SIFTING PROTEINS: Connaught and the Discovery of Starch-Gel Electrophoresis

Some forty years ago Connaught Laboratories was the site of a highly significant discovery that has had a major impact upon the understanding of the fundamental proteins that make up all life. This involved a new method of high resolution protein analysis known as “Starch-Gel Electrophoresis,” developed by Dr. Oliver Smithies. It enabled complex protein mixtures, such as human blood sera, to be much more finely sifted into their basic molecular components using a starch-gel medium in an electric field. Such a fortuitous discovery was made possible by the unique research and production environment of Connaught while it was part of the University of Toronto, coupled with a flash of inspiration drawn from Dr. Smithies’ childhood.

In 1953, Smithies was hired by Connaught to assist with D.A. Scott’s insulin research in the School of Hygiene Building. Dr. Scott, who had worked on the initial mass production of insulin at Connaught in the 1920s, gave Smithies freedom to study anything he wished, as long as it related to insulin. As Banting had been, Smithies was particularly interested in searching for the precursor to insulin. For this he turned to a new method of protein analysis known as “zone electrophoresis” using filter paper. However, insulin did not cooperate; it stuck to the filter paper; and Smithies looked for something better.

On January 23, 1954, Smithies happened to visit the nearby Hospital for Sick Children where he saw a new zone electrophoresis method based on starch grains in which protein molecules passed between the grains. Unlike with filter paper, the proteins were not absorbed by the starch. For Smithies, however, managing this elaborate method in Scott’s small lab was impossible. Yet the idea of using of starch sparked a strong memory in Smithies of when he was a 12-year-old boy and watched his mother starching laundry.

The starch she had used was liquid when hot but turned to a jelly when cooled. Smithies immediately thought that if he cooked some starch and let it cool, the proteins might migrate through the resulting gel in response to an electric current. Smithies’ inspiration might well have been unsuccessful if he had not found a lone bottle of “Starch According to Lintner” that happened to be in one of Connaught’s chemical storerooms. Moreover, this starch happened to be just suitable to produce a useful gel when cooked and cooled. Later that same January day, Smithies conducted his first starch-gel experiment with insulin. The results seemed very promising since the insulin did not stick to the starch.

Two months later, Smithies tried a starch-gel experiment using human blood serum. After this “rough test” he was excited to find that his method had clearly separated out 11 serum protein components where only 5 had ever been seen before. This led Smithies to study the blood serum of many individuals and families and he discovered that there were clear genetic differences that fell into three distinctive groups. Smithies was next able to precisely identify the many previously unknown components of human blood serum and the starch-gel method had sharply revealed. He used a two-dimensional starch gel and filter paper method he devised with M.D. Poulik from the School of Hygiene. The high resolution of this method, which is able to sift proteins at the molecular level, could now differentiate 20 components in human blood serum. Today, a far more refined two-dimensional method can resolve over 750 components!

Smithies developed the starch-gel method further at Connaught between 1955 and 1959 and clearly demonstrated its utility as a valuable tool for biochemical research and diagnostic investigations in hospitals. Out of this work, Connaught began supplying hydrolyzed starch for starch-gel preparations, and later published a still in demand, though long out-of-print, Starch-Gel Electrophoresis Bibliography. By 1959, after a very happy period in his life at Connaught, Smithies returned to Wisconsin and later moved to the University of North Carolina, where he remains very active today in the area of gene targeting. Dr. Smithies is also a current member of Connaught’s Scientific Advisory Committee.

This article is the second in a series called “Connaught’s Healthy Heritage” written for CONNTACT.

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