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 serums, 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 the starch-gel method had sharply revealed. He used a two-dimensional starch gel and filter paper method he devised with **M.D. Poulik** of 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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