CHAPTER 6

Oswald Avery & the Search for the Transforming Factor

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INTRODUCTION

Today most people do not fear pneumonia, but before antibiotics became widely available in the late 1940s, the disease was a dreaded killer. In a moderately large city like Atlanta, Baltimore, or Portland (each of which had about 100,000 people in 1900), 175 to 200 victims of pneumonia might die every year. Not surprisingly, public health authorities and medical researchers placed a high priority on understanding the disease and discovering a cure for it. Oswald Avery and his laboratory at the Rockefeller Institute were at the center of this search.

Avery's work eventually led to one of the most dramatic biological discoveries of the twentieth century: the identification of DNA as the genetic material. This is surprising because Avery was not a geneticist and did not direct his research toward understanding heredity. How could the study of pneumonia open a new field of research in molecular genetics? This case study illustrates how important scientific discoveries may arise from unexpected sources. It highlights the complex relationship between pure and applied science. Although improvements in medicine often result from breakthroughs in pure scientific research, the reverse can also happen. In the case of DNA, one of the most important discoveries in modern biology grew out of the practical problem of finding a cure for a specific disease.

PNEUMOCOCCUS: THE "SUGARCOATED MICROBE"

Pneumonia is a disease with several possible causes, the most important of which is a bacterium (*Streptococcus pneumoniae*) commonly known as the pneumococcus (Figure 6.1). First isolated in 1881, the bacterium quickly became a focus of medical research. By the end of the 1920s, a great deal was known about the pneumococcus. Medical scientists knew that several strains of the bacterium existed. Antibodies that were effective against one strain had little or no effect against others. Chances of surviving pneumonia were dramatically influenced by which strain caused the infec-

tion—mortality rates ranged from 15 percent to 60 percent. At the time when Avery began his work, several major strains had been identified, each designated by a Roman numeral: types I, II, and III (today, over 80 immunological types are known).

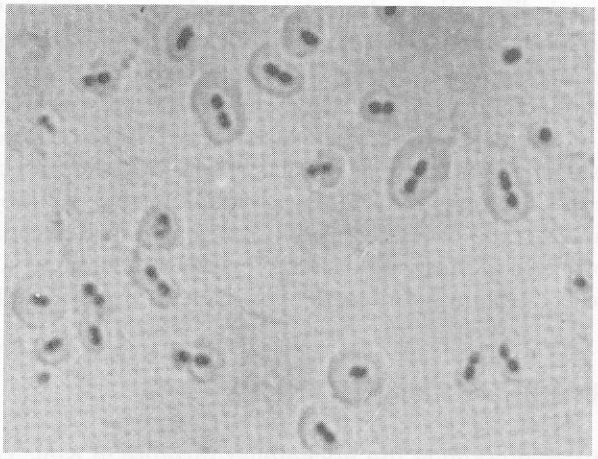

FIGURE 6.1 *Streptococcus pneumoniae,* the principal cause of pneumonia during the early decades of the twentieth century. Because of its role in causing the disease, this bacterium was often referred to as the "pneumococcus." Its early scientific name was *Diplococcus pneumoniae* because of the tendency for two spherical cells to remain attached to one another. In this photograph, the thick capsule is clearly visible around the cells. *Source:* Courtesy of the Centers for Disease Control.

Researchers also knew that disease-causing (pathogenic) pneumococci could be rendered harmless (nonpathogenic) by various artificial culturing techniques. This was usually a permanent change; harmless pneumococci produced only harmless descendants. Billions of nonpathogenic pneumococci could be injected into a mouse with no adverse effect, while only a few pathogenic bacteria quickly caused death. Types I, II, and III of the pneumococcus all included both pathogenic and nonpathogenic forms.

Scientists could easily distinguish between pathogenic and nonpathogenic pneumococci simply by looking at them. Colonies of pathogenic bacteria were larger and had a smooth, shiny appearance. Therefore, they were often referred to as the "S," or smooth, form of the bacterium. Colonies of nonpathogenic bacteria were smaller and had a rough appearance ("R," or rough, form). Under the microscope, pathogenic (S) bacteria were found to be surrounded by a thick coating, or capsule, absent in nonpathogenic (R) forms. Later, scientists discovered that the capsule was composed primarily of polysaccharides—hence Avery's facetious claim that he studied a "sugarcoated microbe." Medical researchers quickly realized that the capsule protected the bacterium against the host's defense mechanisms. Specialized white blood cells (macrophages) readily engulfed nonpathogenic (R) bacteria, but they were repelled by the capsules of pathogenic (S) forms.

The capsule also stimulated the host's immune response (see Chapter 13). Because the molecular compositions of the capsules in types IS, IIS, and IIIS pneumococci were slightly different, each caused a different antibody to be produced by the host. This claim was very controversial when Avery reported it in 1916 because most immunologists believed that only proteins could act as **antigens** (foreign molecules that stimulate antibody production). Avery had carefully purified his capsular extracts to produce a substance that was almost entirely made up of polysaccharides. This purified substance stimulated a specific immunological response when injected into a host.

The problem was that Avery could never completely eliminate minute traces of protein in his capsular extracts. Therefore, skeptics claimed that the antigenic properties could result from that residual protein. Although he turned out to be correct, Avery could not quiet his critics when he made his discovery in 1916. This technical problem of purifying bacterial extracts to eliminate all traces of protein would come back to haunt Avery in 1944 when he reported that DNA is the genetic material.

OSWALD AVERY AND THE ROCKEFELLER INSTITUTE

Avery worked at the Rockefeller Institute in New York City. Funded by oil tycoon John D. Rockefeller, this was the most prestigious medical research center in the United States. Although committed to finding cures for disease, the institute was founded on the belief that medicine must be firmly based upon science. Avery, therefore, worked closely with a diverse group of physiologists, biochemists, and biophysicists, as well as specialists in the more traditional medical fields of bacteriology and immunology.

The unique characteristics of the Rockefeller Institute provided an environment conducive to Avery's research, but his personality also contributed to his success. Former colleagues remember him most for his persistence. Once he had started a project, he rarely gave up until it was successful. The path leading to DNA was filled with obstacles that would have defeated a less tenacious investigator. "Disappointment is my daily bread. I thrive on it," he often said. This apparently fatalistic attitude was, however, based on a fundamental optimism. He took great delight in designing experiments. For Avery, the process of solving problems provided greater excitement than actually reaching the final solution. Like many other great scientists, he also inspired the younger members of his research team. This was done subtly, for he rarely assigned specific tasks to his subordinates. As he liked to claim, the Rockefeller Institute picked good, young scientists, and he "picked their brains."

EXPERIMENTS ON BACTERIAL TRANSFORMATION

In 1928, Avery and other bacteriologists were startled by Frederick Griffith's claim that he had transformed one pneumococcal type into another. Griffith was known as a meticulous scientist, but his discovery of bacterial transformation began as an accident. Before injecting experimental mice, medical researchers routinely suspended bacteria in various organic mixtures (adjuvants) in the mistaken belief that these sub-

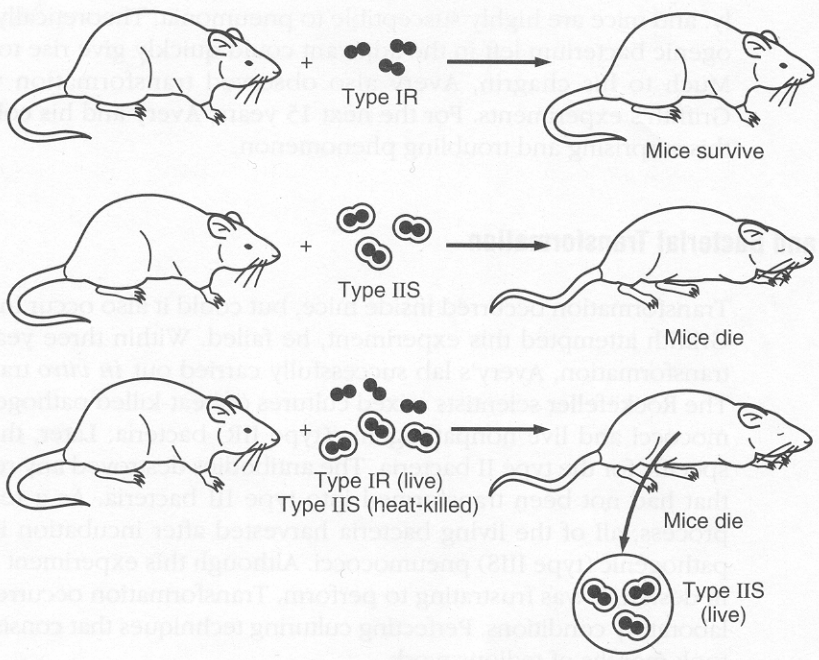

FIGURE 6.2 Basic design of one of Griffith's experiments on bacterial transformation. The use of control groups should have ruled out the possibility that some pathogenic (S) bacteria remained viable when they were heated. At first, however, Avery and other critics believed that this type of experimental error might explain transformation.

stances increased bacterial activity. Griffith just happened to use heat-killed pathogenic (type IIS) pneumococci for an adjuvant in an experiment where he injected live nonpathogenic (type IR) bacteria into mice. The mice developed pneumonia and died. When Griffith examined blood from the mice, he found live pathogenic (type IIS) pneumococci (Figure 6.2).

Somehow Griffith had transformed harmless (R) bacteria into the deadly S form simply by mixing them with an adjuvant made of dead pathogenic cells. This was surprising, but what really caught Avery's attention was the fact that Griffith had transformed pneumococci from one immunological type to another. Pathogenicity could easily be lost, so perhaps it could be gained, but most bacteriologists considered the types to be genetically distinct strains, almost equivalent to distinct species. Going from type I to type II was tantamount to converting one species into another.

Griffith's experiments caused consternation in Avery's laboratory. Avery wanted to stimulate the immune system to destroy pneumococci before they could cause disease. This "serum therapy" depended upon the stability of the immunological types of pneumococci. If types I, II, and III could change from one to another, it might be impossible to develop a cure for pneumonia.

At first, Avery hoped that Griffith's results might be due to experimental error. Griffith had done carefully controlled experiments (Figure 6.2), but perhaps he failed to kill *all* of the S pneumococci in his adjuvant. Bacteria multiply very rapid-

ly, and mice are highly susceptible to pneumonia. Theoretically, even a single pathogenic bacterium left in the adjuvant could quickly give rise to a lethal population. Much to his chagrin, Avery also observed transformation when he replicated Griffith's experiments. For the next 15 years, Avery and his colleagues investigated this surprising and troubling phenomenon.

Avery and Bacterial Transformation

Transformation occurred inside mice, but could it also occur in test tubes? Although Griffith attempted this experiment, he failed. Within three years of learning about transformation, Avery's lab successfully carried out *in vitro* transformation in 1931. The Rockefeller scientists mixed cultures of heat-killed pathogenic (type IIIS) pneumococci and live nonpathogenic (type IIR) bacteria. Later, they added antibodies specific for the type II bacteria. The antibodies destroyed any remaining type II cells that had not been transformed into type III bacteria. As a result of this selection process, all of the living bacteria harvested after incubation in the test tube were pathogenic (type IIIS) pneumococci. Although this experiment was elegantly simple in design, it was frustrating to perform. Transformation occurred only under certain laboratory conditions. Perfecting culturing techniques that consistently yielded results took months of tedious work.

PROBLEM

Avery believed that the *in vitro* experiment was the next logical step in the search for the transforming factor. Why was this step important?

Would transformation occur if Avery used an extract containing no intact cells? Numerous problems frustrated this step in the research. The original extraction process involved repeatedly freezing and thawing the culture, then heating the culture for 30 minutes, centrifuging the cell fragments, and passing the resulting extract through a bacterial filter. As Avery's group discovered, this rough treatment damaged or destroyed the transforming factor. Later improvements in the technique, which involved chemically lysing, or dissolving, the cellular membrane, made it work better. It was several years, however, before Avery's laboratory could consistently cause transformation using cell-free extracts.

Ironically, during this stage in the research Avery literally had the solution to the problem in his hands. In 1932, one of his assistants precipitated a bacterial extract with alcohol. We now know that the thick, fibrous precipitate was DNA. The curious material seemed unimportant, and even if he had known what it was, Avery might have ignored it. At the time, nobody thought that DNA was an important biological molecule. Avery thought the molecule that he was searching for would almost certainly turn out to be a polysaccharide or perhaps a protein.

At the time, the most likely candidate for Griffith's transforming factor was one of the polysaccharides making up the bacterial capsule. Yet one piece of evidence called this hypothesis into question. In his early experiments, Griffith found that transformation occurred when pathogenic bacteria were killed by heating to 60° C

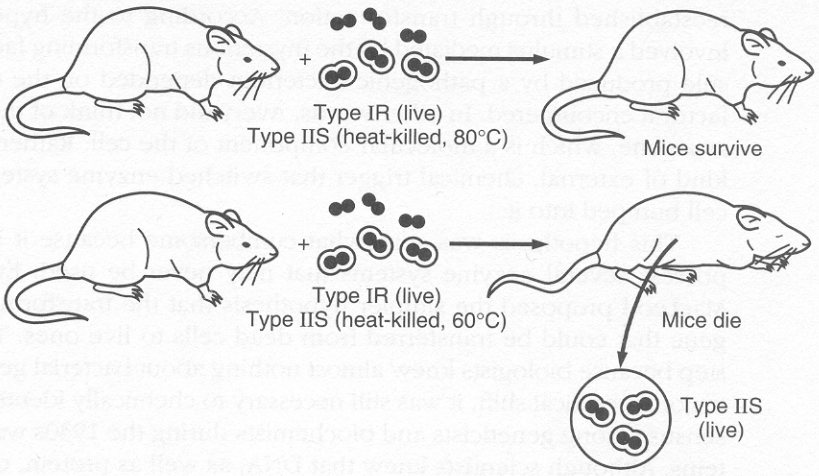

FIGURE 6.3 Variable effects of heat-treating bacteria. Killed bacteria or bacterial extracts heated to 60° C were capable of transforming nonpathogenic bacteria into pathogenic types. This ability was lost if the temperature was raised to 80° C. This experimental result seemed to rule out the possibility that the transforming factor was a polysaccharide, because most carbohydrates are heat stable.

but not when the temperature was raised to 80° C (Figure 6.3). This evidence suggested that the transforming factor was heat sensitive, but Avery knew that most polysaccharides are not damaged by such gentle heating. If not a polysaccharide, what type of molecule was the transforming factor?

Contributions of MacLeod and McCarty

Attempts to isolate and identify the transforming factor began in earnest when Colin MacLeod joined Avery's laboratory in 1934. Like Avery, MacLeod was a physician who had turned to research after a short stint of practicing medicine. He had little training in biochemical research before coming to the Rockefeller Institute—much of what he knew, he learned on the job. During the next seven years, he and Avery perfected the extraction and purification techniques that would ultimately identify the transforming factor. This was painstaking work, and much of the time MacLeod worked on his own. Avery suffered from Graves' disease, a thyroid disorder, and he was incapacitated for more than a year after having his thyroid gland removed.

MacLeod and Avery faced two types of problems: theoretical and technical. When MacLeod began working, neither he nor Avery saw transformation as a genetic phenomenon. After repeating Griffith's original experiments demonstrating that bacteria could change from one immunological type to another, Avery's lab adopted the following working hypothesis: Each pneumococcus contains the necessary enzymes to produce capsules of all major types (I, II, or III). Each capsule is characterized by a slightly different polysaccharide. Nonpathogenic bacteria of each type have lost the ability to produce any of the capsules, but this ability can be

reestablished through transformation. According to the hypothesis, this process involved a stimulus mediated by the mysterious transforming factor. The type of capsule produced by a pathogenic bacterium depended on the type of transforming factor it encountered. In other words, Avery did not think of the transforming factor as a gene, which is a molecular component of the cell. Rather, he thought it was a kind of external, chemical trigger that switched enzyme systems on or off when a cell bumped into it.

This hypothesis was somewhat cumbersome because it implied that bacteria possess several enzyme systems that may never be used. Eventually, Avery and MacLeod proposed the simpler hypothesis that the transforming factor was like a gene that could be transferred from dead cells to live ones. This was not an easy step because biologists knew almost nothing about bacterial genetics. Even with this major theoretical shift, it was still necessary to chemically identify the gene. The consensus among geneticists and biochemists during the 1930s was that genes are proteins. Although scientists knew that DNA, as well as protein, could be found in the chromosomes of many higher organisms, almost everyone dismissed DNA as unimportant for heredity. One of Avery's colleagues at the Rockefeller Institute, an authority on the chemistry of nucleic acids, believed that DNA was composed of four nucleotides monotonously repeated in exactly the same order. DNA could not possibly carry genetic information, he claimed, because all DNA molecules were chemically identical. A theoretical biologist put it more bluntly: because the structure of DNA did not vary, it was "a stupid molecule."

Against this intellectual backdrop, MacLeod faced the daunting challenge of extracting enough transforming factor for chemical analysis. Although billions of bacteria can live in a liter of culture fluid, their combined mass amounts to only a few tenths of a gram. This yield was too small for the extensive chemical tests that MacLeod needed to run, but removing bacteria from larger cultures posed serious technical problems. Each liter had to be spun in a centrifuge for an hour to separate the bacteria from the fluid. At that rate it would take days of nonstop work to get enough bacteria. MacLeod turned to an alternate method: a modified cream separator borrowed from the dairy industry. He could process 50 to 75 liters of culture medium fairly quickly through the device, leaving a large cake of bacterial cells inside a 10-inch metal cylinder.

Although it provided a neat solution to the problem of harvesting bacteria, the cream separator emitted a fine mist of culture fluid. This, of course, posed an unacceptable hazard for scientists working with the bacteria responsible for causing a serious respiratory disease. Therefore, MacLeod and a technician had to modify the device to make it completely airtight. Even so, at the end of a run, they wrapped the cylinder containing the bacteria in a disinfectant-soaked towel to prevent possible contamination. The cylinder was then heated to 60° C to kill the bacteria. At this point the cake of bacteria could be safely handled. This unorthodox extraction procedure, which deviated widely from the traditional sterile techniques used by bacteriologists, bothered Avery so much that he could not bring himself to watch it.

Extraction and purification involved numerous chemical and physical techniques. The bacteria were first treated with a detergentlike substance (sodium deoxycholate) to cause the contents of the cells to be released. Various types of enzymes

could be added to digest particular groups of macromolecules. The extract was then placed in a cellophane dialysis bag, which was immersed in water. Small molecules passed through the pores in the cellophane, but larger molecules remained trapped inside the bag. Various fractions of the extract could also be separated by chemical precipitation. For example, shaking with chloroform removed proteins and adding alcohol caused nucleic acids to precipitate. The physical process of centrifugation could also be used to separate parts of the extract. After these procedures were completed, the purified fractions were tested for their ability to cause transformation in living bacteria.

At the very height of this activity, MacLeod left Avery's lab. He wanted to stay at the Rockefeller Institute, but there were no permanent positions available. Therefore, when he was offered another job, MacLeod felt compelled to accept it. Although he continued to be involved in the transformation project, his new duties prevented him from playing a central role in the final discovery process. In 1941, another young physician, Maclyn McCarty, took his place in Avery's laboratory. McCarty had always wanted to be a medical researcher and, unlike his two senior collaborators, he was trained in biochemistry.

When McCarty arrived at the Rockefeller Institute, the chemical nature of the transforming factor remained unknown. Evidence for DNA had been accumulating, and one of Avery's colleagues recalls that as early as 1936 he "outlined to me that the transforming agent could hardly be a carbohydrate, did not match very well with protein, and wistfully suggested that it might be a nucleic acid!" Whatever private beliefs Avery or MacLeod had, they were unwilling to make any public statements about DNA. Indeed, they did not publish any results of their research before McCarty joined the effort. McCarty was able to build on the earlier work of the team. Combining the techniques developed by MacLeod and Avery with his own considerable chemical skills, he was able to identify DNA as the most likely candidate for the transforming factor. This happened fairly quickly. In 1943, two years after McCarty arrived, the team submitted an article on DNA and transformation to the *Journal of Experimental Medicine*, which published it the next year.

RESPONSE TO THE DISCOVERY

In contrast to the immediate acclaim that James Watson and Francis Crick would later receive for describing the structure of DNA, the response to the paper of Avery, MacLeod, and McCarty was quite muted. Relatively few readers recognized the important implication that DNA was the universal genetic material. One of the few who recognized its significance for genetics, the biochemist Erwin Chargaff, quickly switched to DNA research after reading the paper. He went on to discover that DNA nucleotides always come in specific ratios. This became a critical piece of evidence later used by Watson and Crick. Most biologists, however, remained quite skeptical about DNA.

There were several good reasons for this skepticism. Most important, Avery's group could not conclusively prove that DNA caused transformation. McCarty believed that his DNA extracts were 99.9 percent pure. But he realized that the

0.1 percent protein remaining in the sample might amount to several million molecules. Given the tremendous biological activity of many proteins, one could not rule out the possibility that it was the tiny amount of protein rather than the large quantity of DNA that was actually causing transformation.

PROBLEM

Some biologists believed that genes were composed of both protein and DNA. If McCarty's critics believed that protein was the active portion of the transforming factor, what role might DNA play? Why was the "nucleoprotein" hypothesis plausible during the early 1940s?

Avery was particularly sensitive to this possibility. In his younger years, he had faced exactly this type of criticism when he claimed that polysaccharides sometimes have antigenic properties. Much to the dismay of MacLeod, who had wanted to publish results earlier, Avery worried for months about strengthening the evidence for DNA. He did not want to be forced to retract a hasty conclusion.

In 1944, most biologists were predisposed to believe that genes were proteins. Leading biochemists believed that only proteins had the structural diversity to carry genetic information. Thus even though Avery, MacLeod, and McCarty had found that most of the transforming material was DNA, critics could still claim that the active part of the material was a protein. Avery's problem was made worse when respected colleagues, including scientists who knew much more about biochemistry than he did, criticized his work. Indeed, one of the most vocal opponents of DNA was a Rockefeller biochemist who worked in the same building with Avery. Both publicly and privately, he argued against DNA. Faced with this intense criticism by leading biochemists, it is not surprising that many biologists continued to believe that genes were either entirely protein or some combination of protein and DNA.

The problem of purification and the possible contamination of samples teaches a valuable lesson about science. Experimental results are often ambiguous and may be explained in more than one way. McCarty could never hope to attain 100 percent purity in his extracts. The acceptance of DNA as the genetic material rested upon the accumulation of evidence, only some of which was provided by Avery, MacLeod, and McCarty. For many biologists, the conclusive evidence came from later experiments, particularly the bacteriophage studies of Hershey and Chase, reported in 1952.

Other important factors also influenced the initial response to DNA. Before World War II, almost nothing was known of bacterial genetics. Bacteria were studied almost exclusively from a medical perspective. Classical genetics had developed largely around the study of *Drosophila* and other sexually reproducing organisms. There was a widespread assumption that nothing important about heredity could be learned from studying simple, asexual organisms. Even after Avery's group reported its results, one geneticist mused that although they were very interesting, it seemed unlikely that heredity in bacteria could be important because "the poor things don't have sex." As a result of this attitude, many geneticists viewed transformation as a curiosity. Ironically, much of what we now know about molecular genetics has come from studies of bacteria and viruses, but the importance of these simple organisms was not obvious to geneticists in 1944.

Finally, the time and place of the publication may have influenced the impact of the discovery. The article on DNA and transformation appeared at the height of World War II, when many scientists were engaged in war-related activities. Avery insisted that the article be published in the *Journal of Experimental Medicine*, where most of his previous work had appeared. Although this was a prestigious journal published by the Rockefeller Institute, it reached an audience made up almost exclusively of medical researchers. It was not a journal that most geneticists read. Contrast this with the rapid acceptance of Watson and Crick's article about the structure of DNA, which was published in *Nature*, one of the most widely read scientific journals in the world. Knowing your audience and publishing in the right journal are important ingredients in scientific success. Major discoveries may eventually be accepted regardless of how they are communicated, but rapid acceptance of a controversial idea may require that a large audience be quickly exposed to it.

☐ EPILOGUE

Oswald Avery was not looking for the genetic material when he began his research. At first, he was searching for ways to prevent or cure pneumonia. Why did his interests gradually shift away from medical research toward more general questions about the chemical and biological nature of transformation? Some historians suggest that finding a vaccine against pneumonia became less exciting with the rise of powerful antibacterial drugs (sulfanilamide and penicillin) during the 1930s and 1940s. As the threat of pneumonia receded, Avery became more interested in nonmedical aspects of transformation.

Eventually, other medical researchers did develop vaccines from capsular polysaccharides of *Streptococcus pneumoniae*, but they were administered only to patients at high risk of contracting the disease. For most people, the threat of pneumonia and other bacterial diseases became a thing of the past. Armed with antibiotic "magic bullets," the medical profession reduced mortality from pneumonia by over 95 percent after World War II. Has the tremendous success of antibiotic therapy led to complacency about disease-causing bacteria?

Although pneumococcal pneumonia is now relatively rare in the United States, other streptococcal infections pose major health problems worldwide. This is particularly true of *Streptococcus pyogenes*, which causes a wide variety of diseases including strep throat, one form of toxic shock syndrome, and several skin infections. In developing countries, 1 percent of all children suffer from rheumatic fever, a debilitating complication of strep throat. News reports of "flesh-eating" streptococci, which can quickly cause extensive tissue damage, have caused panic in both England and the United States. Although these sensational stories overstated the threat of the disease, they highlighted that serious streptococcal infections are not limited to the Third World. Knowing that antibiotic resistance has evolved in many disease-causing bacteria, reminds us that the need for effective vaccines did not end in the 1930s.

Avery's original interest in bacterial capsules still holds the key to discovering new vaccines. Unlike *S. pneumoniae*, whose pathogenicity is due to polysaccharides

in the capsule, *S. pyogenes* owes its pathogenicity to a specific capsular protein. Medical scientists hope to use this "M protein" as the basis for a strep throat vaccine. Developing such a vaccine will require the techniques of molecular genetics—the field that Avery and his team pioneered half a century ago. Scientists have now cloned the gene responsible for the M protein and know a great deal about the amino acid sequence of this complex protein molecule. Although parts of the molecule vary among some 55 strains of *S. pyogenes*, other regions are constant for all strains. If the constant regions can be used as antigens, perhaps vaccines effective against all strains of *S. pyogenes* may someday be developed.

QUESTIONS AND ACTIVITIES

1. What does this case show about the following aspects of doing biology?
   — relationship between pure and applied science
   — unexpected sources of discoveries
   — role of personality in scientific discovery
   — scientific teamwork
   — burden of proof and persuasion of skeptical colleagues
2. Before World War II, almost all biologists believed that genes were proteins. Why was this a reasonable hypothesis? Why did critics believe that DNA lacked the characteristics needed for carrying genetic information?
3. The accompanying table summarizes the results from chemical analyses done by Avery's group on four purified samples of transforming factor. Do these data support the claim that DNA is the transforming factor? Do these data contradict the claim that the transforming factor is protein? How might critics of DNA have interpreted these results? How can you explain the variation among the samples and the differences between the expected and observed results?

Sample	Nitrogen (%)	Phosphorus(%)	N/P Ratio
1	14.21	8.57	1.66
2	15.93	9.09	1.75
3	15.36	9.04	1.69
4	13.40	8.45	1.58
Expected results for DNA	15.32	9.05	1.69

4. Avery, MacLeod, and McCarty discovered that adding DNA-digesting enzymes to bacterial extracts destroyed their ability to cause transformation. Protein-digesting enzymes had no effect on transformation. Do these results provide conclusive evidence that DNA is the transforming factor? How might critics of DNA have interpreted these results?

5. Does the evidence presented in Questions 3 and 4 support the claim that the transforming factor is a gene? Would this evidence force critics of Avery, MacLeod, and McCarty to conclude that DNA is the universal genetic material?
6. Study the design of Hershey and Chase's 1952 experiment (it is described in most biology textbooks). How did the results of this experiment support the hypothesis that DNA is the genetic material? To what extent would the early criticisms of DNA also apply to Hershey and Chase's experiment?

SUGGESTED READING

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