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Structures: [Dr. Emil C. Gotschlich]

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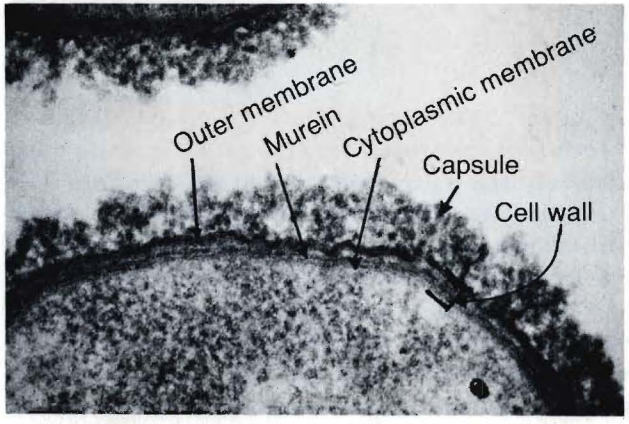

Electron-micrograph (taken by Dr. John Swanson) of a Group A meningococcus shows the capsule, enclosing the entire cell, and the cell wall, which consists of three layers: an outer membrane, a middle layer (murein) characteristic of bacterial cells, and a cytoplasmic membrane.

THE ROCKEFELLER UNIVERSITY

RESEARCH PROFILES

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Structures

In 1978, Professor Emil C. Gotschlich of The Rockefeller University won an Albert Lasker Award for Clinical Medicine for his "creative leadership in developing and then demonstrating the effectiveness of a purified capsular polysaccharide vaccine in preventing meningococcal diseases."

What the citation means is that Dr. Gotschlich's research has helped make it possible to protect millions of people around the world against a neurologically crippling and sometimes fatal disease: meningitis. With characteristically wry humor, he once described his achievement as "draft-induced"; he developed the vaccine in the late 1960s as a member of a team at the Walter Reed Army Institute of Research. His original vaccine works against one form of meningitis called Group C. A second vaccine, which he helped to test and refine, was developed for another form, Group A. At present, he is studying a third, more elusive, form, Group B.

Later this year, Dr. Gotschlich will become head of the University's world-renowned laboratory of bacteriology and immunology, which for many years has been under the co-leadership of Professors Maclyn McCarty and Rebecca C. Lancefield.* He is heir to a long and brilliant tradition. It is no exaggeration to say that the laboratory's seminal findings have profoundly influenced the course of modern biology.

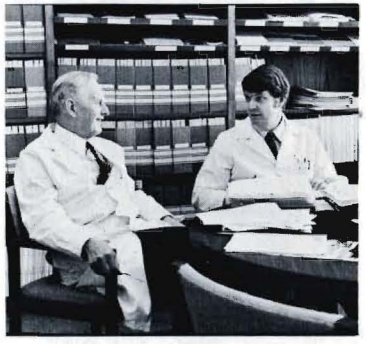
To understand something of the story behind Dr. Gotschlich's achievement—including the tongue-twisting phrase "purified capsular polysaccharide"—requires a look into the complexities of infection, immunization, and research.

Meningitis is an infection of the meninges, the membranes covering the brain and spinal cord. Its symptoms include rash, fever, convulsions, and paralysis. The meningococcal bacteria *Neisseria meningitidis* are responsible for the major epidemic forms of the disease. In any human population there may be a pool of "carriers" whose coughs and sneezes spread the infection, although they themselves experience only the symptoms of what seems to be a cold. Because of its mode of transmission, meningitis has always been a problem wherever large groups of people, especially young people, are brought together in close quarters.

Beginning in the 1940s, meningitis was successfully controlled in the developed countries by the use of the sulfanilamide drugs. But in the early 1960s, the infectious organisms began to develop drug resistance, as has happened with

Dr. Gotschlich

*Died March 3, 1981



Dr. McCarty and Dr. Gotschlich

some other diseases. In the case of the meningococci, however, the resistance soon became total and intractable. By the time Dr. Gotschlich was drafted, in 1966, meningitis was again a major military problem. It had never ceased to be a problem in the meningitis belt that cuts across Africa, as well as in parts of the Middle East, Asia, and Latin America. When attempts to find another safe and effective antibiotic failed, researchers returned to the idea of immunization.

"READY-MADE SUITS"

In the complex set of responses by which an organism defends itself against invaders such as microorganisms, the key fighters are molecules called antibodies. Immunologists seek to understand, among other things, the mechanisms by which antibodies recognize and deal with invaders, specifically the troublemaking foreign proteins and carbohydrates of the invaders called antigens.

Early in this century, Karl Landsteiner and others found that antibodies distinguish among various antigens by recognizing differences in their shapes. To engage the antigen, the antibody must, so to speak, "fit" it. Since Landsteiner's time it has been verified that the organism does not make a new antibody to order. Rather, it has an existing inventory of prototype antibodies to match a virtually limitless array of antigen shapes and sizes, including, remarkably, synthetic ones that don't occur in nature. Landsteiner, who was awarded a Nobel Prize in 1930 for the classification of blood groups, spent more than twenty years of his career at The Rockefeller.

Many years later, another Rockefeller immunologist, Professor Gerald M. Edelman, who won a Nobel Prize in 1972 for determining the chemical structure of immunoglobulin, the key molecule of immunity, described the system this way:

"Antibodies can be likened to ready-made suits. The antigen is a buyer who decides to pick a number of different suits that fit more or less well, rather than instruct a tailor to make one suit to fit him to order. To be satisfied, the buyer must patronize a store with a very large stock of suits in a great variety of sizes and styles. The immune system is like a store with an almost unlimited stock, one ready to please any possible customer. This analogy fails in one important respect: to be complete it should provide that after each somewhat different ready-made suit is picked, the manufacturer would proceed to make thousands of exact copies of it."

Switching metaphors, the antibodies lock in battle with the antigens. If and when they win, they remain alert and mobilized to recognize the invader and repulse another attack before it can begin. That is to say, the antigen-antibody matching process doesn't have to be repeated. The organism is said to have developed immunity to that infection.

A vaccine mimics the process of natural immunity. It must contain the disease antigens, to stimulate production of antibodies, but in a quantity or form that does not cause disease. Vaccines are usually made from killed or weakened infectious organisms or from a related or benign form. An example of the latter is the use of cowpox virus to confer immunity against smallpox.

SUGAR-COATED PROBLEM

But for some diseases, meningitis among them, this classical, whole-organism approach doesn't work. To create his vaccine, Dr. Gotschlich had to find, isolate, and purify the specific antigen molecules, which, in the case of the meningococci, are contained in a coating of material that surrounds, or encapsulates, each bacterium. This coating is composed of complex carbohydrates called polysaccharides, poly meaning "many" and saccharide referring to sugars or carbohydrates.

Purified capsular polysaccharide vaccines like Dr. Gotschlich's, and like one developed against pneumonia by Dr. Robert Austrian of the University of Pennsylvania School of Medicine, have been hailed as the first of "a new era of bacterial vaccines." In fact, most of the basic research that made

them possible began many years ago at the research hospital of what was then The Rockefeller Institute for Medical Research, in work by Oswald T. Avery and Michael Heidelberger, among others. (Dr. Heidelberger, now professor emeritus at New York University, and Dr. Austrian shared the Lasker Award with Dr. Gotschlich.)

Avery, who died in 1955, is remembered today primarily for demonstrating that DNA—deoxyribonucleic acid—is the chemical substance of genes. Avery was a bacteriologist who did most of his experimental work with a single bacterial species, *Streptococcus pneumoniae.* The virulent forms of pneumococci, like meningococci, are covered by polysaccharide capsules. It was Avery, Heidelberger, and Professor Walther F. Goebel, now emeritus, who established in the 1920s that the polysaccharides of the capsules were the specific antigenic determinants in the immunological process. That finding made possible the development of the first vaccine against bacterial pneumonia. Its effectiveness was demonstrated in an epidemic in a military population, but because of the success of new antibiotic therapy, the development of Dr. Austrian's more broadly applicable vaccine was delayed for many years.

The abandonment of earlier efforts to develop vaccines was not capricious. As previously mentioned, diseases like pneumonia and meningitis are caused by many types of organisms. No one vaccine has yet been achieved that works against all forms. Antibiotics appeared to solve that problem. In that sense, they truly were miracle drugs and, for many diseases, still are.

Regarding the meningococci, Dr. Gotschlich states: "As early as the 1930s, polysaccharide material had been isolated and purified with the idea of a vaccine; but by the time I came to Walter Reed, those little bottles of white powder didn't exist anymore. When we first geared up, we really knew nothing about the antigenic structures of the different groups of bacteria. We had to go back and re-establish the benchmarks."

The immediate goal of Dr. Gotschlich's team, which included the late Dr. Malcolm S. Artenstein, who was director of bacteriology at Walter Reed, and Dr. Irving Goldschneider, now at the University of Connecticut Medical School, was a vaccine against Group C meningitis.

"If you define an organism as being Group A or B or C," Dr. Gotschlich explains, "you do it with an antiserum—a serum containing antibodies. But unless you know what the antigen *is* you don't know what your antiserum actually 'sees'. So that was our first job—to determine the antigenic structures and then test them for their ability to induce antibodies."

The initial laboratory work—isolation, purification, testing—took two years to complete. A period of careful trials and refinement followed: in making vaccines, the determination of dosages and mode of administration is very important. The vaccine was found to be almost completely effective in preventing the spread of Group C meningitis. It is now routinely administered to all American military personnel and has been used elsewhere to counter sporadic outbreaks. Group A vaccine, based on the C prototype, has also proved successful in large-scale field trials in Africa and other areas. In 1975 it was administered to the entire population of Finland to stop an epidemic. It has also been used in Brazil.

THE SUM OF INTERACTIONS

Emil Gotschlich had planned on a career in medicine like his grandfather, father, and mother. Born in Bangkok in 1935, where his parents were practicing, he came to the United States in 1950. He did his undergraduate and medical training at New York University and earned his M.D. in 1959.

"I was in my second year in medical school," he recalls, "when I discovered research, and I never looked back. There was a really unusual constellation of people at NYU, Lew Thomas and Al Stetson especially. They generated a sense of enormous excitement in the pathology department, where

students were given the chance to be involved in research projects in a remarkable way."

Rockefeller Trustee Lewis Thomas, who later became president of Memorial Sloan-Kettering Cancer Center where he is now chancellor, and the late C.A. Stetson, Jr., had both worked early in their careers at The Rockefeller. Stetson did his postdoctoral training with Dr. McCarty, one of the world's leading authorities on streptococci and rheumatic fever. In his own early years at The Rockefeller, Dr. McCarty had been the junior member of the team, with Avery and the late Colin MacLeod, that made the landmark DNA discovery.

Dr. Gotschlich joined Dr. McCarty's laboratory in 1960. He was interested at that time in the C-reactive protein, a substance that appears in the blood of patients during the acute phase of certain infectious diseases and is a useful index of the progress of infection. It is called C-reactive because it interacts with a substance known as C-polysaccharide. The chemistry of C-polysaccharide was then unknown, and its determination was Dr. Gotschlich's first research accomplishment, in collaboration with Teh-Yung Liu, a member of the biochemistry laboratory of Nobel Laureate Stanford Moore.

"From that work," he says, "I began to get a feel for how to deal with polysaccharides and that was, in large part, my preparation for the project at Walter Reed."

For the past several years, back at his Rockefeller lab, Dr. Gotschlich has been grappling with the "far more baffling" question of Group B, another epidemic form of meningococcal meningitis.

"You can prepare Group B polysaccharide, you can characterize it, you know exactly what it is, but the problem is, you inject it into a hundred people and only two of them will form antibodies. So you know that the Group B polysaccharide can be antigenic but in most people does not raise their antibody level.

"The polysaccharide consists of many units of sialic acid, a sugar which is present in human tissues. If you think of the polysaccharide molecules as a string of beads, then antibody usually recognizes each pearl or perhaps a few contiguous pearls, the antigenic determinant. But we don't know what the antigenic determinant is in the case of Group B polysaccharide, because when we break the string of beads into pieces we find a bunch of beads, but none of them reacts with the antibody. So the determinant, the pearl, must be in the way the polysaccharide folds and packs."

Although the meningococci engage most of his bench time, Dr. Gotschlich also supervises and collaborates in the research of graduate students and other junior colleagues. The University's students, all Ph.D. candidates, are working scientists. Among current projects are studies of the gonococci, the bacteria of gonorrhea, and the streptococci, which cause both strep infections and some endemic (nonepidemic) forms of meningitis.

Coccal, or round, bacteria are related to one another, but they differ in important ways. For example, it was discovered that the gonococci have little hairlike projections on their surface called pili, which are long strands of proteins existing in many forms and shapes. This finding, reported almost simultaneously by Dr. Gotschlich's lab and a group elsewhere, led to research which showed that the pili are the means by which the bacteria adhere to the host and cause virulence. The task now—the search for the pearl—is to go deeper into the molecular structure of the pili to learn how to interfere with the progress of gonococcal infection.

Dr. Gotschlich is a clinical scientist eager to help cure disease. He is also a biologist fascinated with nature's complex and challenging design.

"I like to think about it structurally. I like to figure out how a particular structure on the bacterium interacts with particular structures of the host for a particular effect. That's the fun. And then one hopes that understanding the sum of these interactions will help explain how disease occurs and, ultimately, point us in the direction of knowing what to do about it." □

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