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# PHILIP ANDERSON SHAFFER

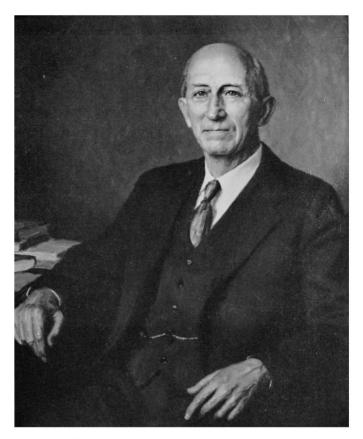
# 1881—1960

A Biographical Memoir by EDWARD A. DOISY

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Biographical Memoir

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Philips a. Shapper

# PHILIP ANDERSON SHAFFER

September 20, 1881–December 4, 1960

# BY EDWARD A. DOISY

Philip ANDERSON SHAFFER was born in Martinsburg, West Virginia, on September 20, 1881. His ancestors on his mother's side had lived in the Shenandoah Valley from pre-Revolutionary War days and on his father's side from 1795. His grandfather, Philip Anderson, was a physician who studied medicine in Philadelphia and upon completion of his studies received a diploma signed by Dr. Weir Mitchell. Apparently inspired by Dr. Mitchell, he stayed in Philadelphia several years for more experience and training and subsequently took a year of graduate work at the University of Virginia. He returned to the Shenandoah Valley, married Mary Dyer, and engaged in the practice of medicine.

The eldest daughter of Dr. Philip Anderson, Hannah, had attended a finishing school and at the time of her marriage to Joseph Shaffer in 1880 she was teaching music in a school in Winchester. The newly wedded couple began married life in Martinsburg, West Virginia, and Philip Anderson Shaffer was born in 1881. It appears that the achievements of his grandfather in medicine, which were recounted in the family circle during his early life, played an important role in his later choice of a profession.

The author is indebted to Mrs. Nan Evans Shaffer for her

authoritative statements regarding the early life of her husband, Philip. She has supplied the following paragraphs, which in a few instances have been slightly altered.

"Philip's father did not have the scholarly background of his grandfather, Dr. Anderson, but possessed a keen mentality and was a well-read person. His personality contained some of the traits we have so admired and enjoyed in Philip Shaffer, a quiet iron-strong gentleness and forthrightness. He had excellent judgment, was consulted by various business interests, was a director of the bank, and, almost incidentally, ran his store that amounted to a wholesale outlet for the area.

"A young clerk in that store was greatly interested in the Shaffer boy, and before Philip Anderson Shaffer was three years old had him plunked on the end of one of the old black-walnut counters learning to read from the Baltimore *Sun* and having great fun doing it. When Philip was of the age to start school he could read almost anything and was terribly bored by school because when the other youngsters were struggling with something new he had nothing new to do. The teacher finally reported to the parents that Philip was a most unsatisfactory child. So he was sent to Miss Betty Wilshire's private school. At Miss Betty's the placing of a pupil depended upon his ability to read: Philip could read anything so he went on being jumped over classes in arithmetic, geography, even spelling, and entered public schools again with the same boredom as before.

"There happened to be a new teacher in the Martinsburg High School, A. B. Carmen, recently graduated from Harvard University. He became acquainted with the boy through contacts other than school, and was convinced that here was a student who, if not superior, was at least different, and he 'took' him on, tutored him, engineered him into and out of high school by intricately shifted courses, and helped him enter the University of West Virginia while he was still fifteen years old—a little before his sixteenth birthday. "In anticipation of entering the University of West Virginia, Philip went to Harper's Ferry to ask the proper officer for cadet appointment. He received it, and with great pleasure told the family and Carmen what he had done. When he entered the University it was in a cadet uniform. Then came the Spanish-American War. Philip, a cadet, was eager to fulfill his obligations and march off to war with other students. His age, however, made it necessary to submit written permission from his parents; this they refused to give, very much to Philip's 'humiliation and chagrin,' and he remained in college."

At the beginning of his junior year he encountered a newly appointed teacher of chemistry, Otto Folin, who had just returned from his studies abroad. Dr. Folin had become interested in medical chemistry but could not find a suitable position in this type of work in the United States. This was very fortunate for Philip Shaffer, as their association led him into biochemistry under the tutelage of Dr. Folin and to an enduring friendship.

Dr. Folin gave courses in quantitative analysis and physiological chemistry. Philip Shaffer took both courses and was particularly interested in the latter. Since equipment was meager many of the experiments were omitted. Apparently this was a stimulus to thinking and theorizing, and Philip must have demonstrated that he was the most promising of the students because he was chosen to accompany Dr. Folin to a newly established position in the McLean Hospital in Waverly, Massachusetts.

The McLean Hospital had a forward-looking director, Dr. Cowles, who not only established this research laboratory to learn if body chemistry had a connection with mental health but also provided an extensive library for the staff. A professional librarian, Nan Jefferson Evans, who later became Mrs. Shaffer, was employed.

Dr. Folin, with his young associate, Philip Shaffer, who had just graduated from the University of West Virginia at the age of nineteen, undertook the study of chemical changes in relation to mental health but soon found that the available analytical methods were not satisfactory. The preliminary work consisted of improvements in procedures for the determination of urinary constituents; the improved methods were used in the work which was published in 1904: "Some Metabolism Studies, with Special Reference to Mental Disorders."

During his work at McLean Hospital Philip demonstrated ability in research, but in spite of his pleasant association with Dr. Folin he decided to take the year of residence required by Harvard University to obtain the doctorate. Therefore, at the opening of Harvard in the fall of 1903 he left the hospital and in June 1904 received the first Ph.D. degree in physiological chemistry ever given by Harvard University. The next day he was married to Nan Jefferson Evans, the librarian of McLean Hospital.

Several industrial positions with good salaries were offered him but only one research place, in the Loomis Laboratory in New York City, a part of Cornell Medical College, Department of Experimental Pathology. The salary of \$85 per month was not attractive but his bride, knowing that his heart was in medical research, encouraged him to accept it. The confidence which she had in his investigative ability was justified, as demonstrated by his appointment to the chair in physiological chemistry at Washington University School of Medicine (St. Louis) six years later.

Of the publications from the Loomis Laboratory, those on the study of the metabolism of typhoid patients were of the most interest. After some discouragement, Philip finally obtained the cooperation of a physician, Dr. Warren Coleman. Together they demonstrated that by feeding a high caloric diet containing a liberal quantity of protein a positive nitrogen balance could be obtained, thereby preventing the loss of body protein. In some instances patients on this diet actually gained weight.

There were other lifelong results of this time in New York. Since his papers in biochemistry had already attracted attention, Philip was invited to attend the preliminary meeting which was called for the organization of the American Society of Biological Chemists. He was one of the twenty-nine who founded the Society in 1906. As a charter member, he was asked to share in the program of the fiftieth anniversary of the Society.

Undoubtedly it was his notable work on typhoid fever that brought consideration of his name when, under Robert Brookings' farsighted direction, a complete reorganization of Washington University Medical School was being undertaken, and undoubtedly it was the galaxy of young and open minds he would be associated with that induced him to accept the offer to head the Department of Biochemistry and to take his place on the "Executive Faculty" (an entirely new idea). Philip Shaffer was the youngest of the new departmental chairmen-he was twentynine at the time of his appointment. In September 1910 he moved his family to St. Louis and joined wholeheartedly in the development of the Medical School. To this end he thereafter devoted his life, often sacrificing his personal preferences or scientific advancement in taking on administrative burdens to maintain the standards which the original Executive Faculty had worked so hard to establish.

Robert Brookings wisely decided to assemble an excellent faculty before undertaking the building of physical facilities for the developing Medical School. Philip Shaffer, together with his staff, Dr. Walter Bloor and Dr. W. McKim Marriott, the newly organized Department of Biochemistry, began teaching in 1910 in the old buildings. Judging by the papers published, the surroundings did not interfere with research.

The Executive Faculty continued planning for the new buildings, which were soon (1912) under construction and were completed in 1914. One of the first national scientific gatherings held in them was the ninth meeting of the American Society of Biological Chemists, which was held on December 27-30, 1914. Philip, who was the secretary of this scientific body, presented a paper during the meeting.

In 1915 he became dean of the Medical School, an office which he held until 1919. When the United States entered World War I, he felt the call of duty and served as a major in the Food Division of the Sanitary Corps from 1917 until 1919. The bibliography below bears eloquent testimony to his absence from the laboratory and the result of his return to scientific work during the latter part of 1919.

During his first term as dean, several brilliant young men were brought to Washington University to head departments in the full-time program in which the Medical School had embarked. Dr. W. McKim Marriott, formerly in the Biochemistry Department, was appointed to the chair in pediatrics in 1917, and Dr. Evarts Graham to the chair in surgery in 1919.

Although Philip's first term as dean ended in 1919, he continued as a member of the Executive Faculty and later served as dean from 1937 to 1946. During his entire association with Washington University, Philip was actively engaged in the quest of promising young men for the Medical School. He played an important role in the appointments of Dr. David P. Barr and, subsequently, Dr. W. Barry Wood in medicine, Dr. Willard M. Allen in obstetrics and gynecology, Dr. E. K. Marshall, Dr. Herbert S. Gasser, and later Dr. Carl Cori and Dr. Gerty Cori in pharmacology. Two medical students who subsequently became chairmen of departments, Dr. Alexis F. Hartmann in pediatrics and Dr. Carl V. Moore in medicine, were encouraged to devote their lives to teaching and investigation by their accomplishments in research in Philip's department during their undergraduate days in the Medical School.

In addition to his outstanding service to Washington Univer-

sity in its development of the Medical School, Philip Shaffer was very active in the affairs of the American Society of Biological Chemists, Inc. He served the Society with such distinction in several offices—councillor for six years, secretary for two, vice president for two, president for two, and many years as chairman of the Editorial Board—that in later years he was frequently referred to by his contemporaries as the Dean of American Biochemistry. At the meeting celebrating the fiftieth anniversary of the founding of the Society, he presented a paper, by invitation, entitled "Origin and Development of the American Society of Biological Chemists." This provided a fine opportunity to review the accomplishments of biochemistry, a review that strongly supported the prophetic statement he had made in his introductory lecture to the freshmen medical students in 1914: "Most of the advances in medicine will come through biochemistry."

Philip Shaffer's first scientific paper, "Ueber die Quantitative Bestimmung der Harnsäure im Harn," was published in 1901 with Otto Folin as the senior author. Most of his subsequent papers for the next few years were studies based on the analysis of urine. While he was at the Loomis Laboratory of Cornell University Medical School his studies led to his proposal of the revolutionary idea, at that time, of a high caloric diet for typhoid patients. Together with Warren Coleman, he clearly demonstrated that this was an important innovation in the care of typhoid patients. After he moved to St. Louis, his publications dealt mainly with methods for the determination of components of urine and blood. One of these, on the determination of blood sugar, was the cause of his continuing interest in the subject and led to a consideration of diabetes. A series of papers based both on balance studies previously published by others and on his own experiments was published under the general heading "Antiketogenesis." With his interest in the metabolism

of diabetes already developed he was ready, after the announcement of the preparation of insulin by Banting, Best, Collip, and Macleod, to see this new product used in the Pediatrics Department of Washington University School of Medicine in the treatment of a diabetic baby. Since insulin could not be supplied by the Toronto group, he hurriedly started the extraction of it from beef pancreas. The first preparation proved to be effective in tests on animals and relieved the severe symptoms of diabetes in the baby. Continuation of the extraction, purification, and characterization of insulin led to (1) the use of sufficient strong sulfuric acid to ensure inhibition of tryptic activity, (2) the discovery of isoelectric precipitation of insulin for its purification, and (3) recognition of the protein nature of highly purified insulin.

The deanship and other administrative duties again interfered with scientific work so much that in his later years publication was less frequent. However, he was intrigued by oxidationreduction reactions and published under the general title "Equi-valence Change Principle." He found that reactions between ions in which valence changes were not equal proceeded very slowly unless catalyzed by stepwise transfer of electrons.

Philip was a kind, thoughtful, and considerate man. His analytical mind enabled him to come promptly to a conclusion which he expressed forcefully. On one occasion, during a discussion on the changing of the time of the meeting of the American Society of Biological Chemists from winter to spring, he listened attentively to the other speakers. Then he finished the discussion by saying, "How can anyone be opposed to the change; this is a group of experimentalists. If we make a change and don't like it, we can revert to the winter meeting." The vote for the change was affirmative and after forty years the meetings are still held in the spring.

The writer and Philip were close friends for forty years.

Each of us discussed many problems with the other; this was beneficial to me because of Philip's capacity to think clearly. In fact, his friendship was so enjoyable that almost invariably my wife and I helped him celebrate his birthday by a call to deliver a small token of our affection.

On many occasions Philip stated, "I am enjoying what I am doing so much that if I could afford to do so I would be happy to pay Washington University for the privilege of doing just what I am doing."

In 1946 Philip Shaffer was given the title Distinguished Service Professor of Biological Chemistry by Washington University, a title amply warranted by his accomplishment in biochemistry and his devoted service to Washington University. He became an emeritus professor in 1952 but continued his laboratory work as long as his health permitted. After several months of hospitalization, Philip A. Shaffer passed away on December 4, 1960.

# BIBLIOGRAPHY

#### KEY TO ABBREVIATIONS

Am. J. Physiol. = American Journal of Physiology

J. Am. Chem. Soc. = Journal of the American Chemical Society

J. Biol. Chem. = Journal of Biological Chemistry

Washington Univ. Med. Alum. Quart. = Washington University Medical Alumni Quarterly

Z. physiol. Chem. - Hoppe Seyler's Zeitschrift für physiologische Chemie

## 1901

With Otto Folin. Ueber die Quantitative Bestimmung der Harnsäure im Harn. Z. physiol. Chem., 32:552-72.

# 1902

With Otto Folin. On phosphate metabolism. Am. J. Physiol., 7:135-51.

#### 1903

On the quantitative determination of ammonia in urine. Am. J. Physiol., 8:330-54.

#### 1904

With Otto Folin. Some metabolism studies. With special reference to mental disorders. American Journal of Insanity, 60: 699-732; continued in 61:299-364.

### 1905

- With B. H. Buxton. Enzymes in tumors. Journal of Medical Research, 8:543-54.
- With S. P. Beebe. The chemistry of malignant growths. IV. The pentose content of tumors. Am. J. Physiol., 14:231-38.
- Some observations on the enzyme catalase. Am. J. Physiol., 14: 299-312.
- With Loring Jackson. The action of methyl alcohol on hexabromorthoquinopyrocatechin ether. American Chemical Journal, 34:460-67.

- With B. H. Buxton. Die Agglutination und Verwandte Reaktionen in Physiologischer Hinsicht. I. Z. physiol. Chem., 57:47-63.
- Metabolism experiments upon a woman with a permanent biliary fistula. Am. J. Physiol., 17:362-91.

### 1907

Protein metabolism in exophthalmic goitre. J. Biol. Chem., 3: xiii-xiv.

### 1908

- With C. G. L. Wolf. Protein metabolism in cystinuria. J. Biol. Chem., 4:439-72.
- Diminished muscular activity and protein metabolism. Am. J. Physiol., 22:445-55.
- Metabolism in typhoid fever. Journal of the American Medical Association, 51:974-78.

The excretion of kreatinin and kreatin in health and disease. Am. J. Physiol., 23:1-22.

A method for the quantitative determination of  $\beta$ -oxybutyric acid in urine. J. Biol. Chem., 5:211-23.

## 1909

The destruction of body-protein in fever. J. Biol. Chem., 6:xxvii.

With Warren Coleman. Protein metabolism in typhoid fever. Archives of Internal Medicine, 4:538-600.

### 1910

- With E. A. Reinoso. Note on the determination of kreatinin. J. Biol. Chem., 7:xiii-xiv.
- With E. A. Reinoso. Do muscle and blood serum contain kreatinin? J. Biol. Chem., 7:xxx.

# 1912

Note on a new salt of  $\beta$ -oxybutyric acid. J. Biol. Chem., 11:xi.

# 1913

With McKim Marriott. The determination of oxybutyric acid. J. Biol. Chem., 16:265-80.

- The effect of glucose on autolysis: a possible explanation of the protein-sparing action of carbohydrates. J. Biol. Chem., 17: xlii-xliii.
- Observations on creatine and creatinine. J. Biol. Chem., 18:525-40.
- On the determination of sugar in blood. J. Biol. Chem., 19:285-95.
- On the normal level of blood-sugar of the dog. J. Biol. Chem., 19: 297-302.

# 1915

With R. S. Hubbard. The level of blood sugar in the dog. J. Biol. Chem., 20:xxxiv.

# 1916

With R. S. Hubbard. The determination of  $\beta$ -hydroxybutyric acid. J. Biol. Chem., 24:xxvii.

### 1920

With Otto Folin and A. P. Mathews. Report on the teaching of biochemistry. Association of American Medical Colleges, 30: 107-14.

- Further observations on the mechanism of the ketolytic (antiketogenic) action of glucose. J. Biol. Chem., 46:vi-viii.
- Metabolism in diabetes from the standpoint of antiketogenesis. Proceedings of the Washington University Medical Society, December 12, p. 2.
- With A. F. Hartmann. The iodometric determination of copper and its use in sugar analysis. I. Equilibria of the reaction between copper sulfate and potassium iodide. J. Biol. Chem., 45: 349-64.
- With A. F. Hartmann. The iodometric determination of copper and its use in sugar analysis. II. Methods for the determination of reducing sugars in blood, urine, milk and other solutions. J. Biol. Chem., 45:365-90.

With A. P. Briggs. The excretion of acetone from the lungs. J. Biol. Chem., 48:413.

Antiketogenesis. I. An in vitro analogy. J. Biol. Chem., 47:433-48.

- Antiketogenesis. II. The ketogenic-antiketogenic balance in man. J. Biol. Chem., 47:449-73.
- Antiketogenesis. III. Calculation of the ketogenic balance from the respiratory quotients. J. Biol. Chem., 49:143-62.

# 1922

- Antiketogenesis. The ketogenic-antiketogenic balance in man and its significance in diabetes. J. Biol. Chem., 50:xxvi-xxvii.
- Antiketogenesis. IV. The ketogenic-antiketogenic balance in man and its significance in diabetes. J. Biol. Chem., 54:399-441.

# 1923

- With E. A. Doisy and Michael Somogyi. Some properties of an active constituent of pancreas (insulin). J. Biol. Chem., 55: xxxi-xxxii.
- With Ethel Ronzoni. Ether anaesthesia. I. The determination of ethyl ether in air and in blood and its distribution ratio between blood and air. J. Biol. Chem., 57:741-60.
- Antiketogenesis: its mechanism and significance. Harvey Lectures, 1922/23, 18:105-36; Medicine, 2:375-404.

# 1924

- With T. E. Friedemann. Antiketogenesis. V. The ketolytic reaction; action of glycolaldehyde and of glyoxal. J. Biol. Chem., 61:585-623.
- With Michael Somogyi and E. A. Doisy. On the preparation and properties of insulin. J. Biol. Chem., 59:xxxiii-xxxiv.
- With Michael Somogyi and E. A. Doisy. On the preparation of insulin. J. Biol. Chem., 60:31-58.
- Ketosis and carbohydrate metabolism. Annals of Clinical Medicine, 3:93-95.

# 1927

Metabolism of carbohydrates in relation to ketosis. Journal of the American Dietetic Association, 3:148-58.

- With T. E. Friedemann and M. Cotonio. The determination of lactic acid. J. Biol. Chem., 73:335-58.
- On coupled reactions: the intermediate peroxides in the oxidation of ferrous salts. J. Biol. Chem., 74:xlvi-xlvii.

With N. Ariyama. Potentiometric determination of relative reducing rates of sugars for ferricyanide and iodine. J. Biol. Chem., 78:1i.

## 1929

With B. K. Harned and W. B. Wendel. Further studies on antiketogenesis: the oxidation of acetoacetate, induced by air oxidation of sugars, and by aeration of tissue suspensions. Am. J. Physiol., 90:513.

### 1930

- With W. B. Wendel. Induced oxidations in blood. Oxidation of lactic to pyruvic acid by methylene blue. J. Biol. Chem., 87: xx.
- With T. E. Friedemann. Sugar activation by alkali. I. Formation of lactic and saccharinic acids. J. Biol. Chem., 86:345-74.

### 1931

With B. K. Harned. Oxidations induced by sugars. I. The formation of barium peroxide. J. Biol. Chem., 93:311-25.

#### 1932

- With Ethel Ronzoni. Carbohydrate metabolism. Annual Review of Biochemistry, 1:247-66.
- With F. Urban. The acidic property of sugars. J. Biol. Chem., 94:697-715.

#### 1933

- With Michael Somogyi. Copper-iodometric reagents for sugar determination. J. Biol. Chem., 100:695-714.
- Reaction velocity and the "equi-valence-change principle." J. Am. Chem. Soc., 55:2169-70.

The influence of equivalent-valence change on the velocity of aqueous oxidation-reduction reactions. J. Biol. Chem., 105: lxxviii-lxxix.

# 1935

Otto Folin. Science, 81:35-37.

- A simple factor affecting the velocity of ionic oxidation-reduction reactions in aqueous solutions: equivalence of valence change. Science, 81:464-65.
- With R. D. Williams. Sugar determination by the ferricyanide electrode. J. Biol. Chem., 111:707-23.
- Fat. In: Cyclopedia of Medicine, rev. ed., 1934/35, Vol. 8, pp. 846-60.

### 1936

- With E. S. Hill. Semiquinones of anthraquinone sulfonates. J. Biol. Chem., 114:1i.
- Catalysis of ionic oxidation-reduction reactions by dyes and its probable mechanism. Journal of Physical Chemistry, 40:1021-26.

### 1937

- Slow ionic oxidation-reduction reactions: their mechanism and catalysis. Science, 85:53.
- Stanley Rossiter Benedict. J. Biol. Chem., 117:429ff.

### 1939

The mode of action by sulphanilamid. Science, 89:547.

The "equi-valence change principle" in ionic oxidation-reduction reactions. Cold Spring Harbor Symposia on Quantitative Biology, 7:50.

### 1942

Joseph Nash McDowell. Washington Univ. Med. Alum. Quart., 5:170-74.

# 1946

With L. Berger. Kinetics of the iodination of tyrosine. Federation Proceedings, 5:121-22.

- Robert S. Brookings. Washington Univ. Med. Alum. Quart., 13: 121, 124-27.
- Biographical notes on Dr. Leo Loeb. Archives of Pathology, 50: 661-62.

# 1952

Otto Folin, 1867-1934. National Academy of Sciences, Biographical Memoirs, 27:47-82.

# 1954

Otto Folin. Journal of Nutrition, 52:1-11.

# 1957

Evarts Ambrose Graham 1883-1957. American Philosophical Society Year Book, 11:121-26.

# 1959

With P. W. Preisler, E. S. Hill, and R. G. Loeffel. Oxidationreduction potentials, ionization constants and semiquinone formation of indigo sulfonates and their reduction products. J. Am. Chem. Soc., 81:1991-95.