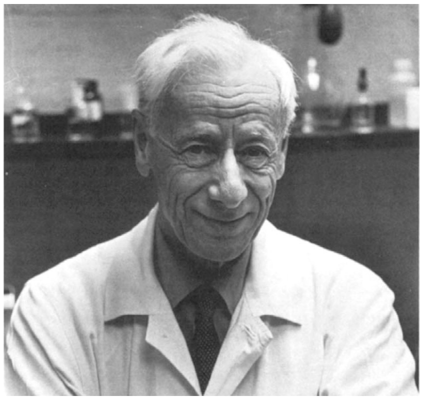
How Heidelberger and Avery sweetened immunology

In 1923, a young chemist-turned-microbiologist and his mentor made the startling discovery that bacterial sugars could be targeted by the immune system—a groundbreaking finding that helped launch the field of immunochemistry.



Michael Heidelberger.

In the early 1900s, decades before the introduction of penicillin, pneumococcal pneumonia was a major cause of illness and death for which the only effective treatment was the injection of anti-pneumococcal antisera. In 1917, microbiologists Alphonse Dochez and Oswald Avery (The Rockefeller Institute) showed that virulent pneumococcal bacteria released a "soluble specific substance," that fell out of solution when incubated with type-specific antisera (1).

All about nitrogen

Avery and Dochez's initial characterization of this pneumococcal substance showed that it was resistant to both heat and trypsin—features unbefitting most proteins—but that it did contain nitrogen, a component of proteins. But its true nature was not revealed until 1923, when Michael Heidelberger—then in the chemistry department synthesizing drugs against poliomyelitis and African sleeping sickness—teamed up with Avery.

The more they purified the reactive substance the less nitrogen it contained. When it was virtually nitrogen-free, recalled Heidelberger in a 1979 article, Avery ventured a guess: "Could it be a carbohydrate?" (2). Chemical analysis confirmed its sugary character, and subsequent studies of other pneumococcal serotypes revealed that each bacterial capsule had a distinct polysaccharide signature. It was this signature that dictated the serological specificity of the organism. The duo published these findings in two articles in the *Journal of Experimental Medicine* (3, 4).

Their results were met with considerable skepticism, as it was then thought that only proteins could incite a specific immune response. "Nobody believed it," says Emil Gotschlich (Rockefeller University), whose later work on polysaccharide-based vaccines stemmed in large part from Heidelberger and Avery's discoveries. "It took them a lot of effort to convince people that the polysaccharide was the immunoreactive component."

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Antibodies solidified

Heidelberger and Avery's discovery came at a time when antibodies were regarded—by those who believed they existed at all—as mysterious substances that floated around in serum. "It appeared to me that there was a crying need to determine the true nature of antibodies," wrote Heidelberger in 1979, "and that until this was done there could be no end to the polemics and uncertainties that were plaguing immunology" (2). Heidelberger later purified the antibodies from his precipitin reactions and showed that they themselves were proteins. As a result, says friend and colleague Victor Nussenzweig (New York University), "there were no more mystical ideas about what antibodies were."

Heidelberger and his postdoctoral fellow Forrest Kendall later quantitated the precipitin reaction (5), bringing much-needed mathematics to the study of antibody–antigen interactions and lifting antibodies even further out of the realm of the mysterious (see the next "From the Archive").

Renaissance man

Heidelberger's contributions to science were not limited to his data. He counted among his achievements the invention of the refrigerated centrifuge—an invention borne of compassion for his laboratory assistant, who was inflicted with recurrent colds due to frequent trips to the cold room to centrifuge heat-sensitive materials. Heidelberger asked the centrifuge company to build a machine with an insulated brine coil around it. He then attached the centrifuge to the hospital's circulating brine supply, which was used to cool the refrigerators and cold rooms. His profit for his (deliberately unpatented) invention was a mere 50 dollars—his fee for writing the first users' manual (2).

But it was his science that won Heidelberger recognition. His early work with Avery laid the foundation for the development of the polysaccharide-based vaccines against pneumonia and meningitis that are still administered today (6, 7, 8). Their collaboration also allowed Avery, Colin MacLeod, and Maclyn McCarty to use the changing sugar coat as a marker of genetic transformation, and thus to identify DNA as the genetic material (9).

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