FRAMING ANALOGY: TACTICAL LABOR INHIBITION

During World War I, Germany was fighting a two-front war, with most of Western Europe attacking them from one side and Russia attacking from the other. To reduce the power of at least one of their enemies, Germany created a devious strategy to take Russia out of the equation.

German leaders recognized that Russia was in a state of social turmoil and poised for economic collapse. The Russian economy depended on a large group of people working for low wages. Factory workers and other laborers in Russia were treated unfairly by their wealthier bosses, worked in harsh and dangerous conditions, and had low status and little power in making decisions in the country. Because of this, the potential for labor organizers to cause massive strikes were a major concern for the Russian government: Russian workers wanted to take power into their own hands, and they were ready to listen to anyone who encouraged them. To try to prevent this, the Russian government exiled many prominent Russian labor organizers, among them Vladimir Lenin, whose name you may recognize.

To capitalize on this turmoil and weaken their enemy, German leaders drew up a plan with Alexander Parvus (like Lenin, a Marxist revolutionary). The goal of this plan was to cause widespread labor strikes in Russia, known as “labor inhibition”. These, in turn, would result in the country’s economic paralysis and force its withdrawal from the war. The plan arranged for Germany to fund Russian Marxist revolutionaries who would act as labor agitators and precipitate strikes all across the country. To increase the success of this plan, the Germans smuggled Lenin back into Russia on a sealed diplomatic train. The conspirators hoped that unleashing Lenin on a vulnerable Russia would cause massive social upheaval and widespread strikes.

Even before the plan was enacted, many war-weary and frustrated Russian factory workers had already begun to strike. The German tactics bore fruit as massive and widespread strikes, accompanied by intense social unrest and the voicing of long-suppressed resentments, effectively shut Russia down. Russia was economically and socially destabilized by these events and had to withdraw from the war. Labor agitation with German sponsorship fanned the fires of economic and social dissatisfaction into a conflagration known as the Bolshevik Revolution, which ended with the murder and/or exile of many of Russia’s former leaders,
and led to the Communist Party’s takeover of Russia and the establishment of the Union of Soviet Socialist Republics (now dismantled). Germany, however, ended up losing the war.

**Scientific Connection**

When groups of workers band together and forcibly prevent productivity it is known as a strike. Strikes can deal financial deathblows to businesses and are neither initiated nor responded to lightly. If one company’s employees go on strike, their nation’s economy might suffer a little, but if every major industry were to go on strike at once there would be far-ranging social, political, and economic consequences, as in the above example.

Like industries, biological systems must continuously do work and maintain order if they want to survive. The production of ATP is essential because it provides energy. Energy is the potential to do work, but potential is only valuable if it can be realized. A factory without workers to make its product is in as weak a position as workers who have no one to compensate them for their labor. Possessing sufficient energy to complete a task is as important as having the means to carry it out.

Proteins are the workers of the biological world. They are responsible for maintaining the health and integrity of the cell as well as accomplishing the cell’s other goals or functions. These tiny and seldom appreciated laborers are the base on which biological systems are built and their constant toiling allows cells, tissues, organs, and organ systems to stay viable. Any substance that prevents proteins from being made or distracts them from their duties is usually phenomenally toxic. Inhibiting the activity of proteins on a wide scale will almost assuredly result in cellular death. Microbes are locked in a constant struggle for survival; they fight hard, play dirty, and in their own way are more devious than any human. The inhibition of cellular work by interfering with protein synthesis is a commonly used tactic that is both effective and deadly. When bacterial toxins interfere with protein synthesis in human cells the result is disease. Humans have caught on to this trick and utilize drugs that selectively disrupt bacterial protein synthesis to fight infections.

**Take Home Message**

Proteins are the workers of the biological world. A substance that inhibits widespread protein synthesis or protein function is typically extremely deadly.
STORY 1: THE EPIDEMIC- JANUARY, 1925.

Winter in Alaska makes the winters of New England seem like spring, thought Dr. Lawrence Harberg, physician for the rural town of Nome. Travel in and out of the town was impossible in the record levels of snow, ice and cold. This was his first winter here and he was afraid it might be his last winter anywhere. “Where is Annie?” he asked his nurse. “I told her mother to bring her back in today if that sore throat didn’t get better—what’s wrong?”

“Annie died two days ago,” Sister Mary Katherine told him with tears in her eyes. Dr. Harberg snapped, “Don’t get emotional now, Nurse, I won’t have it,” but he was badly shaken. The fifth of his young patients to die in a week—but surely sore throats were normal in the winter? Sister Mary Katherine blew her nose and reminded him, “Doctor, you have a patient waiting.”

“Well, well,” he said when he saw the two Yupik girls, “which one of you is my patient?”

“Her,” the older girl said, pointing at her sister. “She doesn’t speak English. Her throat hurts and it’s hard for her to eat. And she says she’s hot. She keeps throwing the blankets off.”

Cold as the weather was, a chill went down Dr. Harberg’s spine. “Well, let’s have a look,” he said, and gestured for the little girl to open her mouth. She complied, and his fear increased: instead of the clear pink of a healthy child’s mouth, the back of her tongue and throat were gray. He scraped at them with a tongue
depressor, and the substance came off on the wood like a spreadable cheese. In medical school he had learned about the symptoms of diphtheria, but he had never seen a case until now. He remembered, with icy clarity, that it was highly contagious, particularly lethal to children, and impossible to treat without diphtheria antitoxin—which he didn’t have. He barely even had any tongue depressors left. And the snow kept falling. If that toxin could not be delivered, thousands of people were going to die. With the snow blocking the every major route and the temperature dropping rapidly, Dr. Harberg had no idea how it could even be done.

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The story is history now: how Nome was cut off by the harsh winter, before planes and helicopters and snowmobiles; how the fastest way to reach Nome was by dogsled; how Alaskans gathered diphtheria antitoxin in the town of Nenana and several teams of brave men and dogs worked in a relay to deliver the medicine. Thanks to their courage and endurance, Nome was able to save many of its children from diphtheria, and Balto, the lead sled dog of the first team to arrive in Nome, became an instant national celebrity. To this day in Alaska, dogsled teams run the Iditarod race from Nenana to Nome to commemorate this heroic feat.

**Scientific Connection**

Diphtheria is caused by Corynebacterium diphtheriae. These bacteria, however, are only indirectly responsible for the symptoms of the disease. The actual damage is done by a protein they produce: diphtheria toxin, which destroys cells by preventing the creation of new proteins. The effect is similar to initiating a cellular labor strike: slipping diphtheria toxin into a cell just as the German government slipped Lenin back into Russia.

Proteins are assembled inside of ribosomes from amino acids that are gathered by tRNAs. The directions for how to make the protein are contained in the mRNA, which are like notes scribbled from DNA. Diphtheria toxin is extremely effective at disabling ribosomes, thereby preventing the production of new proteins. Without the ability to produce new proteins, the cell runs out of workers to maintain it. The result is cellular death.

Diphtheria toxin is so potent that a single molecule is capable of killing an entire cell. Corynebacterium diphtheria is inhaled and takes hold first in the back of the throat. Soon after these bacteria colonize, they begin to produce diphtheria toxin which kills the surrounding cells. The thick grey “pseudomembrane” in the back of the little girl’s throat was the remains of all the cells that Diphtheria toxin had killed. If allowed to progress, the bacteria will spread into the blood and diphtheria toxin will destroy major organs like the heart and the kidneys; diphtheria kills 40% of all infected individuals who don’t treat it.

Because diphtheria is communicated through inhalation, it’s highly contagious and can quickly become an epidemic. Diphtheria was such a major health problem in the past that a vaccine was developed
to protect against it. This vaccine introduces destroyed and inactivated diphtheria toxin molecules—known as diphtheria toxoids—into the bloodstream. A toxoid acts as a kind of “Wanted” poster for the immune system. Protein “bounty hunters” known as antibodies are created by the immune systems to seek out and destroy diphtheria toxin molecules. Antibodies remain in the bloodstream even after their target is eliminated and are continually produced, which is why vaccinations confer extended periods of immunity. If you were born in the U.S., you were almost definitely vaccinated against diphtheria when you were a small child. Antitoxins, on the other hand, are collections of antibodies made in an animal (like a horse) that are designed to track down and destroy a target protein; they give only temporary immunity, but are the treatment of choice when a protein toxin is already inside of your body. Due to the heroism of many men and animals the children in Nome were injected with the diphtheria antitoxin before it was too late.

Vaccinations and modern antibiotic therapy have largely eradicated diphtheria in the developed world, although it was a deadly and uncontrollable disease less than a century ago. However, there are many lessons to be learned from diphtheria toxin’s mechanism of action. Bacterial ribosomes are different from those found in human cells and therefore represent tactical targets in the war against disease. Scientists have developed ways to turn this ribosomal inhibiting trick against the enemy with fantastic results. A huge number of modern antibiotics selectively target bacterial ribosomes in hopes of killing or at least containing them. This therapy has revolutionized the practice of medicine...

STORY 2: RED RASH OF THE ROCKIES

You are a pediatrician in Hoboken, New Jersey. You’re surprised when one of your healthiest patients, an eight-year-old boy named Van, is brought into your office complaining of muscle aches and a terrible headache. He’s had a fever and shaking chills for five days, and his mother tells you that she thought he had the flu until she saw his rash. It started, she says, on his wrists and ankles, spread to his palms and the soles of his feet, and over the past two days has crept up his legs and arms.

To narrow down the possibilities for these symptoms, you ask if Van has had any bug bites recently. Van pipes up, sounding more like his old cheerful self: “Yeah, me and Sarah were playing with grandma’s dog and I got bit by three ticks and they stuck on me and they got all filled up with blood and we had to burn them to get them off!” Van’s mom sighs and confirms this story, explaining that they were visiting family in the South Carolina countryside a couple weeks ago, where the dog and the kids ran around outside all day. As you suspected, Van has Rocky Mountain spotted fever; you prescribe the antibiotic doxycycline, which he must take for several days, and in two weeks his mother reports that he’s in perfect health.
**Scientific Connection**

Van had a classic case of Rocky Mountain spotted fever. Despite its name, you don’t need to be in the Rockies to catch it. You’re most likely to contract it in the eastern and western coastal regions of the United States; the disease is most prevalent in the southeastern coast of the U.S. It is caused by a bacterium known as Rickettsia rickettsii, typically transmitted to humans through the bite of a dog tick. Bites can transmit disease-causing microorganisms to humans, so always mention tick bites or any other animal or insect bites to your doctor to help in your diagnosis.

Symptoms of Rocky Mountain spotted fever usually appear a week or two after the initial bite. Its early symptoms of fever, headache, malaise (feeling weak and tired), and muscle aches mimic the flu and are often missed. The telltale sign and the source of its name is the rash, which comes 2-4 days after the other symptoms begin. Rocky Mountain spotted fever is an extremely nasty disease that can quickly result in death due to failure of multiple organs. The spots represent tissue damage and though it is visible on the skin, these areas of damaged tissue are in many internal organs as well.

The disease would be fatal in many cases if it were not for modern antibiotic therapy. In a sense, doxycycline does to bacterial ribosomes what diphtheria toxin does to human ribosomes: targets them and shuts them down. In this case, ribosomal vulnerability works in humans’ favor. Without a fresh supply of proteins to do the necessary order-promoting work, the bacteria are in big trouble: the inhibition is not enough to kill them, but they can no longer divide (reproduce) and are easily finished off by the immune system. Van’s rapid recovery indicates that the bacteria are largely dead or at least are on the losing end of the battle, showing how effective this ribosomal inhibition is. To ensure that the bacteria are dead, patients taking antibiotics must always take the full course; if they stop when they begin feeling better, some bacteria may still remain and start reproducing again. These bacteria could be resistant to the antibiotic, which would make them much more difficult to treat. Drugs that disrupt bacterial protein synthesis are deadly weapons in any physician’s arsenal and have led to the eradication and control of many previously fatal bacterial diseases.

**Take Home Message**

Ribosomes are essential to protein synthesis. Inhibition of ribosomes can have serious benefit in the case of antimicrobial medications or serious consequences in the case of toxins.