So Why Aren’t We Always Sick? Our Bodies’ Defenses.

In the last few lessons we have covered the central parts of the immune response. In this lesson we will put all these parts together and we will apply them to understanding how vaccines work. Then we will use this knowledge to investigate the pros and cons of vaccination, including the interesting ethical question: should people have the right to chose to be unvaccinated?

Putting it all together

The cytokines only enhance B and T cell function, they still need antigen to be activated!
Pathogens and toxins can be manipulated to generate an immune response and memory even if a damaging infection is absent.

Edward Jenner lived from 1749-1823. At the age of 13, he was apprenticed to a Dr. Ludlow in Sodbury, in the English countryside. At that time smallpox was a scourge. Young Edward saw that dairymaids never caught smallpox, even though they often caught cowpox. He wondered if there might be a connection, but Dr. Ludlow wasn't interested and Jenner soon left for medical school. After graduation a smallpox epidemic struck Jenner's hometown, but the farmers told him that cowpox could prevent smallpox infections, confirming his youthful suspicion.

Some years later, Sarah Nelmes, a local milkmaid, contracted cowpox and went to Jenner for treatment. Jenner took the opportunity to test his theory. He inoculated James Phipps, his gardener’s eight-year-old son, with cowpox taken from one of Sarah’s pustules. After an extremely weak bout of cowpox, James recovered. Jenner then tried to infect James with smallpox but (fortunately) nothing happened—the boy was immune to smallpox.

Jenner reported his observations to a skeptical Royal Society, who advised him to repeat his unexpected observations. Jenner soon accumulated a further 23 cases, including his son Edward, who were successfully protected from smallpox with an inoculation of cowpox.

By 1800 Jenner’s work had been published in all of the major European languages and his ‘vaccination process’ was being performed all over Europe and the United States (this is shown in the figure above, taken from a medical text that settlers used). The death rate from smallpox became close to zero. Smallpox vaccination was continued until around 1974 in the UK. At that time the typical death rate from the vaccination itself was roughly one per million, making it the most dangerous immunization that was widely provided in modern times. Thanks to the development of the smallpox vaccine, the disease was officially eradicated in 1979.
A vaccine stimulates immune responses (B and T cell memory and antibodies) to antigens in the absence of disease.

In essence, a vaccine allows a person to develop immunity to a disease without contracting the disease. It does this by stimulating B and/or T cell responses to establish memory in the absence of a dangerous infection. Then if a person comes into contact with the real pathogen they have memory B and T cells and there is no delay in adaptive immune responses. This allows the host to mount a strong and fast adaptive immune response when the real pathogen is encountered. In addition, a vaccine may generate neutralizing antibodies that prevent infection and toxin actions. In order to do this the infectious pathogen is disabled, either by killing it or purifying a relevant antigen from it.

A vaccine works by tricking the immune system into responding to an antigen in the absence of disease.

The above figure shows how vaccines trick the immune system:

1. Vaccines contain an antigen from a select pathogen that stimulates innate cells. The purple cell is an innate cell and the yellow halo shows that it has been activated. The innate cell presents the antigen to T cells and secretes cytokines to stimulate them. The Helper T cell that is specific for the antigen becomes activated (the red cell with the halo). This leads to clonal expansion and the development of effector T cells, just like a response to a normal infection.

2. The activated T cells then release cytokines like IL-2 that give antigen specific B cells (shown in pink) permission to activate and make antibodies. The B cell then undergoes clonal expansion and becomes an effector B cell that makes antibodies. Some of the B and T cells become memory cells, making antibodies and patrolling in case the intact and active pathogen is encountered.

So what's the trick? Most of the processes that are described above occur normally during an infection. However, a vaccine is able to simulate innate cells in the absence of an intact active pathogen. Remember, an innate cell needs to recognize a pathogen before it responds. Vaccines need to pretend to be pathogens and activate innate cells through PAMPs; the vaccine needs to be recognized as non-self to generate a response.
The four types of vaccines:

1. **Viruses or bacteria could be killed by heating or by treating with chemicals.** In this case, the virus remains intact but is unable to replicate. The inactivated pathogen still has its PAMPs and its antigens, so the immune response thinks the dead pathogen is dangerous and responds. This approach can be dangerous if the inactivation fails, so the other methods are generally preferred.

2. **Live viruses and bacteria could be weakened (attenuated) by removing a dangerous gene, such as one for a toxin or for infectivity, while keeping other antigens intact.** This approach tricks the immune system because the vaccine still has PAMPs, so immune cells will mount a response to antigens that are in the pathogen. The approach is limited because the very factors you may need to remove to weaken the pathogen may be the same antigens you need to make antibodies against. For example, if you remove tetanus toxin from tetanus this bug certainly would not cause disease, but the relevant antigen is also gone! Attenuation could theoretically be unsuccessful, but practically the risk is insignificant. The smallpox vaccine is an example of a live attenuated vaccine.

3. **The antigen that most readily stimulates the immune system could be isolated and used.** This is the best approach in terms preventing unwanted infection, but sometimes single antigens don’t stimulate the innate immune system very well because they lack PAMPs. To get around this problem, a stimulant called an **adjuvant** is used. An adjuvant can take the place of PAMPs to activate and stimulate innate cells. The tetanus vaccine is made like this. It uses a part of the toxin that is not dangerous but allows B cells to make antibodies, and also includes an adjuvant.

4. **Perhaps the best approach is to genetically engineer a pathogen that contains all of the important antigens to stimulate both innate and adaptive immunity, but none of the dangerous ones, like those that cause infectivity.** This would be the safest, because there is more control over the end product. However, as you might imagine it is a huge genetic engineering project. Scientists are trying hard to make artificial viruses and bacteria that could be used like this in vaccines.