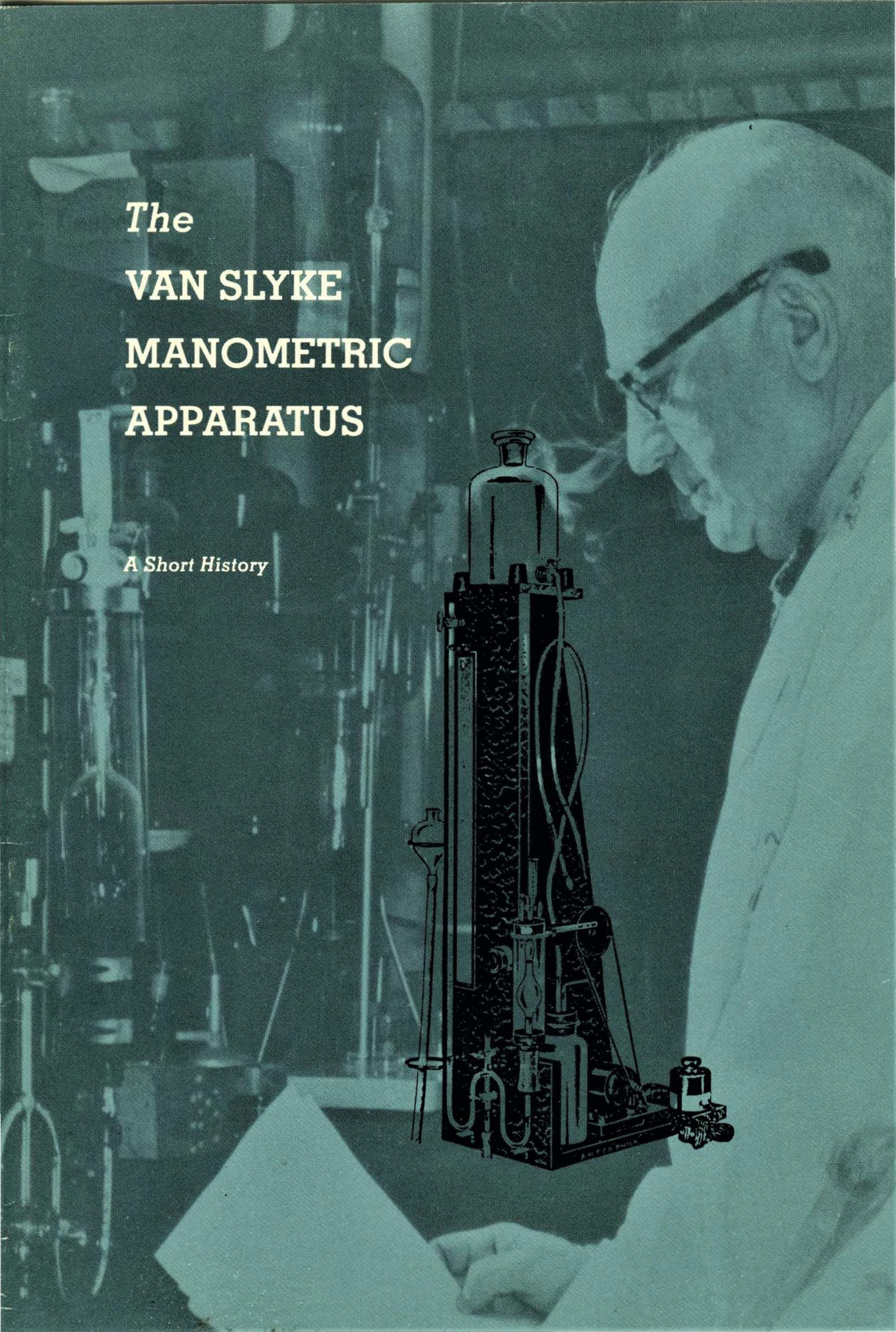
The VAN SLYKE MANOMETRIC APPARATUS

A Short History



Donald D. Van Slyke

Throughout history mankind has wondered about the nature of blood. What kind of fluid was it? Why was it necessary for life? What did it do inside the body? The Van Slyke manometric apparatus helped to advance our understanding of the chemical and physiological role of blood in health and disease. Best described as a "quantitative gas analyzer," the Van Slyke instrument determined the amount of a given substance in the blood or other fluid by measuring the small volume of gas released during a chemical reaction. The first instrument of this type was used in 1921 and was initially reported and described in the *Journal of Biological Chemistry* in 1924 (vol. 61, pp. 523-584). The term "manometric" referred to the liquid-filled glass column used as a measuring device.

The Van Slyke apparatus is particularly interesting because of its influence on the history of biomedicine. In the early part of the twentieth century, scientists and physicians sought to integrate laboratory techniques with clinical practice in order to make medicine more scientific. Their efforts were predicated on the dictum of William Thompson, Lord Kelvin, a nineteenth-century British physicist, who stated: "When you can measure what you are speaking about and express it in numbers, you know something about it." The Van Slyke apparatus enabled physicians for the first time to obtain reliable quantitative data on the physiologic status of their patients. It thus not only reflects the interrelationship between basic research and clinical practice, but also illustrates how technological advances can open new fields of basic research. Moreover, at a time when contemporary biomedical research laboratories abound with amino acid analyzers, immunofluorescence analyzers, mass spectrometers, spectrofluorometers, and computers, the Van Slyke instrument demonstrates how analytical research was carried out before the advent of electronics. Surprisingly complex analytical studies could be performed using only simple materials such as wood, glass, rubber tubing, and few chemical reagents. The Van Slyke apparatus attests to the power of human ingenuity.

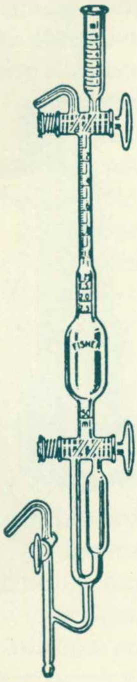
Background to Development

Credit for the concept of the apparatus belongs to Donald D. Van Slyke of the Rockefeller Institute for Medical Research (now called Rockefeller University). Two other people, however, also made a significant contribution to its development and construction. James M. Neill, also of the Rockefeller Institute, collaborated with Van Slyke on this effort and did so much of the work of testing and refining the instrument that some references refer to the device as the Van Slyke and Neill apparatus. John Plazin, who served as Van Slyke's technical assistant, constructed the first manometric device and performed many of the studies used in developing the gasometric methods. Plazin personally directed the construction of the apparatus in this exhibit.

Van Slyke received his Ph.D. in organic chemistry from the University of Michigan in 1907. He planned to follow his father's footsteps and become an agricultural chemist; however, a serendipitous encounter between his father and a chemist from the Rockefeller Institute redirected the young man's focus. During his early years at the Rockefeller, Van Slyke developed quantitative methods to measure amino groups through chemical reactions involving the release of gaseous nitrogen. His techniques made possible analysis of amino acid concentration in blood and other biological fluids and revealed his talent for applying physical laws and analytical chemistry to biological problems.

In 1914 Van Slyke was named chief chemist of the newly opened hospital of the Rockefeller Institute. In combating disease, this hospital used an approach very similar to that adopted at the NIH Clinical Center: uniting basic science with clinical research. Until this point, there were few examples of an organized attempt to apply the techniques of physical and organic chemistry to medical problems.

Fig. 1 Van Slyke Volumetric Blood Gas Device



After he assumed the duties of hospital chemist, Van Slyke began collaborating with Frederick M. Allen, who was studying diabetes. Before the advent of insulin, physicians sought other ways to control the blood sugar levels of their diabetic patients, and Allen utilized low caloric diets to this end. The treatment met with some success but, unfortunately, putting patients on a virtual starvation diet led to serious complications. With no overt clinical signs, patients developed acidosis and lapsed into a fatal coma (acidosis is a pathological condition resulting from the accumulation of acid in the blood or body tissues). Van Slyke speculated that if a means could be found to monitor blood pH – the acidity or alkalinity of the patient's blood – the patient's diet could be adjusted to avoid the onset of acidosis and its fatal sequelae.

Van Slyke and his assistant Glenn E. Cullen decided that the best approach to the problem would be to monitor the levels of the patient's plasma bicarbonate as a means of tracking the pH level of the patient's blood. They devised a technique, using a small glass apparatus that became known as the "volumetric" device (see Fig. 1). The instrument was read by noting the actual volume of gas released from a blood sample. The innovative technique worked, preventing further deaths from acidosis.

Because of its success, the volumetric device was quickly adopted by hospitals and clinical research laboratories across the country. Monitoring a patient's condition by chemical analysis, as opposed to clinical observation, opened new doors for understanding disease. For example, researchers involved with respiratory diseases found that the instrument could be used to track blood oxygen concentrations as new treatments were explored.

Development of the Manometric Device

In 1920 Lawrence J. Henderson of the Harvard Medical School and his associates had begun to investigate blood as a physicochemical system, attempting to understand the role of hemoglobin in the transportation of oxygen and carbon dioxide and the chemical interplay between red blood cells and plasma. Their studies, however, were hindered because they lacked methods accurate enough to test their theories. Recognizing Van Slyke's success in investigating the acid-base balance of the blood, Harvard and the Rockefeller Institute began to collaborate in this effort. Franklin C. Mclean left Harvard and joined Van Slyke's team to explore these questions.

Van Slyke realized that exact measurement of the chemical constituents of blood would require an instrument more accurate than the volumetric device. In order to improve its sensitivity, Van Slyke focused on the weakness of the volumetric technique: the bubble of gas resulting from the chemical reaction was often so small that, when measured at standard atmospheric pressure, the change in volume was extremely difficult to read on a graduated scale. The error in measuring the volume was 10-100 times as great as the degree of error in measuring the pressure. Because the analysis was dependent on the accuracy of both numbers, reducing the error in reading the volume of gas would improve the overall accuracy of the instrument.

The new instrument was designed in such a way that the volume of the gas in the reaction chamber was controlled by a mercury vacuum. The operator kept the volume of gas set at a constant level, usually .5, 2, or 50 cm (you can see these levels marked on the reaction chamber in the exhibit.) This allowed

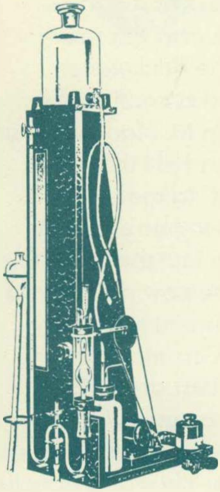


Fig. 2 Van Slyke Manometric Apparatus

accurate pressure measurement to enhance the accuracy of the delicate gas volume measurements. This technical refinement improved sensitivity almost 10-fold over the volumetric device. Another advance was the incorporation of a glass water jacket around the reaction chamber. This ensured that the temperature would remain constant during the experiment, eliminating temperature variation as a factor affecting the analysis. An illuminated panel was added behind the manometric scale as an aid in reading the change in the level of the meniscus. A large glass bottle on the top of the instrument was filled with distilled water for flushing the reaction chamber between each reading.

With the manometric instrument, Van Slyke and his collaborators made significant advances in understanding the interrelationships between the different gases in blood and tissues, the role of water and electrolytes, and the nature of the acid-base balance of blood. Further, the apparatus was applied to many other areas of investigation, including studies involving carbohydrates, fats, proteins, amino acids, calcium, and many other compounds that play important roles in human physiology. Over the next forty years, the Van Slyke manometric apparatus found its way into clinical and research laboratories around the world. One observer noted that "the Van Slyke manometric apparatus was almost all the special equipment needed to perform most of the clinical chemical analysis customarily performed prior to the introduction of photocolorimeters and spectrophotometers for such determinations."

Although at one time ubiquitous, the apparatus was eventually displaced by more advanced electronic analyzers. There are few surviving examples of this instrument today.

Facts about the Van Slyke Apparatus in This Exhibit

This instrument was donated to the Stetten Museum by Rollin D. Hotchkiss, Professor Emeritus, Rockefeller University, who used it for 15 years, between 1941 and 1956, in studies on deoxyribonucleic acid (DNA). It was constructed expressly for Dr. Hotchkiss at the shops in the Rockefeller Institute in 1941. His efforts helped to confirm the findings of Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarthy, who showed in 1944 that the bacterial "transforming agent" (a material that conferred properties, unique to one strain of bacteria, to another strain) was in fact the material responsible for heredity – what we now call "genes." Dr. Hotchkiss also used this instrument to identify and measure the composition of Gramicidin, the first peptide antibiotic. Between 1961 and 1968, Dr. Hotchkiss served on advisory councils for the National Institute of Allergy and Infectious Diseases and the National Cancer Institute. He was a Scholar-in-Residence from 1971 to 1972 at the Fogarty International Center.

For Further Information on This Subject

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Hastings, A. Baird. "Donald Dexter Van Slyke." *Journal of Biological Chemistry* 247 (1972): 1635-1640.

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Hawk, Philip B. *Practical Physiological Chemistry*. Philadelphia: Blakiston, 1947.

The DeWitt Stetten, Jr. Museum of Medical Research collects and exhibits biomedical research instruments and other artifacts relating to the history of the National Institutes of Health. Questions concerning this exhibit should be directed to Dennis Rodrigues, Curator, 301/496-6610.