**TEACHER GUIDE for “Three Steps Toward Isolating the Heredity Factor”**

*Students process the readings for all three experiments by working in groups to create a comic strip series of images to describe the approach and results. Each experiment builds on the previous one, so they cannot be easily divided up among groups and shared in a jigsaw activity.*

*Here we have added illustrations of the experiments for your understanding. These same images appear as optional slides in the PowerPoint. We discourage you from simply showing them to students as this is an opportunity to have them try to piece together some rather complex stories on their own and t translate them. If you choose to review using the slides in more of a lecture format, be sure to have a discussion at the end asking students to link the evidence from the experiments to the inferences each scientist or group of scientists made.*

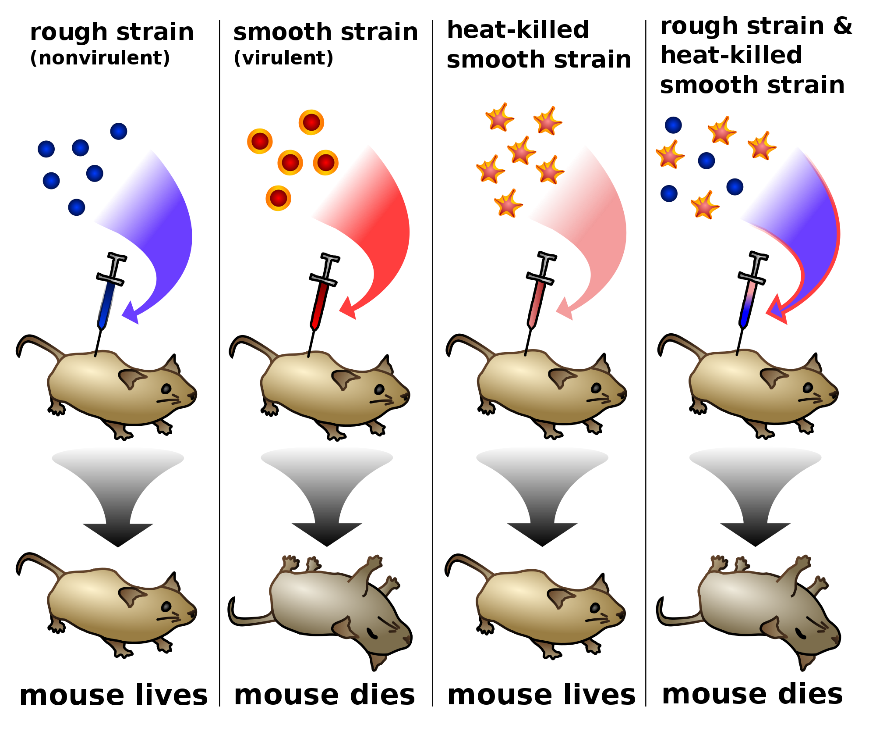
**Step 1: Griffith’s Transforming Agent**

In 1928 a biologist named Frederick Griffith ran the first experiment suggesting that free living cells such as bacteria were capable of transferring genetic information through a process known as “transformation”. This was one of the first strong pieces of evidence that some microscopic portion of the cell was responsible for providing the information involved in the model of inheritance Mendel and others had worked to build.

Following World War I in Europe, pneumonia was a huge problem and a very deadly disease. Griffith was studying the possibility of creating a vaccine. At this time in history (and even today in many cases), one of the early steps in making a vaccine was to infect the blood of a healthy animal in order to see how the animal’s immune system responded. Griffith used two strains (kinds) of pneumococcus bacteria (related to the kind of bacteria which causes strep throat in humans) to infect some mice. He used type III-S or a “smooth” variety which was capable of infecting and killing mice, and a type II-R or “rough” strain which was nonvirulent, meaning it couldn’t seem to harm the animal. The “smooth” strain looked smooth because it covered itself with a polysaccharide or sugar capsule that protected it from the host's immune system—kind of like a protective shell around bacteria that keeps it from being attacked. This meant that the mouse’s immune system couldn’t attack it and therefore the mouse died. However, the “rough” strain did not have that protective capsule and was defeated by the host's immune system every time Griffith injected it into a healthy mouse.

In a follow-up series of experiments, Griffith tried infecting the mouse with both kinds together. When he did this, the mice got sick and died. Importantly, he also tried one other series of experiments. He took bacteria from the “smooth” killer strain and killed *them* by using extreme heat. These bacterial cells could no longer kill the mice when they were injected into the blood. This made sense: the bacteria were dead themselves and couldn’t attack the mouse. However, if he took these same dead “smooth” cells and added them to live “rough” strain bacteria, the combination was able to kill the mice he injected! Griffith was then able to isolate both live “rough” and live “smooth” strains of pneumococcus from the blood of these dead mice. Where did the live “smooth” cells come from?!? It was like magic! Griffith concluded that the “rough” type had been "transformed" into the deadly “smooth” strain by a "transforming principle" that was somehow part of the dead smooth strain bacteria.

—adapted from Wikipedia Article, “Griffith’s experiment”



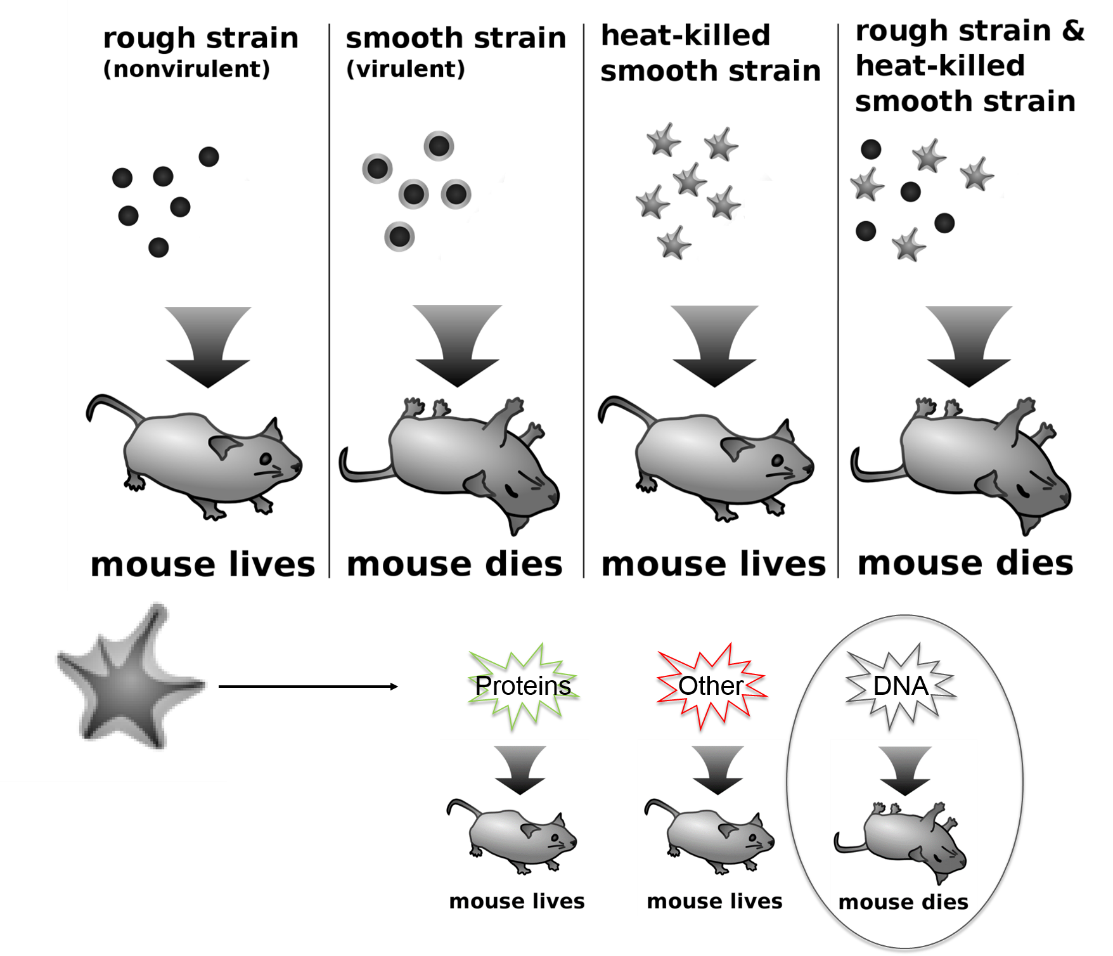
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**Step 2: Avery, McLeod, and McCarty’s Follow-up**

Griffith’s experiments in 1928 showed that some portion of dead bacterial cells could mysteriously transform the character of living bacterial cells. In the case of Griffith’s experiments, the “factor” from the dead bacteria made the live bacteria that came in contact with it “virulent” or able to cause disease. This ability to make the mice sick was somehow being moved from the dead cells to the live ones in a kind of “transformation”. Avery–MacLeod–McCarty set out to characterize the "transforming principle”. In their paper published in the February 1944 issue of the *Journal of Experimental Medicine*, Avery and his colleagues suggested that DNA, rather than protein as might be the hereditary material of bacteria.

The main contribution that these three scientists made was to chemically extract (or pull out) portions of the dead bacterial cells and to test them individually to see what the transforming “factor” might be. Using their knowledge of chemistry, they isolated a number of different compounds from the dead cells. They then injected each separately into the blood of mice, along with the non-virulent “rough” strain bacteria. Since the “rough” bacteria were unable to cause disease on their own, the only way they could become deadly is if the compounds Avery, McLeod and McCarty injected with the cells somehow transformed them into deadly bacteria. Proteins and other sorts of compounds were unable to make the rough bacteria into deadly agents of disease. In only one case did all of the mice die. The compound in this case was determined to be DNA.

—adapted from Wikipedia Article, “Avery-McLeod-McCarty experiment”

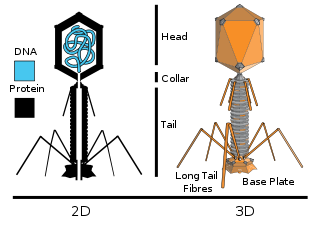


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**Step 3: Hershey-Chase and Their Clever Experiment**

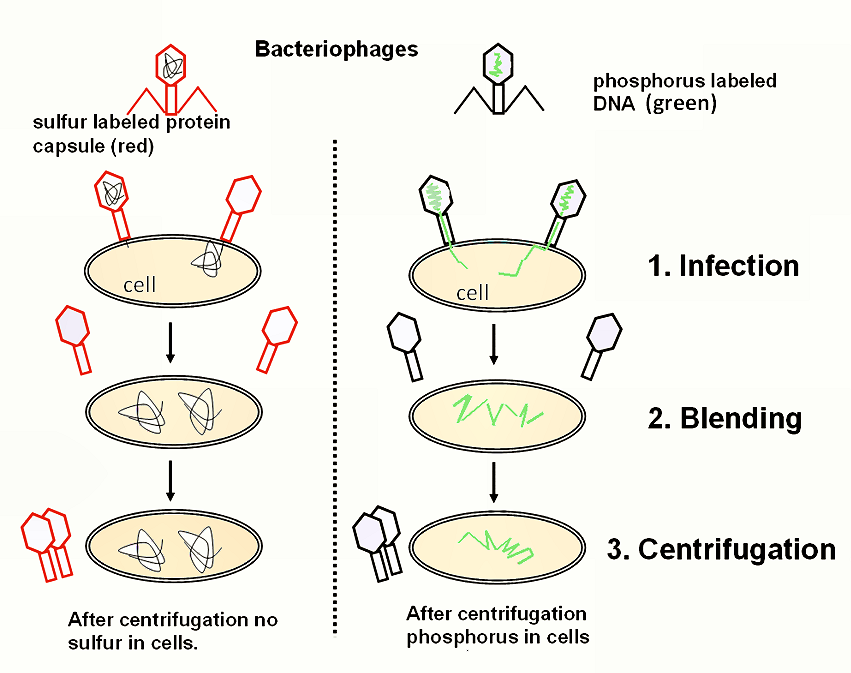
A series of experiments conducted in 1952by Alfred Hershey and Martha Chase helped to confirm that DNA is genetic material. While DNA had been known to biologists since 1869, many scientists still assumed at the time that proteins carried the information for inheritance because DNA appeared simpler than proteins. In their experiments, Hershey and Chase showed that when bacteriophages, which are composed of DNA and protein, infect bacteria, their DNA enters the host bacterial cell, but most of their protein does not.

A bacteriophage is a kind of virus that is built to infect bacteria. It actually looks a bit like a spacecraft NASA might build to land on the moon or Mars. Once the bacteriophage virus lands on the surface of a bacterial cell, it squats down and injects its core materials through the cell wall. Hours later, the cell bursts and out fly millions of copies of the original virus which go on to infect other cells. Scientists were still studying this process in the mid-twentieth century, but they had figured out some of the basics, including the structure of the bacteriophage.

To really prove it was DNA that entered the cell, Hershey and Chase needed to be able to examine different parts of the phages they were studying separately. They needed to isolate the phage subsections. Viruses are very simple. They provided the ideal test case because they were known to be composed of only two components: a protein shell and DNA. In order to track what happened to the protein and DNA separately, Hershey and Chase chose to uniquely label each with a different radioactive tag. This allowed each to be observed and analyzed separately. Since phosphorus is contained in DNA but not amino acids, radioactive phosphorus-32 was used to label the DNA contained in bacteriophage. Radioactive sulfur-35 was used to label the protein sections of the phage, because sulfur is contained in amino acids but not DNA.

Hershey and Chase inserted the radioactive elements into the bacteriophages by adding the isotopes to vials within which bacteria were allowed to grow for 4 hours before bacteriophage introduction. After the bacteriophages infected the bacteria, the [new](https://en.wikipedia.org/wiki/Progeny_%28genetic_descendant%29) ones that flew out of the broken cells hours later contained the radioactive isotopes in their structures. This procedure was performed once to create the sulfur-labeled-protein phages and once to create the phosphorus-labeled-DNA phages. The labeled viruses of each kind were then allowed to infect unlabeled bacteria. The phage coats remained on the outside of the bacteria, while genetic material entered. The results of their experiment are depicted in the diagram on the back of this sheet. See if you can understand why their data proves that DNA (and not protein) was the molecule of inheritance that was injected into the bacterial cells.

—adapted from Wikipedia Article, “Hershy-Chase experiment”



“Diagram of the Hershey Chase experiment” by Thomasione, Wikimedia Commons [CC3.0]