr. Ricci, legal counsel for the Cooper family, addressed the judge. “I would like to bring our expert witness, the medical examiner and forensic pathologist, Dr. Pepyr to the stand.”

After Dr. Pepyr was sworn in, Mr. Ricci proceeded with a series of questions to demonstrate Dr. Pepyr’s credentials. Dr. Pepyr obtained a medical degree from a prestigious medical college, held a medical license in her state, had completed a residency in clinical anatomy, had completed a fellowship in forensic pathology, and had been the senior medical examiner for the city for the past seven years.

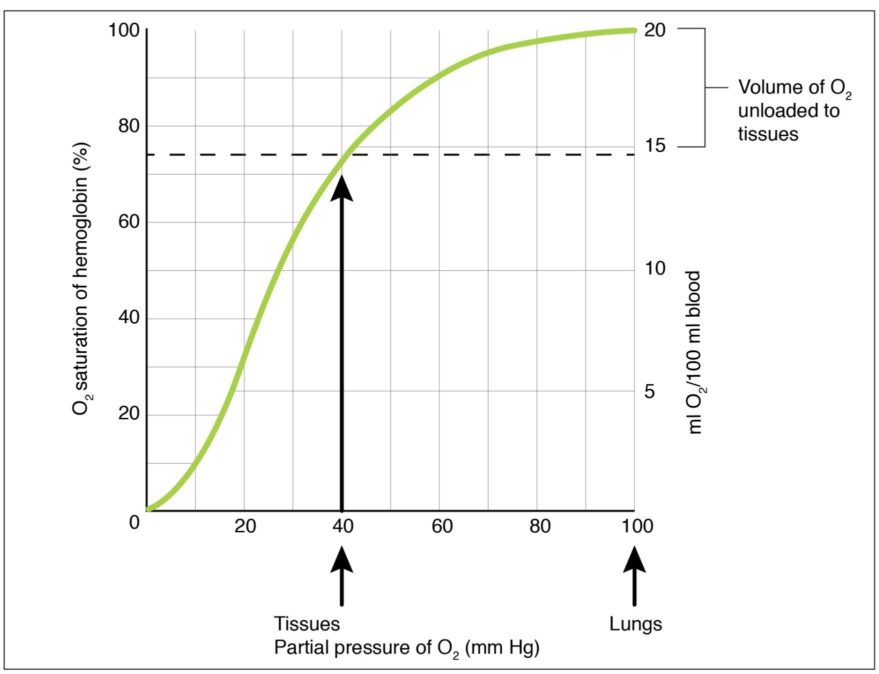
Proceeding with questions, Mr. Ricci asked, “Dr. Pepyr, can you explain to the jury what you believe was the cause of the victim’s death?”

Dr. Pepyr responded confidently, “Mason Cooper died from hypoxia, or insufficient oxygen in the tissues, due to carbon monoxide poisoning.”

Mr. Ricci continued to ask Dr. Pepyr a series of questions, allowing the medical examiner to provide evidence supporting carbon monoxide poisoning. Dr. Pepyr noted that Mason’s complexion appeared pink at the time of death. For White individuals, pink skin is an indicator of carbon monoxide poisoning. Mason’s autopsy revealed significant hypoxia-related tissue damage in the heart and brain.

Mr. Ricci, hoping to help the jury understand, asked Dr. Pepyr, “I traditionally think of blue lips or pale skin as a sign of an individual with a lack of oxygen. You stated Mason appeared pink at the time of death. Can you explain this apparent contradiction?”

Unphased, Dr. Pepyr replied, “It all relates to a concept known as affinity. To help the jury understand, I would like to present and describe a figure.” With the help of Mr. Ricci, Dr. Pepyr entered Figure 2 into evidence, and proceeded to explain the oxygen-hemoglobin dissociation curve.



(a) Partial pressure of oxygen and hemoglobin saturation

Figure 2. Oxygen-hemoglobin dissociation curve. *Credit:* Betts et al., 2013, *Anatomy and Physiology.* OpenStax: Houston, Texas. CC BY 4.0. <https://openstax.org/books/anatomy-and-physiology/pages/22-5-transport-of-gases>

Questions

Pretend you are Dr. Pepyr. Answer the following questions to help the jury comprehend the oxygen-hemoglobin dissociation curve.

14. What is represented by the *x*-axis?
    a. The partial pressure of oxygen.
    b. The partial pressure of carbon dioxide.
    c. The amount of oxygen that is not bound to hemoglobin.
    d. The percentage of hemoglobin available to bind oxygen.

15. What is represented by the *y*-axis?
    a. The partial pressure of oxygen.
    b. The ratio of hemoglobin bound to oxygen.
    c. The amount of oxygen dissolved in the plasma.
    d. The number of oxygen molecules bound to each red blood cell.

16. Define affinity as it relates to the relationship between oxygen and hemoglobin.

17. What does the oxygen-hemoglobin dissociation curve graphically represent? Please explain in terms of affinity and describe how easily oxygen dissociates from hemoglobin.

18. Explain cooperative binding.

19. Explain how the shape of the curve is caused by cooperative binding between oxygen and hemoglobin.

20. Hemoglobin cycles between two allosteric states, the *T* (tense) state and the *R* (relaxed) state. The *T* state favors the binding of carbon dioxide and oxygen unloading. The *R* state, also known as oxyhemoglobin, favors oxygen loading. The *T* state has a lower affinity for oxygen and higher affinity for carbon dioxide and the *R* state has a higher affinity for oxygen and lower affinity for carbon dioxide. In the *R* state the binding of oxygen disrupts the ionic and hydrogen bonds between the hemoglobin's polypeptides, leading to allosteric changes favoring the *R* state. The *R* state can also be referred to as the liganded form and the *T* state as the unliganded form. Look back at Figure 1 and label the *R* and *T* states of hemoglobin, and then answer the following questions.
    a. The ___ state of hemoglobin is dominant in blood leaving healthy pulmonary capillaries; these vessels have an approximate partial pressure of oxygen equal to 104 mmHg.
    b. The ___ state of hemoglobin is dominant in blood leaving active systemic tissues; suppose these vessels have an approximate partial pressure of oxygen equal to 20 mmHg.
    c. The ___ state of hemoglobin favors oxygen loading, whereas the ___ state of hemoglobin favors oxygen unloading.

21. Hemoglobin binds carbon dioxide, carbon monoxide, and oxygen. For which of these gases does hemoglobin display the strongest affinity?
    a. carbon dioxide b. carbon monoxide c. oxygen

Part V – Variables Impacting the Oxygen-Hemoglobin Dissociation Curve

Mr. Ricci continued his questioning of the expert witness. "Can you now explain to the jury how even small amounts of carbon monoxide can be dangerous?"

Dr. Pepyr explained, "Carbon monoxide has a strong affinity for hemoglobin, 200–300 times that of its affinity for oxygen. Carbon monoxide out competes oxygen. When carbon monoxide is present, it more readily occupies hemoglobin's binding sites. Even mild carbon monoxide concentrations can be very dangerous. Even if carbon monoxide does not fill all the binding sites, the binding of one molecule of carbon monoxide to hemoglobin causes a change in the structure of the hemoglobin, exponentially increasing the hemoglobin's affinity for oxygen."

Mr. Ricci attempted to clarify. "Dr. Pepyr, are you saying carbon monoxide makes hemoglobin more likely to bind to oxygen?"

"Yes," replied Dr. Pepyr, "but a higher affinity also means it is harder for hemoglobin to release oxygen. Instead of releasing oxygen to the tissue, hemoglobin holds on to the oxygen. This results in what we refer to as a left-shift of the oxygen-hemoglobin dissociation curve."

Mr. Ricci continued his line of questioning in order to give the jury more information on the impacts of carbon monoxide poisoning.

Questions

22. Use Figure 2 (the oxygen-hemoglobin dissociation curve) to determine the oxygen saturation of hemoglobin (%SO_2) at each partial pressure of oxygen (pO_2) given in Table 2. Add your answers to the blank spaces in Table 2.

    Table 2. The impact of the partial pressure of oxygen on the oxygen saturation of hemoglobin.

Partial Pressure of Oxygen (pO_2 in mmHg)	*Oxygen Saturation of Hemoglobin % (%SO_2)*
30	
70	
100	

23. Now use Figure 2 (the oxygen-hemoglobin dissociation curve) to determine the partial pressure of oxygen (pO_2) at each given oxygen saturation of hemoglobin (%SO_2) in Table 3. Add your answers to the blank spaces in Table 3.

    Table 3. The relationship between oxygen saturation and partial pressure of oxygen.

Partial Pressure of Oxygen (pO_2 in mmHg)	*Oxygen Saturation of Hemoglobin % (%SO_2)*
	10
	75
	90
	100

24. The oxygen-hemoglobin dissociation curve can be shifted to the right or left. Typically, a right shift is caused by the Bohr effect and a left shift is caused by the Haldane effect, both of which are physiologically advantageous. Complete the following questions on or utilizing Figure 3 below.

a. Label the *x*- and *y*-axis of the oxygen-hemoglobin disassociation curve.

b. The red and blue lines represent physiological shifts of the curve. Label each of these shifts as either the Bohr or Haldane effect and right- or left-shift.

c. Complete Table 4 (next page) to determine which line, the Bohr effect or Haldane effect, would result in more oxygen being unloaded to the plasma. For columns three and five, to determine the percentage change, find the difference of the oxygen saturation of hemoglobin between the non-shifted (middle, green) line and the line being examined. Your numbers do not have to be exact; approximations are fine. As the oxygen-saturation of hemoglobin decreases, more oxygen is unloaded in the plasma and available for diffusion into the tissues. Two examples have been provided for you.

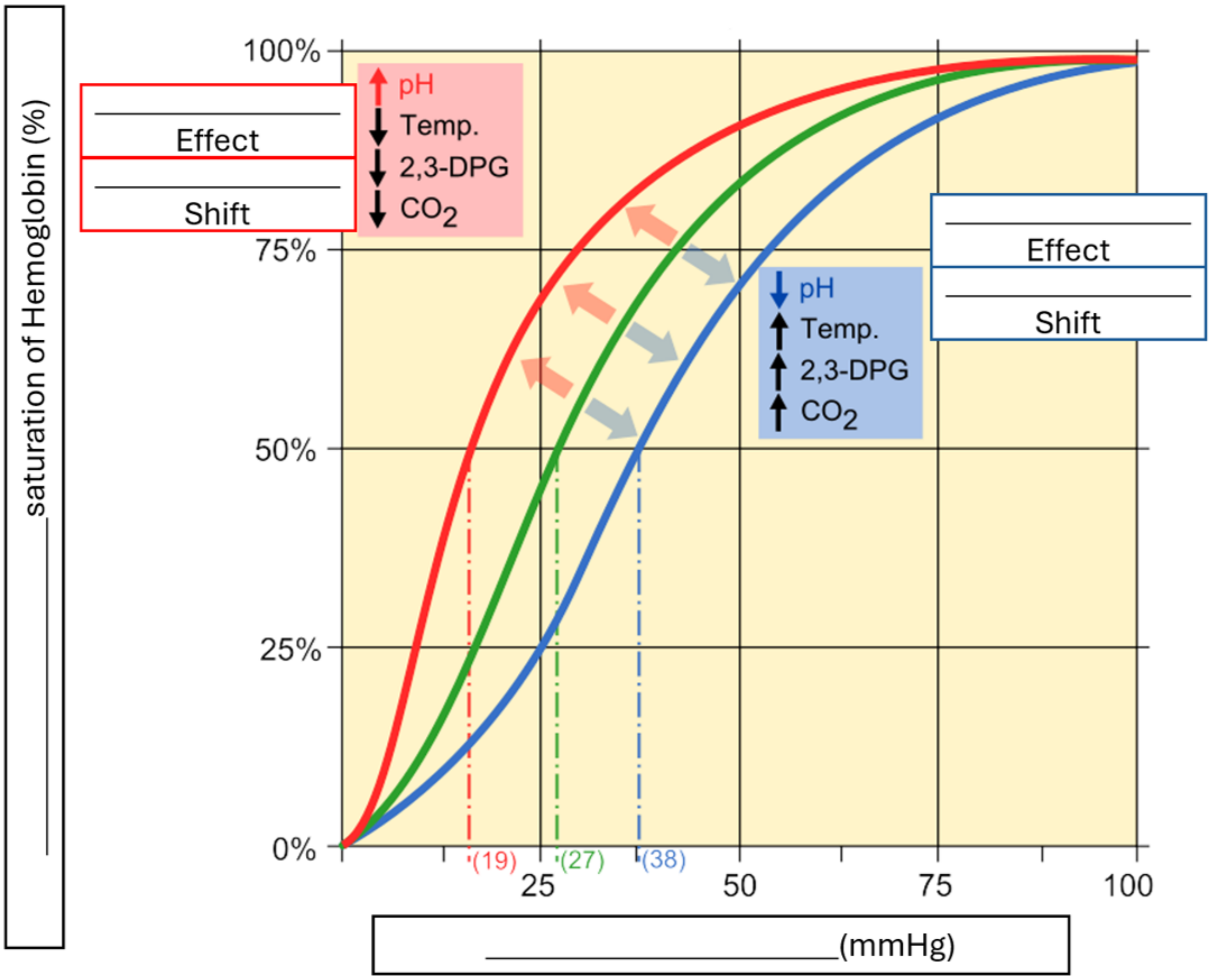


Figure 3. Physiological shifts of the oxygen dissociation curve. *Credit:* Michał Komorniczak | Wikimedia Commons, adapted, CC BY-SA 3.0.

Table 4. Impact of the Bohr and Haldane effects on oxygen saturation of hemoglobin and oxygen unloading.

Partial Pressure of O2 (mmHg)	*Haldane Effect*			*Bohr Effect*		
	Oxygensaturation of hemoglobin % (%SO_2)	*Compared to the non-shifted **(middle line)**, how much more or less is the oxygen saturation of hemoglobin (SO_2%)?*	*Is more or less O_2 free (not bound to hemoglobin)?*	*Oxygen saturation of Hemoglobin % (%SO_2)*	*Compared to the non-shifted **(middle line)**, how much more or less is the oxygen saturation of hemoglobin (SO_2%)?*	*Is more or less O_2 free (not bound to hemoglobin)?*
25	Approximately 70	**Haldane effect – non-shifted line** 70 – 45 = 35% more				
50						
75				Approximately 90	**Bohr effect – non-shifted line** 90 – 98 = 8% less	

25. The ___________ (Bohr or Haldane effect) leads to a decrease in oxygen's affinity for hemoglobin and an increase in oxygen unloading.

26. Blood pH, blood temperature, and the level of certain chemicals in the blood (e.g., 2,3-DPG and CO_2) change the affinity of hemoglobin for oxygen. Do some research to determine how an increase or decrease in each of these variables affects affinity, and what circumstances can lead to changes in these variables. Put your answers in the appropriate columns in Table 5.

Table 5. Variables impacting the oxygen-hemoglobin dislocation curve.

Variable	*Variable Increase*	*Variable Decrease*	*Circumstance(s) altering this variable*
2,3-DPG levels			
CO_2 levels			Exercise and increased cellular respiration increase carbon dioxide levels in blood plasma.
pH		Affinity decreased	
Temperature	Affinity decreased		

27. For each of the following indicate whether a right (R) or (L) shift of the oxygen-hemoglobin disassociation curve would occur.
    a. ___ Visiting a town at a higher altitude (decreased atmospheric oxygen).
    b. ___ Participating in intense aerobic activity.
    c. ___Experiencing a fever due to infection.

28. Typically, when the oxygen hemoglobin dissociation curve shifts to the left or right, this is beneficial and helps to meet the oxygen demands of the body. However, carbon monoxide poisoning causes a shift that is not beneficial. Based on what you have learned, in which direction, right or left, does carbon monoxide poisoning shift the curve? Explain your answer.

29. How would this shift explain why Mason's skin appeared pink at the time of death?

Part VI – Medical School Bound

As the trial continued, Chloe, a jury member, grew increasingly interested in the causes behind carbon monoxide poisoning. Due to her newfound interest, she joined her roommate in her anatomy and physiology class. The teacher lectured on the difference between maternal and fetal hemoglobin.

Nearing the end of class, a case study was provided to cement the class's understanding of adult hemoglobin's affinity for oxygen compared to fetal hemoglobin, and how hydroxyurea (a drug that increases fetal hemoglobin and helps red blood cells stay rounder and more flexible) can treat sickle cell anemia. Chloe was reminded of the Cooper family case because it supplemented the lecture seamlessly.

Remembering her recent class discussion, Chloe reflected on the significance of fetal and maternal hemoglobin in treating sickle cell anemia in her case study that read as follows:

> *Sickle cell anemia is an autosomal recessive blood cell disorder associated with a mutated hemoglobin. The altered protein, sickle-cell hemoglobin (HbS) displays a lower affinity to oxygen. When oxygen is released from HbS, the proteins polymerize (clump together) transforming erythrocytes into a crescent or sickle shape. In addition to reducing the oxygen-carrying capacity of the blood, sickle shaped erythrocytes can occlude blood vessels and lead to numerous health issues.*
>
> *Enhancing fetal hemoglobin expression serves as one mechanism to treat sickle cell anemia. Unlike adult hemoglobin (HbA), composed of two alpha and two beta subunits, fetal hemoglobin (HbF) is composed of two alpha and two gamma subunits. The structural differences enhance the affinity of HbF to oxygen. Fetal hemoglobin saturates with oxygen more readily than HbA. At a partial pressure of 19 mmHg, fifty percent of HbF is saturated with oxygen, whereas fifty percent saturation occurs at 27 mm Hg for HbA. Stimulating expression of HbF in patients with sickle cell anemia enhances the oxygen-carrying capacity and reduces erythrocyte polymerization.*

Questions

30. Fetal hemoglobin has a __________(higher/lower) affinity for oxygen compared to maternal hemoglobin. This means that the oxygen-hemoglobin dissociation curve for HbF shifts to the ______ (right/left).

31. Why is it necessary for fetal hemoglobin to have a higher affinity for oxygen than maternal hemoglobin?

Part VII – Bioethics

Thus far this case study has focused on the physiology of carbon monoxide poisoning. But the case also raises several ethical questions.

Questions

32. Is the hotel liable even though the accident resulted from Mason leaving the stove on?

33. Is it ethical for hotels to forego safety measures like carbon monoxide detectors? If so, should they be legally required in each room?

34. To what extent would safety regulations infringe on a property owner's freedom to run and manage their business how they see fit?

35. How should the legal system compensate victims and families in instances related to carbon monoxide poisoning?

36. If Mason Cooper did not die, should the family still sue the hotel? Or put another way, would the hotel be liable if Mason Cooper did not pass away and instead made it to a hospital?

Addendum – Raising Awareness

In the end, the Cooper family case continued for many days, leaving a lasting impact on all involved. As a result of the trial, the now pre-med student, Chloe, was inspired to prevent other families from experiencing a similar kind of tragedy. Little did she expect that her passion would ignite a movement at her university to raise awareness about the silent threat of carbon monoxide poisoning and educate the community.

The real-life stories below highlight the importance of carbon monoxide detectors and proper ventilation. Carbon monoxide is clear, odorless, and tasteless.

Real Life Stories

- AirBnB Related Carbon Monoxide Posionings. Since 2013, there have been 19 deaths linked to carbon monoxide poisoning in AirBnB properties. In 2014, AirBnB committed to require all hosts to obtain and confirm that they have installed carbon monoxide detectors in every listing (Goggin & Khogeer, 2023).
- Construction Works at Yale. In January 2024, construction workers mysteriously collapsed. After conducting blood tests, it was discovered that there were possibly lethal amounts of carbon monoxide from a propane-fueled saw in an enclosed space. Thirteen people were hospitalized. After being interviewed, the construction workers believed that the building was ventilated correctly. “A typical home carbon monoxide detector sounds an alarm when it detects 35 parts per million. There were 350 parts per million in this situation, or ten times the permissible level” (Associated Press, 2024; Fox 9 Staff, 2024).
- Sandals Resort in the Bahamas. In May 2022, three U.S. tourists were found dead at a Sandals resort in the Bahamas. They did not know if there were carbon monoxide detectors or if they were even working correctly. The source of carbon monoxide was never found (Danica, 2022).

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