Applications of microbial toxins and virulence factors

Mummy, Aunt Sarah used to have those funny lines between her eyes and look grumpy, but now they are gone. What happened?

Before

After

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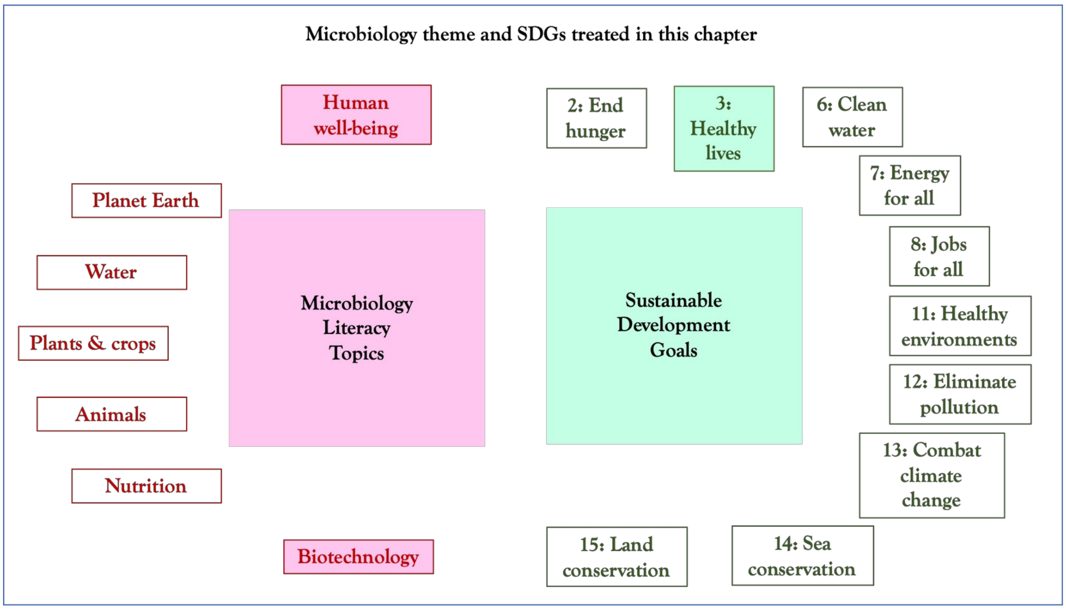
Storyline

When thinking about the impact of microbes on human health, we often divide them into “good” microbes and “bad” microbes. The good microbes, our microbiota, live on surfaces of our bodies and in our intestines and provide numerous benefits (see *Section 2, Human Wellbeing* for a more detailed treatment of this subject). They boost our immune system, aid in nutrition, and help protect us from harmful microbes, or pathogens. Most of the microbes that we encounter in our life are beneficial or neutral, but we occasionally encounter pathogens. These microbes have characteristics that allow them to attach or invade, avoid the host immune system, and in some cases, produce toxins that damage or kill the cells of their host. In reality, the dividing line is not so clear. Members of our microbiota may be able to breach the surface barriers and cause damage, especially if the immune system has become weakened. And there are pathogens that may take up residence for a period of time without our ever being aware that they are there. The outcome of these encounters depends on both the microbe and the host. In studying how pathogens cause disease, scientists have discovered that some of their toxins can be tamed and turned to beneficial uses.

The Microbiology and Societal Context

The microbiology: improving human health and well-being; using biotechnology.
Sustainability issues: healthy lives.



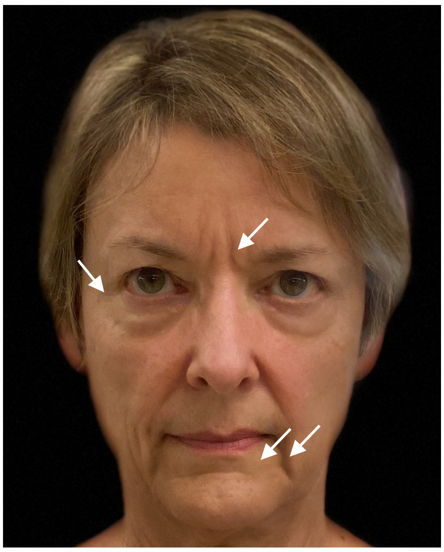
Applications of microbial toxins and virulence factors: the Microbiology

1. **Botulism toxin**. Many bacterial pathogens produce toxins that damage human cells or tissues. One of the best known is *Clostridium botulinum*, which causes botulism. Consuming food contaminated with the toxin produced by these bacteria results in muscle paralysis, which if it affects breathing, can result in death. Another form of the disease is associated with ingestion of spores, a stable form of the bacteria, which are found in soil and can contaminate plants or raw honey, for example. The spores germinate, and the bacteria grow and produce the toxin in the intestine. This form of the disease occurs most often in infants.

The first outbreaks of botulism were described in the late 1700s and were traced to eating contaminated sausage. The bacterium and disease get their name form the Latin *botulus*, meaning sausage. Modern canning and preserving practices eliminate the pathogen or prevent its growth, but infrequent cases of botulism still occur. These are generally associated with home canning, in which there was not sufficient heating, or infant botulism that occurs when the baby ingests the bacteria in food or drink.

The toxin acts by binding at the neuromuscular junction, the point at which the nerve connects with the muscle and controls when the muscle contracts. Binding of the toxin prevents the nerve from stimulating the muscle; the muscle remains flaccid and is unable to contract. This can cause difficulty swallowing, problems with vision, difficulty breathing, muscle weakness and paralysis. The severity of symptoms depends on the amount of toxin. When the toxin is ingested, it can spread throughout the body and affect a number of sites.

Beneficial use of the toxin was pioneered by an ophthalmologist, Alan Scott, who worked on treatments for double vision and other conditions associated with improper contraction of the eye muscles. He tried injecting extremely small amounts of the toxin into the affected muscle. The toxin caused the muscle to relax and allowed more normal vision. The toxin, marketed as Botox, has also been used to treat severe muscle spasms, strabismus (cross-eyes), and chronic migraines. The most famous use of Botox is in reducing wrinkles caused by muscle movement: the lines on forehead such as those that Aunt Sarah had in the “before” picture, laugh lines, and crow’s feet at the eyes. The toxin paralyzes or relaxes those small muscles and reduces the appearance of the wrinkles. It is also used at the edges of the lips to relax the small muscles and make the lips appear larger and fuller. Because the toxin binds very tightly to its target, the effects of Botox can last weeks or even months. Botulism toxin is an extremely dangerous toxin, but by carefully controlling the amount and location of the toxin, contraction of specific muscles can be prevented.

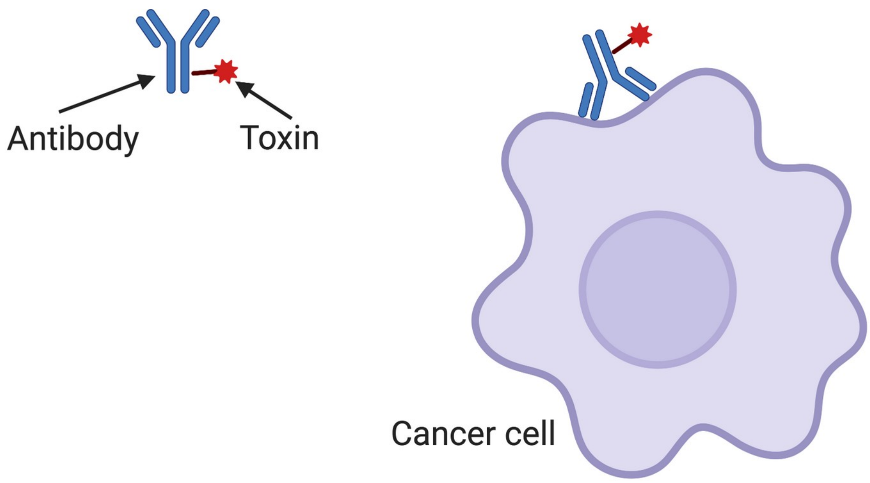


Typical sites of injection of Botox

The arrows indicate points where Botox is often injected to reduce the appearance of wrinkles.

2. Streptokinase. Another example of harnessing a microbial toxin for human benefit is the use of streptokinase. Streptococci, which cause strep throat and other invasive diseases, produce an enzyme, streptokinase, that dissolves clots. During an infection, the bacteria secrete the toxin and it prevents the body from forming fibrin clots around the bacteria and walling them off. Because clots forming in the bloodstream can cause a heart attack, Lederle Labs purified the toxin and tested it for its ability to dissolve the clots following a heart attack. At the time it was introduced, streptokinase was an important treatment and reduced mortality. Stretokinase has been replaced by other, more effective or more rapid treatments in some countries, but it is still used in many parts of the world as an effective aid in reducing mortality following a heart attack or certain other clot-related diseases.

3. Repurposing toxins. Many of the toxins that have been tested for beneficial activities are in a group called AB toxins. These toxins have an A (active) and B (binding) region or subunit. The A portion is the toxic part, but it requires the B portion to bind to a receptor on a cell and deliver the A fragment. By changing the B fragment, the toxin can be delivered to a different cell type in the body. This idea has been tested as a way to target cancer cells for destruction. If the B fragment can be modified so that it recognizes and binds to the cancer cell, but not to normal cells, then the toxin can destroy the cancer cells without harming the patient. The major impediment to this approach is finding protein receptors on the surface of the cells that are not present on other cells and altering the B fragment to recognize the receptor. More recent approaches are called antibody-drug conjugates (ADCs) or immunotoxins. An antibody that recognizes the cancer cells is coupled to a toxin, such as diphtheria toxin. Once the antibody binds the cell, it delivers its payload and the toxin kills the cell.



Immunotoxin
A toxin is attached to an antibody that recognizes a cancer cell. The toxin-antibody conjugate will bind and be taken into the cell. This allows the toxin to gain entry into the cancer cell and kill it (image created with Biorender.com).

Relevance for Sustainable Development Goals and Grand Challenges

- **Goal 3. Ensure healthy lives and promote well-being for all at all ages** (*improve health, reduce preventable disease and premature deaths).* Therapeutics are often made by chemical synthesis. This may involve the use of toxic chemicals and create hazardous waste. Because microbes are so diverse, it is possible to find microbes that carry out almost any reaction and they produce an incredible array of products. Isolating natural products, including botulism toxin, or using microbes to carry out specific reactions can reduce our dependence on chemical syntheses and help protect the environment. Microbes can also be genetically manipulated to produce altered products, such as less toxic forms of botulism toxin.

Further reading

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Glossary

AB toxin – A toxin that has two components, an active (A) portion and a binding (B) portion

Antibody – a protein made by a B cell, one of the white cells in the body, that binds to a pathogen or toxin to help prevent it from damaging the body

Botulism – the disease caused by the bacterium *Clostridium botulinum*. The bacterium produces a toxin that prevents the muscles from responding to messages from the nervous system. This causes paralysis.

Fibrin – a component of the blood that produces clots.

Germination – the transition from inactive spores to actively growing bacterial cells.

Immunotoxin – a toxin that has been compbined with an antibody.

Microbiota – the collection of microorganisms that are normally found in and on the human body.

Neuromuscular junction – the connection between a neuron and the muscle it controls.

Pathogen – a microorganism that causes disease

Spores – an inactive, very stable form of some microorganisms.

Strep throat - disease caused by the bacterium *Streptococcus pyogenes.* The disease is associated with dore throat and fever. It can lead to more serious disease if untreated.

Strepococci – a group of bacteria that form round (coccid) cells.

Therapeutics – treatments for diseases

Toxin – a substance produced by a plant, animal or microorganism that is harmful to other organisms.