CHAPTER X

THE CHEMISTRY OF PHYSIOLOGY AND NUTRITION

BY GRAHAM LUSK

In passing on to discuss the theme assigned to us, Medical Chemistry, we find ourselves entering upon a broad domain of investigation. We might enlarge upon the many and wide bearings of chemistry upon medical practice and show how indispensable it is to the best success of the practitioner; point out its grand achievements in the departments of physiology and pathology, and show how inseparable it is with the progress of medical science in all its departments.—THEODORE GEORGE WORMLEY, 1876.[1]

The Development

Born a hundred years ago, Theodore G. Wormley (1826–1897) pronounced the words inscribed above, words which might have been written by one of us today. In 1877 Wormley succeeded Robert E. Rogers as professor of chemistry and toxicology in the medical department of the University of Pennsylvania. The year before this, in 1876, *John Marshall* (1855–) entered the medical school and shortly became assistant to Wormley. Marshall was lecturer, quiz master, as well as laboratory janitor in the service of his chief. In 1879 he studied at Göttingen with Wöhler, and later at Tübingen with Hüfner, and also at Christiania. He was closely associated with the medical department of the University of Pennsylvania throughout his life, becoming assistant professor of chemistry in 1889, and professor from 1897 until 1922. He taught the old-fashioned medical chemistry which he had learned from Wormley.

In 1903 he introduced *P. B. Hawk* (1874–), a pupil of Atwater and especially of Chittenden, into his laboratory. Hawk transferred Chittenden's course in physiological chemistry to Philadelphia, and therefore the Chittenden influence was responsible for the introduction of physiological chemistry in the modern sense into the University of Pennsylvania.

[1] Address on "Medical Chemistry," Centennial International Medical Congress of Philadelphia.

Until nearly the end of the last century chemistry was almost exclusively in the hands of the medical schools. Thus Marshall invited Theodore W. Richards, of Harvard, then a schoolboy at Germantown, to come to his laboratory on Saturdays and found the boy regularly sitting on his laboratory steps waiting for him on Saturday mornings.

R. Ogden Doremus (1824–1906) was a pupil and assistant of John W. Draper, of New York University, between 1843 and 1850. He was one of the founders of the New York University and Bellevue Hospital Medical College in New York City in 1861. He was a brilliant lecturer and an extraordinary teacher of undergraduates. He was succeeded in 1897 by *John A. Mandel* (1865–), who in 1901 invited *H. C. Jackson* (1875–), of Chittenden's laboratory at Yale, to be his assistant. The combination of the two men gave a strong department.

Charles Frederick Chandler (1836–1924) studied chemistry under Wöhler, took his Ph.D. degree in Göttingen in 1856, then accepted the position of janitor and assistant chemist at Union College in 1857, and became professor of chemistry there the following year. Between the years 1872 and 1897 he was professor of chemistry and medical jurisprudence at the College of Physicians and Surgeons in New York and a brilliant lecturer and teacher of undergraduates. In 1897 Columbia University invited Chittenden to superintend the installation of a department of physiological chemistry in their medical school. Chittenden established *William J. Gies* (1872–) in this institution to carry on and develop the traditions of the Yale laboratory.

Rudolf A. Witthaus (1846–1915), a proficient toxicologist, was professor of chemistry at the Cornell University Medical College between 1885 and 1911. He belonged to the old school of laboratory worker. He was succeeded by *Stanley R. Benedict* (1884–), a master of analytical technic. Benedict was a pupil of Mendel. He has discovered that the urine of the spotted coach hound contains uric acid, as in the case of man, and not allantoin, as in other varieties of dogs. He has found that the uric acid content of ox blood is wholly present in the corpuscles and occurs there in combination with a pentose. He has recently prepared from human and other bloods a new crystalline compound containing sulfur which he calls "thiasine." This is a substance which has long interfered with the accurate determination of uric acid in the blood by the colorimetric methods of Folin and of Benedict.

The United States is recognized as a leader in the development of new methods of rapid biological chemical analysis, and Otto Folin and Stanley Benedict are the dominant exponents of this art.

Victor C. Vaughan (1851–), long known as a most eminent toxicologist, was one of the earliest Americans to become interested in modern physiological chemistry. He attracted such men as W. H. Howell, J. J. Abel, and Arthur R. Cushny (1866–1926) to the University of Michigan and, because of his scientific knowledge, created there a medical school far in advance of its time. One of the men attracted thither was *Frederick G. Novy* (1864–), who has studied the chemistry of bacterial life, including the production of ptomaines and leucomaines. He has recently reported on the respiratory quotients developed by bacteria, pioneer work in this field.

Samuel J. Meltzer (Russia, 1851—New York, 1920), M.D., Berlin, 1882, was a man of the highest ideals, stimulating to thought and to action. His influence still lives in several societies which he founded. He discovered the anesthetic value of magnesium salts when they are injected into the spinal canal. His earlier years combined research with the practice of medicine, but the last years of his life were spent as a most honored member of the Rockefeller Institute for Medical Research.

With the advent of the great spirit of *Otto Folin* (1867–) in 1907, the Harvard Medical School grew in grandeur. Folin discovered a method for the ready determination of creatine and creatinine. He demonstrated that creatinine was a constant normal product of cellular metabolism and was uninfluenced by the amount of protein in the diet. He extended and more sharply defined the conception of an endogenous protein metabolism, as first enunciated by Burian. Especially celebrated is his "Laws Governing the Chemical Composition of Urine."[1] He was the first to follow to their destinations in the body amino acids orally administered.

It must not be thought that the last twenty-five years of the nineteenth century were devoid of accomplishment. At the centennial meeting of the International Medical Congress (1876) *Austin Flint, Jr.* (1837–1915), read a paper on "Experimental Researches into a New Excretory Function of the Liver." This work had been performed in 1862, had received honorable mention by the Académie des Sciences of Paris, and had been awarded a prize of 1500 francs. Flint demonstrated that biliary cholesterol is converted by bacterial action into a body called "stercorine,"

[1] *Am. J. Physiol.*, **13**, 66 (1905).

in which form it appeared in the feces. The following quaint minute is culled from the record of the congress: "On motion the conclusions in Dr. Flint's paper were adopted as expressing the opinion of the section." The weight of Hoppe-Seyler's great name denied the validity of Flint's discovery, and it was not until Bondzynski in 1896 rediscovered stercorine that Flint's work was vindicated. With a not too delicate sense of scientific amenities, Bondzynski insisted upon retaining the name "koprosterin," which he had given to the compound isolated by him, even after Flint's priority had been established. Following this work of Flint his activity as an investigator lapsed, with the exception of some inaccurate calculations upon the effect of a six-day walk upon the protein metabolism of Weston.

Though there was no general influence making for better things during the last quarter of the nineteenth century, yet the years were not entirely barren. Thus, *Willard Gibbs* (1839–1903), of Yale, during the years 1874 to 1878 published articles in the *Proceedings of the Connecticut Academy* concerning the laws of surface tension and adsorption and the development of heat in the cell. These papers were translated into German by Ostwald in 1896 and presented by him to an astonished scientific world.

The Chemists in Biology

The founding of the Johns Hopkins University in 1876 was under the guiding influence of *Daniel C. Gilman* (1831–1908), who, when affiliated with the American diplomatic establishments in St. Petersburg and Berlin, had made a profound study of the systems of education in those countries. *Ira Remsen*, the discoverer of saccharin, was born in New York in 1846, received his M.D. at Columbia in 1867, Ph.D. at Göttingen in 1870, was assistant at Tübingen 1870 to 1872, was professor of chemistry at the Hopkins from 1876 to 1913, and president of the university from 1901 to 1913. With such men as Gilman and Remsen in control, it was not difficult to stimulate a young student who went to Baltimore in 1883 and who afterwards became the most outstanding individual among the chemists in physiology in America, *John J. Abel* (1857–). Abel studied in European universities between 1884 and 1890 (M.D., Strasbourg, 1888). Between 1890 and 1893 he taught pharmacology at the University of Michigan and then, in 1893, he became professor of pharmacology at the newly founded Johns Hopkins Medical School. He spent his summer holidays in European laboratories and had as his ideal the transplantation of the German scientific atmosphere into his own American laboratory. He has made many outstanding contributions. He prepared the blood pressure raising principle of the suprarenal capsules in the form of a benzoyl derivative and named the active substance "epinephrine." It was but a step for another to prepare the hormone itself, which was renamed "adrenaline." Abel was also the first to isolate a free amino acid (alanine) from the circulating blood. In recent years he, with his co-workers Rouiller and Geiling, has shown that the potency of a purified pituitary tartrate is such that maximal contractions of the virgin guinea-pig uterus are obtained when the substance is in dilution of 1:15,000,000,000. The latest announcement of Abel (1926) is that he has prepared pure crystalline insulin which gives the ordinary reactions for protein and contains an extremely labile sulfur group which is essential to the activity of the hormone. This substance, when given in doses of 0.01 milligram to the kilogram, reduces the blood-sugar level of the rabbit to the convulsive stage. It is "a hormone which in very high dilution influences carbohydrate metabolism, acting, as it were, like a catalyst in a chemical solution."

E. C. Kendall (1886–), a man of a later generation than Abel, has isolated thyroxin, the effective hormone of the thyroid gland, and has found that it contains 65 per cent of iodine. He believes that thyroxin incorporated into protoplasm functions as a catalyst. According to Kendall the activity of epinephrine and glutathione is of an analogous order.

These pieces of work stand in striking contrast to the welter of absurdity put forth by "clinical endocrinologists" and to the frauds of some of the pharmaceutical houses.

A pioneer in the field of pure chemical research is *Thomas B. Osborne* (New Haven, 1862–). He took his Ph.D. degree at Yale in 1885. Since 1886, as research chemist of the Connecticut Agricultural Experiment Station, he has been active first in the chemical analysis of various proteins and later (with Mendel) in the determination of their physiological importance. With infinite care he has determined the quantity of different amino acids contained in many varied proteins. He may properly be called the world's foremost authority on the chemistry of the vegetable proteins. This work was at first continued by *C. O. Johns* (1870–) and later by *D. Breese Jones* (1879–), a pupil of Osborne, at the United States Department of Agriculture, Washington, D. C.

Phoebus A. Levene (St. Petersburg, 1869–) migrated to this country in 1891 after receiving an M.D. degree at St. Petersburg.

Educated in many laboratories both in America and in Germany, he has been an inspiring influence at the Rockefeller Institute since its foundation. Here he for the first time determined the structural formula of nucleic acid, a problem the solution of which had evaded some of the world's master chemists. His work on the chemistry of mucoproteins shows that they contain conjugated sulfuric acid, and he has given a chemical formula for chondroitin sulfuric acid.

Henry D. Dakin (London, 1880–) came to this country about 1905. He has devoted his life to the study of the intermediary metabolism and to the oxidations and reductions in the animal body. He has made it probable that methyl glyoxal is an important and usual intermediary product in carbohydrate metabolism. He isolated β-hydroxyglutamic acid as a constituent of casein and has produced the substance synthetically. A careful investigator and a sound critic, his work has been beyond reproach.

Walter Jones (1865–) took his Ph.D. at the Johns Hopkins in 1891 and studied with Kossel at Marburg in 1899. He has made a lifelong and fruitful study of the nucleic acids and their derivatives. He has shown that the absence of guanase from the pig's liver prevents the transformation of guanine into xanthine and hence favors the production of guanine gout in the pig.

The Biological Chemists

Russell H. Chittenden (New Haven, 1856–) has rightly been called the "Grand Old Man of Physiological Chemistry in America." He received the degree of Ph.B. at Yale in 1875, worked with Kühne in Heidelberg in 1878 to 1879, was granted a Ph.D. from Yale in 1880, became professor of physiological chemistry there in 1882, and director of the Sheffield Scientific School in 1898. Denying himself all holidays, he worked unceasingly far past middle life in the fulfilment of that supreme mission, the preparation of young men to become teachers. His influence over them was phenomenal. Thus, he diverted Harvey Cushing from the contemplated study of architecture to the pursuit of medicine, and he gave to such men as Theodore C. Janeway, John Howland, and Elliott P. Joslin the touch of chemical insight necessary for the great clinicians which they became. They received a greater stimulus from his courses than was obtainable in the medical schools of their day. At his hands several great teachers received their doctorates, Lafayette B. Mendel, in 1893; William J. Gies, in 1897; Yandell Henderson, in 1898; Holmes C. Jackson, in 1899; Alfred N. Richards, in 1901; and Frank P. Underhill, in 1903. Also, H. Gideon Wells in 1893 received the degree of Ph.B. after work in his laboratory.

Chittenden's earlier work was concerned with the chemistry of protein, albumoses, and peptones. In 1875 he discovered glycogen and glycine in "scallops," the central muscle of *pecten irradians*. His most famous research was published in 1904 entitled, "Physiological Economy in Nutrition, with Special Reference to the Minimal Protein Requirement of the Healthy Man. An Experimental Study." In this he demonstrated that a man could live in vigorous health after taking half to a third the quantity of protein allowed in the standard diets of the period. On account of this work his name became well known in Germany and elsewhere in 1914 to 1918.

In 1898 he was called to administer the department of physiological chemistry in the medical school of Columbia University, New York City. He established a course there, placing his pupil, *William J. Gies* (1872–) in charge of most of the instruction, and in 1903 retired as head of the department, when Gies was placed in full control.

Lafayette B. Mendel (1872–), Ph.D., Yale, 1893, the most influential of all of Chittenden's pupils, studied also with Heidenhain at Breslau and with Baumann at Freiburg in 1895 and 1896, and on his return home became again closely associated with Chittenden, gradually relieving him of much of the direction of the laboratory work, especially after 1898 when Chittenden became director of the Sheffield Scientific School. Of the many scientific offspring of Mendel who hold academic positions, usually chairs of physiological chemistry, may be enumerated Robert E. Swain (Ph.D., 1904), Stanford University; Harold C. Bradley (Ph.D., 1905), University of Wisconsin; Tadasu Saiki (Ph.D., 1907), director, Nutrition Institute, Tokio; Stanley R. Benedict (Ph.D., 1908), Cornell University Medical College, New York City; Mary Swartz Rose (Ph.D., 1909), Columbia University; Victor C. Myers (Ph.D., 1909), University of Iowa; John F. Lyman (Ph.D., 1909), Ohio State University; William C. Rose (Ph.D., 1911), University of Illinois; Howard B. Lewis (Ph.D., 1913), University of Michigan; Ruth Wheeler (Ph.D., 1913), Nutrition, University of Iowa; Amy L. Daniels (Ph.D., 1914), Iowa; D. Wright Wilson (Ph.D., 1914), University of Pennsylvania; and Raymond L. Stehle (Ph.D., 1915), McGill University.

In this connection it should be recalled that E. V. McCollum took his Ph.D. degree under the chemist Treat B. Johnson at

Yale in 1906 and that he spent the academic year 1906–1907 in Mendel's laboratory.

Mendel's work has been prodigious in quantity, painstaking and accurate in quality. Always an omnivorous reader, a well-balanced critic, a sound adviser of men, and judge of the affairs of men, he has wielded a great and beneficent power upon his day and generation.

The bound reprints of the work of his laboratory constitute ten large volumes. At first his researches dealt largely with the metabolism of the purines, he then took part in the experiments of Chittenden on the protein minimum, and later, with T. B. Osborne, he developed the valuable line of investigation regarding the question as to what constitutes an adequate diet. The basis of this work was founded upon the growth curves of young rats, as influenced by diet, following a procedure originally adopted by Gowland Hopkins, of Cambridge, England. McCollum began similar experiments almost at the same time. The two sets of investigations have been somewhat at variance with each other, especially in the earlier years before the exact methods of analysis were clearly defined, but America may well be proud of the results obtained by both groups of workers.

Osborne and Mendel have clearly shown that rats grow and thrive when the protein contained in their diet is casein (devoid of glycine), whereas if the wheat protein, called "gliadin" (deficient in lysine), is substituted, body weight is barely maintained, and if the protein of Indian corn, called "zein" (devoid of glycine, lysine, and tryptophan), be given, even the maintenance of body weight is impossible. If the missing amino acids in the last two proteins are added to the food, normal growth is obtained.

Elmer V. McCollum (1878–), and independently Osborne and Mendel, discovered that growing rats, given a satisfactory diet, ceased to grow if lard were substituted for butter fat. And Osborne and Mendel reported that in the absence of butter fat an eye disease called "xerophthalmia" developed. Addition of butter fat to the diet caused renewed growth and cured the xerophthalmia. In Denmark during the World War butter fat was exported to Germany and cocoanut oil was substituted for it in the milk supply of the Danes to such an extent that malnutrition, stunting of growth, and xerophthalmia arose among the children. When the American work became known in Denmark the Danish government arranged to ration butter among the children and remedied the difficulty.

McCollum has given the letters of the alphabet to the various vitamins, pending the time when their composition shall be exactly determined. The one described above as being contained in butter fat is called "fat-soluble A." The vitamins may be described as follows:

Fat-soluble A, growth producing; antixerophthalmic.
Water-soluble B, antineuritic; appetite promoting.
Water-soluble C, antiscorbutic.
Fat-soluble (?) D, antirachitic.
Fat-soluble E, fertility promoting.

Given these factors as variants in the dietaries, as well as such factors as chemical differences in proteins, fats, and carbohydrates, it can well be imagined that an immense literature has grown up with regard to the dietetic influence of various foods. In his "Newer Knowledge of Nutrition" McCollum lists the special dietary properties of one hundred and sixty different materials which are commonly employed as foods. Though the work has been interesting and important, much of it still lacks the quantitative element which will appear when the different vitamins are isolated. The immensity and relative newness of the literature make the selection of salient points difficult.

Walter H. Eddy (1877–) and his associates report the preparation from yeast of "bios," which stimulates the growth of yeast and is perhaps the antineuritic vitamin B. It is a crystalline substance melting at 223° C., contains nitrogen, and is possibly a true "vit-amine."

In the study of pellagra *Joseph Goldberger* (Austria, 1874–) and *Carl Voegtlin* (Switzerland, 1879–) have been prominent, without effecting a definite solution of this problem. Voegtlin has also studied the effect upon the body of salvarsan and related arsenicals.

Alfred F. Hess (1875–) has made extensive investigations into the subject of infantile scurvy and has found the tomato to have effective curative properties and therefore to contain much of vitamin C. He was the first to discover that direct exposure of children to sunlight alone would cure rickets.

John Howland (1873–1926), professor of pediatrics at the Johns Hopkins Medical School, has made notable contributions to the physiological pathology of rickets. Working first with Marriott and then with Benjamin Kramer and Tisdale, he concluded that in uncomplicated human rickets there is a normal calcium content (10–11 mg. per 100 cc. of blood serum) of the blood but a low phosphate concentration. If the calcium of the blood falls below the normal in children, tetany ensues, tetany being due to a deficiency of the normal amount of calcium ions (7–5 mg. Ca per 100 cc. of blood serum). This corresponds with the previous discovery of *William G. MacCallum* (1874–) that the tetany following parathyroidectomy is due to a decrease in the calcium content of the blood.

The experimental proof by Raczynski in 1912 that deprivation of light in a puppy dog was the cause of rickets brought a host of interested workers into this field. Hess shortly afterward proved by X-ray examination of the bones that exposure to sunlight cured rickets in children.

McCollum, P. G. Shipley, and E. A. Park have induced rickets in rats when these animals were reared indoors on diets too low in either calcium or phosphorus. Rats do not develop tetany. But when the animals so treated had acquired rickets, the addition of cod liver to their rickets-producing ration, or mere exposure to ultra-violet radiation, or to sunlight itself, caused a return of the normal quantities of calcium and inorganic phosphorus in the blood serum and in consequence cured rickets. Finally, Howland, Kramer, and Shipley have found that when the rachitic cartilage of rats is suspended in a saline solution of calcium and phosphorus in the proportion found in normal blood, calcification occurs in the diseased tissue. Also, when rachitic cartilage is suspended in normal human serum, calcification occurs *in vitro*, but there is none when rachitic serum is used.

The rachitic vitamin D is undoubtedly a radioactive principle derived from sunlight. Thus, *Harry Steenbock* (1886–) found that irradiation with ultra-violet rays caused inactive vegetable oils to acquire antirachitic potency. He showed that the antirachitic potency of butter fat is due to the consumption by the mother of irradiated food materials, and Hess has discovered that irradiation of green vegetables and spinach increased their value in this regard.

Powers, Park, and Simmonds find that the radiant energy of the sun will not prevent the development of xerophthalmia in rats but delays its onset. They conclude that radiant energy very likely raises the level of cellular activity of the organism to the point where the onslaughts of disease are held for a time in check.

Herbert M. Evans (1882–), of California, has unveiled the presence of a fertility vitamin which he at first called "vitamin X," but which McCollum classifies as vitamin E. Evans found that when rats were reared on a standard diet wholly sufficient for their normal growth (casein 18, cornstarch 54, lard 15, butter fat

9, salts 4, with 0.5 gram yeast), they became sterile, both male and female. The unknown fertility-conferring factor was shown to be present in lettuce, meat, wheat germ, oats, alfalfa, and (sparingly) in milk fat, and is essentially different from vitamins A, B, C, and D. Very small amounts of wheat germ oil will restore fertility to the animals. Evans also reports that a specific "bios" contained in natural foods, such as wheat germ oil, is necessary for normal lactation.

Howard B. Lewis (1887–), a pupil of Mendel and now professor of biochemistry at the University of Michigan, has studied especially the metabolism of sulfur compounds in the body. He has found that the oxidation of sulfur in cystine cannot take place normally if the process of deamination is prevented.

William C. Rose (1887–), Ph.D., Yale, 1911, professor of biochemistry at the University of Illinois, has been interested in amino-acid chemistry and finds that arginine and histidine are not mutually interchangeable in the nutrition of animals, that arginine is not a precursor of creatinine, but that probably histidine is a precursor of the purines.

Carl P. Sherwin (1885–) received a degree of Sc.D. under Thierfelder at Tübingen in 1915. He and Thierfelder found that in man phenylacetic acid unites with glutamic acid to form phenylacetyl-glutamic instead of phenaceturic acid, as in the dog, and in this form appears in the urine. This was the beginning of much work upon the intermediary metabolism of aromatic compounds.

The Agricultural Experiment Stations

Samuel W. Johnson (1830–1909) was the son of a Connecticut farmer of old colonial ancestry. For many years he taught school and tried to save enough money to go to Germany to study scientific agriculture, there fostered by Liebig. His father reproved him for his fantastic ideas, but finally consented to give him in cash the equivalent value of that which he had given to his other children in lands, buildings, and farm stock. Writing his father in 1854 from Munich, he says he can live there for five hundred dollars a year and "when I think of Heidelberg and the great Bunsen; of Berlin and the glorious old Heinrich Rose—my heart, my stomach, something in that neighborhood, aches. I have just got to be able to appreciate and enjoy Germany."

In 1861 Johnson was lecturing on agricultural chemistry five times weekly at the Sheffield Scientific School, New Haven. Here W. O. Atwater became a pupil and afterward his private assistant. Through Johnson's influence the Connecticut legislature in 1875 had the honor of establishing at Middletown the first state agricultural experiment station in the United States, of which Atwater was placed in charge. In 1877 the legislature correctly defined it as existing "for the purpose of promoting agriculture by scientific investigation and experiment." At this time Johnson became its director. The other members of Johnson's staff at this, the model of all other similar state institutions in the country, were E. H. Jenkins and Henry Prentiss Armsby, both former pupils of Johnson. In 1886 T. B. Osborne joined the staff of the station and at Professor Johnson's desire began with the oat kernel to separate its protein constituents in a condition of purity. Osborne, who was Johnson's son-in-law, labored at these problems for many years. He was startled at one time to receive a German translation of his work.

Johnson's private library was a complete storehouse of scientific information on the subject of scientific agriculture. His pupils, Atwater and Armsby, achieved high distinction. And agricultural stations modeled on his own, that is, so ordered that appointments are free from political control, have reached high distinction.

The Pennsylvania State Agricultural College was established in 1859 under the presidency of *Evan Pugh* (1828–1864). A blacksmith in his youth, but inheriting a small fortune, he went abroad to study, and took a Ph.D. degree at Göttingen in 1856. He was an American associate of Johnson when he was in Germany. The college prospectus announced the ambition to become "the best agricultural college in the world," but the state refused adequate support. Even so great a scientist as *Henry Prentiss Armsby* (1853–1921) was terribly handicapped in his work by the niggardly support of the state. Armsby was trained under Johnson at Yale, receiving his Ph.D. there in 1879. The year of 1876 he spent at Leipzig. From 1887 until his death he was the outstanding personality at the Pennsylvania Agricultural Experiment Station. He built in 1902 the only calorimeter (Atwater-Rosa type) which has ever been successfully operated with large animals, such as cattle. His life's work was devoted to the study of the basal metabolism of cattle and the net energy value of the feeding stuffs on which they subsisted. The plan and execution of these researches, the best of their kind, are the monument of his life.

Calorimetry

William Olin Atwater (1844–1907), as has been said, was a pupil of Johnson at Yale. He obtained his Ph.D. in 1869 upon the basis of the first analyses of maize fodder made in this country, using modern methods. Between 1869 and 1871 he studied in Leipzig and Berlin.

Atwater became professor of chemistry at Wesleyan in 1873. He later (1888) became founder and chief of the Office of Experiment Stations, United States Department of Agriculture. Johnson writes of him then, "I have, with others, favored Atwater's appointment because he has the spirit of prophecy and appears to me to be a chosen vessel." Twenty-six years later his pupil, *Charles F. Langworthy* (1864–), at the time chief of nutrition investigations, United States Department of Agriculture, wrote in a private letter, "One of Professor Atwater's most marked characteristics was his almost prophetic insight into the needs and possibilities of nutrition investigation."

In 1887 Atwater spent some time in Voit's laboratory in Munich, where he came in close personal contact with Max Rubner, then Voit's first assistant. It was through these influences that he became interested in calorimetry. Rubner perfected his calorimeter for dogs in 1891. The Atwater-Rosa calorimeter for work on man was begun in 1892 and completed in 1897. Of the latter calorimeter Armsby wrote at the time, "By far the most important form of respiration-calorimeter yet devised, not only as regards accuracy but particularly in view of the range of the work of which it is capable, is that of Atwater and Rosa." Time has justified this eulogy.

Atwater and his associates were able to verify the law of the conservation of energy as applied to the human being. That is to say, they demonstrated that the quantity of heat produced by an individual during a given period is that quantity which can be derived from the energy liberated in the oxidation of food materials during the same period. The analytical tables of food materials prepared in 1899 by Atwater and Bryant have remained the standard work of reference since their publication and were eagerly sought in many countries during the war.

The cost of the calorimeter work was largely defrayed from United States government funds. Representative, afterward Senator, Morrill, of Vermont, was the farsighted individual most largely responsible for these grants. But money came from other sources, the state of Connecticut, the university at Middletown, and private subscriptions. The work on the calorimeter was a coöperative affair, but its signal success was undoubtedly due to the distinguished physicist, *E. B. Rosa* (1861–1921), then professor of physics at Wesleyan University and later chief physicist of the Bureau of Standards at Washington.

Just before Atwater's invalidism and death the Carnegie Institution of Washington agreed to endow the work and to build a special nutrition laboratory for him. Atwater especially desired to devise means to measure the oxygen consumption of a man while he was in the respiration-calorimeter. In this work he had the ardent support and assistance of a highly ingenious young assistant, F. G. Benedict, who succeeded him after his death.

Francis Gano Benedict (1870–) received his M.A. at Harvard in 1894 and a Ph.D. at Heidelberg in 1895. He joined Atwater's staff at Wesleyan in 1896 and was closely associated with him for ten years. In 1907 he was chosen director of the Carnegie Nutrition Laboratory at Boston.

One of the most striking pieces of work ever accomplished was Benedict's investigation into the metabolism of a fasting man. One hundred and twenty-five quantitative measurements of various kinds were daily recorded during a fasting period of thirty-one days.

Following Du Bois' lead, Benedict, out of the wealth of his statistical material, has given us standards for measuring the basal metabolism, i. e., the heat production of a person resting quietly in the postabsorptive state.

In association with *Elliott P. Joslin* (1869–), he has done much to promote a knowledge of the processes which go on in diabetes. And with *Fritz B. Talbot* (1878–) a long and very complete study has been made of the metabolism in children from infancy to maturity. This has given accurate standards. During the war Benedict made an important contribution to our knowledge regarding the relation between undernutrition and muscular efficiency. The body was shown to have a real measure of self-defense in that the basal metabolism falls rapidly under conditions of undernutrition, even though there be no great depletion of the protein reserves of the body.

Graham Lusk (1866–) received his Ph.B. in chemistry at Columbia University in 1887 and his Ph.D. from Baeyer in Munich in 1891. He lived in Munich for three years, two years of which time he spent in the research laboratory of Carl Voit.

At the Yale Medical School he discovered that the urinary dextrose-nitrogen ratio (the $D:N$ ratio of Minkowski) in the fasting and meat-fed dog under the influence of phlorhizin was usually 3.65, and later at the New York University and Bellevue Hospital Medical College he, with *A. R. Mandel* (1876–), established the same ratio for the totally diabetic man. S. R. Benedict found the same figures in a phlorhizinized man.

With *A. I. Ringer* (1883–) he determined the quantity of sugar yielded by various amino acids in metabolism. This work was later extended by Ringer when he went to the laboratory of physiological chemistry of A. E. Taylor at the University of Pennsylvania.

When called to the Cornell University Medical College in 1909 Lusk was given sufficient funds to build a respiration apparatus. John R. Murlin, who had been associated with him for six years, spent the early summer of 1909 with Benedict in the Carnegie Nutrition Laboratory at Boston. Here Murlin and *Thorne M. Carpenter* (1878–) investigated the energy metabolism of mothers and their children before and after birth. It was found that the heat production of the mother and new-born child was the same as that of the mother before parturition. The respiration-calorimeter was so near to perfection that it was decided to construct for the Cornell Medical College a duplicate for the measurement of the respiratory metabolism and the heat production of dogs and babies. For the project Dr. Benedict supplied an expert mechanic, and the whole undertaking was then put in the hands of *H. B. Williams* (1877–), now professor of physiology, Columbia University, who had a rare combination of attributes, being a physicist, a mechanic, a physician, as well as a medical scientist and a classical scholar. It was due to Williams' technic that John Howland was able to determine that a sleeping infant, six months old and weighing only 3 kilograms, absorbed 2.36 grams oxygen per hour, from which it was calculated that 7.71 kilocalories should have been produced, whereas 7.57 calories were actually measured by the calorimeter during the hour.

With this apparatus many experiments have been carried out on dogs in the study of the behavior of various foods and individual metabolites.

In this same laboratory *John R. Murlin* (1874–), working with H. C. Bailey, showed that the heat production of new-born babies was exceedingly low for their size. Here, also, he worked for many months upon the all-engrossing problem of the effect of pancreatic extracts on pancreas diabetes. In 1913 he and Benjamin Kramer actually had a potent boiled extract of the pancreas in their hands, one that caused an oxidation of glucose in a depancreatized diabetic dog, as determined by an increase in the respiratory quotient. The year previous to this *Ernest Lyman Scott* (1877–), in Carlson's laboratory, prepared an extract from the pancreas which greatly reduced the $D:N$ ratio in a completely depancreatized dog. These were the two outstanding

American contributions of the pre-insulin period of diabetic glandular therapy.

During the war Murlin became Lieutenant Colonel in the Sanitary Corps, and between 1917 and 1919 he was director of the Division of Food and Nutrition, Medical Department, U. S. A. Under him were marshalled Carlson, Shaffer, Woodyatt, Gephart, and many others whose business it was to improve the quality of the food and diminish its waste in Army cantonments and in the field. And the task was well done.

Rudolph J. Anderson (Sweden, 1879–), B.S. at Tulane, 1906; did graduate work at Upsala, London, and with Emil Fischer at Berlin; took his Ph.D. at Cornell, 1919. Some work with Lusk showed conclusively that the energy production in a fasting dog during a period of running at a rate of three miles per hour was exclusively derived from the oxidation of fat, as indicated by a non-protein respiratory quotient of 0.713 on the thirteenth day of the fast. He has studied the phytosterols of vegetable oils. He has found that the coloring matter of Norton and Concord grapes consists of a glucoside, anthocyanin.

The Russell Sage Institute of Pathology, through the use of its comparatively small funds, established a respiration-calorimeter in Bellevue Hospital, New York City, the success of which is directly attributable to its medical director, *Eugene F. Du Bois* (1882–). For the first time a respiration-calorimeter was built in a hospital and this was done in a city-owned hospital. The undertaking was under the control of a full-time staff. Here accurate normal standards of basal metabolism for people in good health were for the first time established. The difference between these standards and those afterwards given out by Benedict is slight. If the general average of metabolism tests is taken, Du Bois' values are more likely to be right than Benedict's. If the lowest of three observations is accepted as the basal value of metabolism, then Benedict's tables should be used.

After establishing basal values in normal people, Du Bois and *Warren Coleman* (1869–) investigated the metabolism of patients suffering from typhoid fever, extending the knowledge of the "high calorie diet" originally commended by Warren Coleman and Philip A. Shaffer. This work, together with one on malarial fever by Du Bois and *David P. Barr* (1889–), now professor of medicine, Washington University, St. Louis, presented a most complete record of the heat production and the heat loss during fever. It was found that in malarial chill the evaporation of water remained at its former level, that the heat loss by radiation and conduction was unchanged, and that all the extra heat produced by the muscular activity of shivering during the chill was stored in the body, raising its temperature accordingly.

Du Bois also made important studies on exophthalmic goiter. With *Frederick M. Allen* (1879–) and with *J. C. Aub* (1890–), working on diabetic patients of record severity, much was learned. In one instance it was discovered that a potentially diabetic man, whose urine was made free from sugar by dieting, was converted into a completely diabetic individual with a $D:N$ ratio of about 3.65 on the second day of a diet containing fat and much protein.

William S. McCann (1889–), now professor of medicine, Rochester University, New York, and D. P. Barr made use of the calorimeter in the investigation of tuberculosis. They found that a large protein intake increased the metabolism as in normal men, and since this results in increasing respiratory movement, a limited protein intake was recommended to put the lungs at rest. The food requirements of the tuberculous patient were found not to be large, and forced feeding they believed to be unnecessary and harmful.

James H. Means (1885–), of the Harvard Medical School, has shown that as a rule the metabolism in obesity conforms to the normal surface area standards.

Francis W. Peabody (1881–), professor of medicine at the Harvard Medical School and physician to the Boston City Hospital, has made important contributions to knowledge concerning acidosis and dyspnea in renal and cardiac disease and (with A. L. Meyer and Du Bois) has shown that, although the metabolism is often increased in these conditions, yet the quality of the metabolism remains quite as under normal conditions, as indicated by the respiratory quotients revealed.

In 1912 it was said of the United States that, although physiological chemistry and biology flourished here as nowhere else, yet the country was singularly barren in the field of scientific masters of medicine. The whole aspect of affairs has changed within the last decade and largely through those who have followed biochemical work. It may be of note that when John Howland was a practicing physician in New York he met Du Bois, then just out of an internship at the Presbyterian Hospital, and advised him to abandon bacteriology, which he planned to study in Germany, and turn to chemistry.

Attention has already been called to the work of Joslin, Lusk, Scott, Murlin, and others upon the subject of diabetes. Frederick

M. Allen, at the Rockefeller Institute, recommended complete fasting as a remedy for diabetes. This was a more drastic application of the principle of undernutrition recommended by Naunyn. Both *Henry R. Geyelin* (1884–) and *Isidor Greenwald* (1887–) have reported cases of complete human diabetes in which the $D:N$ ratio on a meat-fat diet approximates 3.65:1.

The question of the occurrence and disappearance of the acetone bodies in diabetes is one which has occupied the interest of several American investigators. The first philosophical consideration of this subject was by *Rollin T. Woodyatt* (1878–) in 1910, who wrote concerning the possibility of certain metabolites of sugar reacting to produce the oxidation of β-oxybutyric acid. He gave glycolaldehyde to a diabetic dog and saw that it was antiketogenic, i. e., prevented the production of β-oxybutyric and acetoacetic acids. These acids are the end products of the oxidation of fatty acids, palmitic acid, for example. A. I. Ringer suggested in 1913 that acetaldehyde, believed to be produced in carbohydrate metabolism, united chemically with β-hydroxybutyric acid in the normal organism, enabling a final oxidation of the substance.

It is illuminating to compare the statement of Rosenfeld in 1885, "The fats burn in the fire of carbohydrate," with that of Woodyatt in 1916, "When the mixture of metabolites oxidizing in the body contain more than three molecules of higher fatty acid" (plus one of glycerol) "to one of glucose, then the body 'smokes' with acidosis compounds like an automobile with too much oil in the cylinders."

Woodyatt has demonstrated that to be certainly free from acidosis in practice an individual must have at least 1 gram of glucose to provide for the normal oxidation of 1.5 grams of fatty acid. Such a relation is found in a diet made up of protein, 50 grams; carbohydrate, 57 grams; and fat, 139 grams. In making the computation one must remember that fat yields 10 per cent of glycerol (a glucose derivative), and protein yields 58 per cent of glucose and 54 per cent of fatty acid.

Philip A. Shaffer (1881–), the distinguished pupil of Folin and professor of physiological chemistry at Washington University, St. Louis, has shown *in vitro* that acetoacetic acid in alkaline solution is not oxidized by peroxide of hydrogen, but that if glucose or glycolaldehyde be added to the solution, complete oxidation follows, just as occurs *in vivo*. Shaffer has also made most beautiful calculations of the millimols of glucose and of the millimols of fatty acid which were oxidized together in the mixture of metabolites, as calculated from various published metabolism experiments. In 1922 he concluded that the presence of one molecule of glucose was sufficient to cause the proper and complete oxidation of two molecules of fatty acid.

The rationale of the high fat diet of *Louis H. Newburgh* (1883–) is based on supplying the caloric needs of the body of the diabetic with a diet low in protein, high in fat, and with just enough carbohydrate to prevent the appearance of acetone bodies in the urine.

Such may be the useful practical results of the cultivation of pure theoretical science. Of the men engaged in this development Woodyatt and Ringer have worked in the clinic of Friedrich Müller, in Munich; Newburgh with Eppinger, in Vienna; and Du Bois with Kraus, in Berlin. There must exist an "atmosphere" to promote scientific enthusiasm.

Walter M. Boothby (1880–) has accomplished interesting work at the Mayo Clinic. After injecting a myxedematous patient, whose basal metabolism was 30 per cent below normal, with 16 milligrams of Kendall's thyroxin, an increased heat production of 16,125 calories occurred during the following six weeks over and above the quantity this patient would otherwise have produced. Boothby made a similar analysis of the action of epinephrine. He calculates that, whereas 1 milligram of thyroxin induces an extra heat production of 1008 calories, 1 milligram of epinephrine increases the basal metabolism only 50 calories. A molecule of thyroxin is stated to be sixty-four times more potent than one of epinephrine.

Joseph C. Aub (1890–) and his associates at the Harvard Medical School have demonstrated that the action of thyroxin upon the metabolism of cats is not influenced by the presence of the adrenal glands; and also that the 25 per cent fall in the metabolism of cats after the removal of the adrenals takes place whether the thyroid is present or not. He has also studied intensively the subject of lead poisoning.

David Marine (1880–) demonstrated in 1917 that the prophylactic administration of small amounts of sodium iodide to the school children of Akron, Ohio, a district in which goiter was prevalent, prevented a goitrous enlargement of the thyroid in over 99 per cent of the children treated. The demonstration was on a very extended scale.

The Chemistry of the Blood

William Henry Howell (1860–), the distinguished professor of physiology at the Johns Hopkins Medical School, has separated thrombin from its union with fibrinogen and found that it is thermostable in boiling water, is free from calcium, and will form a chemical union with fibrinogen to form fibrin. According to Howell, antithrombin present in the fresh blood prevents calcium salts from converting prothrombin into thrombin. Howell has also advanced evidence to show that the inhibition of the heart following the stimulation of the vagus is due to the liberation of potassium ions. And he was the first to discover a pressor substance in extracts of the posterior lobe of the pituitary gland.

The modern knowledge of the acid-base equilibrium of the blood was first placed before us by *Lawrence J. Henderson* (1878-), of Harvard University. He has also dealt in masterful manner with the philosophy of science.

Frank C. Mann (1887-), of the Mayo Foundation, with extraordinary skill, has devised a method for extirpating the liver in dogs, and finds that in the absence of this organ the regulation of the blood sugar is lost; the blood sugar falls to the level which produces convulsions. Injections of glucose for a time remedy the condition. He has shown conclusively that the seat of urea formation is in the liver and that the oxidation of uric acid to allantoin takes place there also. Furthermore, that the bile pigments arise in the bone marrow and in the spleen.

Donald D. Van Slyke (1883-), a pupil of Levene, has labored for many years upon the tension of gases in the blood. He was the first to devise a method for the direct determination of amino acids in the blood and tissues. He also invented an apparatus for the easy measurement of the CO_2-combining power of the blood and showed that the fall in this combining power was directly proportional to the intensity of acidosis in diabetes and in other diseased conditions. Many men have been carefully trained under his guidance and stimulated to correct scientific behavior by his painstaking thoroughness.

Walter R. Bloor (Canada, 1877-) obtained his Ph.D. at Harvard in 1911 under Folin and is one of his most eminent pupils. He is now professor of biochemistry at the University of Rochester, Rochester, New York. Bloor has especially investigated the time relations of the absorption of fat into the blood stream and has analyzed the distribution of lipoids in the blood in health and in diabetes, anemia, nephritis, etc., separately determining in whole blood, plasma, and corpuscles the content of total fatty acid, fat, lecithin, and cholesterol. He is a master of the chemistry of the lipoids.

Anton J. Carlson (1875-), the eminent physiologist of the

University of Chicago, has invaded the field of chemistry in his contributions on the control of hunger in health and disease, especially as regards the composition of the gastric juice.

The Function of Organs

Charles C. Guthrie (1880–), of the University of Pittsburgh (with Carrel as his pupil), was a pioneer in the work of transplanting organs. It was he who removed a kidney and transplanted it in the neck. The kidney, thus isolated and supplied with carotid blood, functioned perfectly.

Alfred N. Richards (1876–), professor of pharmacology at the University of Pennsylvania, has introduced a micro-pipette into an individual glomerulus of a frog's kidney and, using microchemical methods, has found that the composition of the glomerular filtrate is almost the same as that of the blood.

Jacques Loeb (1859–1925), the noted biologist of the Rockefeller Institute, was first to develop free swimming larvae from the unfertilized eggs of sea urchins through treatment of the eggs with certain saline solutions. He called the process "artificial parthenogenesis."

Loeb demonstrated that the laws of general chemistry hold true for protein, that the error of the colloid chemists lay in their lack of consideration of the hydrogen-ion concentration of their solutions, and that they investigated proteins in the presence of an excess of electrolytes. "The Dynamics of Living Matter," published in 1906, was an early masterpiece and included his studies on tropisms. He stimulated a great group of co-workers and was inspired with genius and true greatness.

William Mansfield Clark (1884–) received his Ph.D. at the Johns Hopkins in 1910. He devised methods for the study of the influence of hydrogen-ion concentrations upon bacterial metabolism. He has studied the growth optima of bacteria in relation to the hydrogen-ion concentration of the fluids in which they develop.

Albert P. Mathews (1871–) was with Kossel in Marburg in 1895 to 1897, and received his Ph.D. at Columbia in 1898. He is professor of physiological chemistry at Cincinnati. He has contributed much to chemical theory and has written a textbook on physiological chemistry which ranks as the best of its kind.

Martin H. Fischer (Germany, 1879–), M.D., Rush, 1901, has been professor of physiology at Cincinnati since 1910. His books, one on the theory of nephritis and the other on edema, have attracted world-wide attention.

G. H. A. Clowes (England, 1877–), Ph.D., Göttingen, 1899, is research director of Eli Lilly & Company, a physical chemist of high repute, whose scientific knowledge was largely contributory to the commercial preparation of insulin on a large scale.

Edmund N. Harvey (1887–), of Princeton University, demonstrated that the production of light by the firefly is due to oxidation. He dried the photogenic organ of the firefly *in vacuo* and found that it would emit light by the addition of water containing oxygen.

Public Welfare

It would seem that biological chemistry best serves the people through its aid to agriculture and through nutrition. The country is greatly indebted to *Harvey W. Wiley* (1844–) for the passage of the pure food laws. His successor, *Carl L. Alsberg* (1877–), who studied at Strasbourg under Schmiedeberg, contributed greatly to the scientific distinction of the important position of chief chemist of the United States Department of Agriculture. After the United States entered the war *Herbert Hoover* (1874–), head of the Commission for Relief in Belgium, organized the United States Food Administration. *Alonzo E. Taylor* (1870–), one of the early pupils of Arrhenius, and formerly professor of physiological chemistry of the University of Pennsylvania, a man of high scientific attainments, became Hoover's principal scientific adviser. He was also a member of the important War Trade Board. Chittenden and Lusk were sent abroad by Hoover in the winter of 1918 as members of the Interallied Scientific Food Commission, and the following autumn Mendel and Armsby went on the same mission. The problem was to solve the way to nourish a population of 225 million people on scientific principles.

The education of the masses upon the question of home economics has been widespread in the United States, and especial emphasis has always been placed upon the subject of nutrition. *Henry C. Sherman* (1875–), who was early associated with Atwater and now for many years with Columbia University, has been one of those through whose investigations, writings, teachings, and pupils this knowledge has been constantly promoted. He has found the requirement of calcium in the diet of an adult to be 0.42 gram per day and he has never ceased the advocacy of a large intake of milk to cover this requirement.

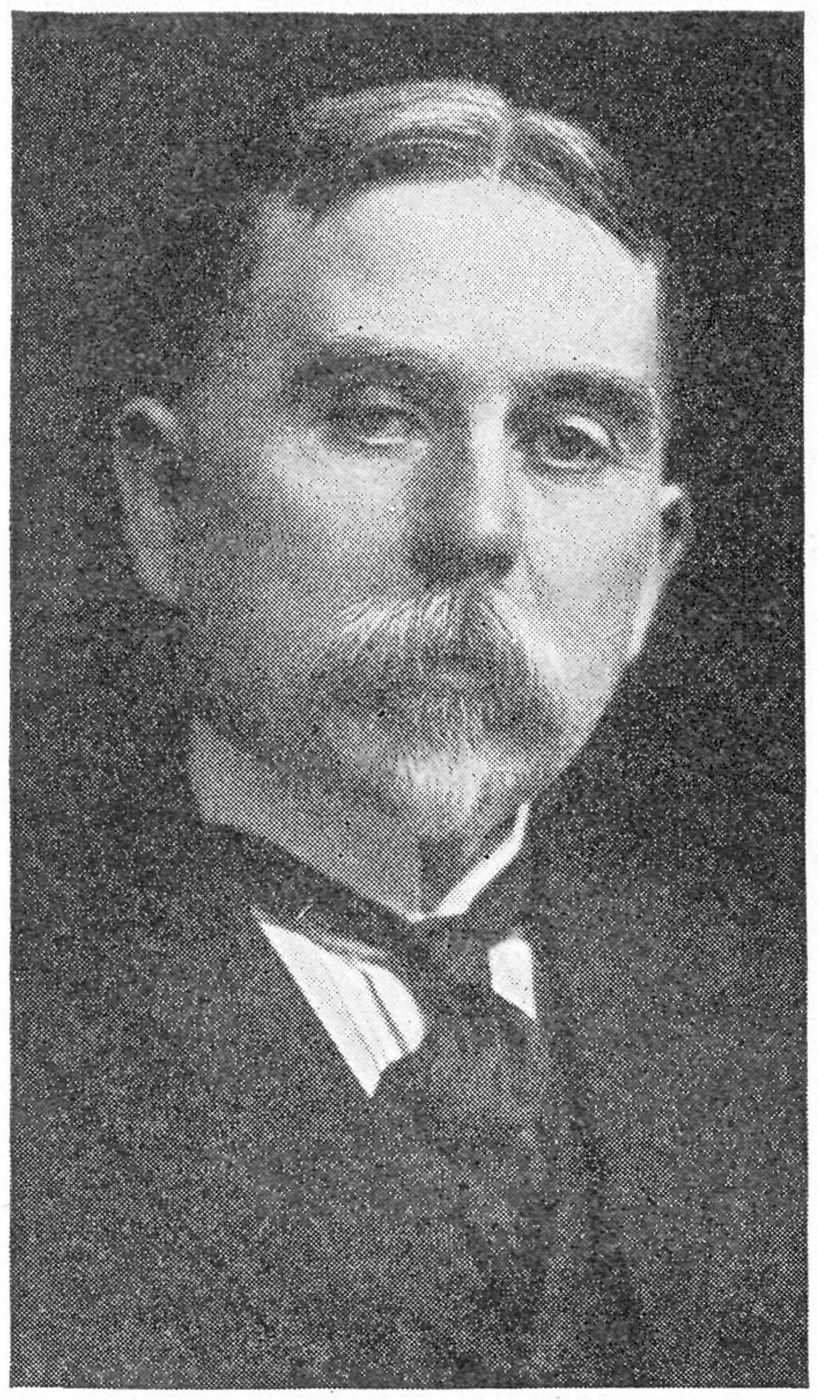
Women such as *Isabel Bevier*, *Helen Atwater*, *Ellen H. Richards*, *Amy L. Daniels*, *Mary Swartz Rose*, *Grace MacLeod*, and *Katharine Blunt* have fixed dietary standards for women and children on the basis of metabolism studies which have great value. And they have carried the torch of learning into the home itself.

Conclusion

It would seem unfriendly in conclusion not to mention our friends and neighbors, A. B. Macallum, a great original pioneer, Macleod, Banting, Collip, and Andrew Hunter, who across the great border of the Dominion of Canada have contributed largely to inspire our own work.

In reviewing this brief and incomplete summary of American contributions to physiological chemistry, the part that Germany has played in educating American scientists stands out strongly. It is a question whether we, in the United States, are not really living in the reflected glory of another country which has been exported hither, but which we cannot develop properly in succeeding generations. Is our own intellectual sustenance really an adequate diet containing the proper building stones and the fertility vitamin E? Are we now on the crest of productivity or are we just beginning? As to this, the next half-century of the AMERICAN CHEMICAL SOCIETY will bear witness.

During the winter of 1898–1899 a few men met at one another's homes in New York and became acquainted. These were J. K. Thatcher, Christian Herter, E. K. Dunham, Frederic Lee, Benjamin Moore (late professor of biological chemistry at Oxford), W. H. Park, and Graham Lusk. About 1902 a small group formed a journal club on biological chemistry which met at the Bellevue Medical College, because it was the only medical college whose doors could then be opened in the evening, and, after hearing papers, partook of beer and sandwiches. Here were to be found Levene, John Mandel, Horst Oertel, George Wallace, Jackson, Gies, E. K. Dunham, A. N. Richards, and Lusk. Here lifelong friendships were formed. It seems in retrospect like the origin of all things in New York. It is a parochial story. But the same kind of gatherings were then beginning or were in their infancy all over the country; helpful and stimulating they were, both at that time and throughout the lives of the individuals affected. For progress is deeply interwoven with human contacts.



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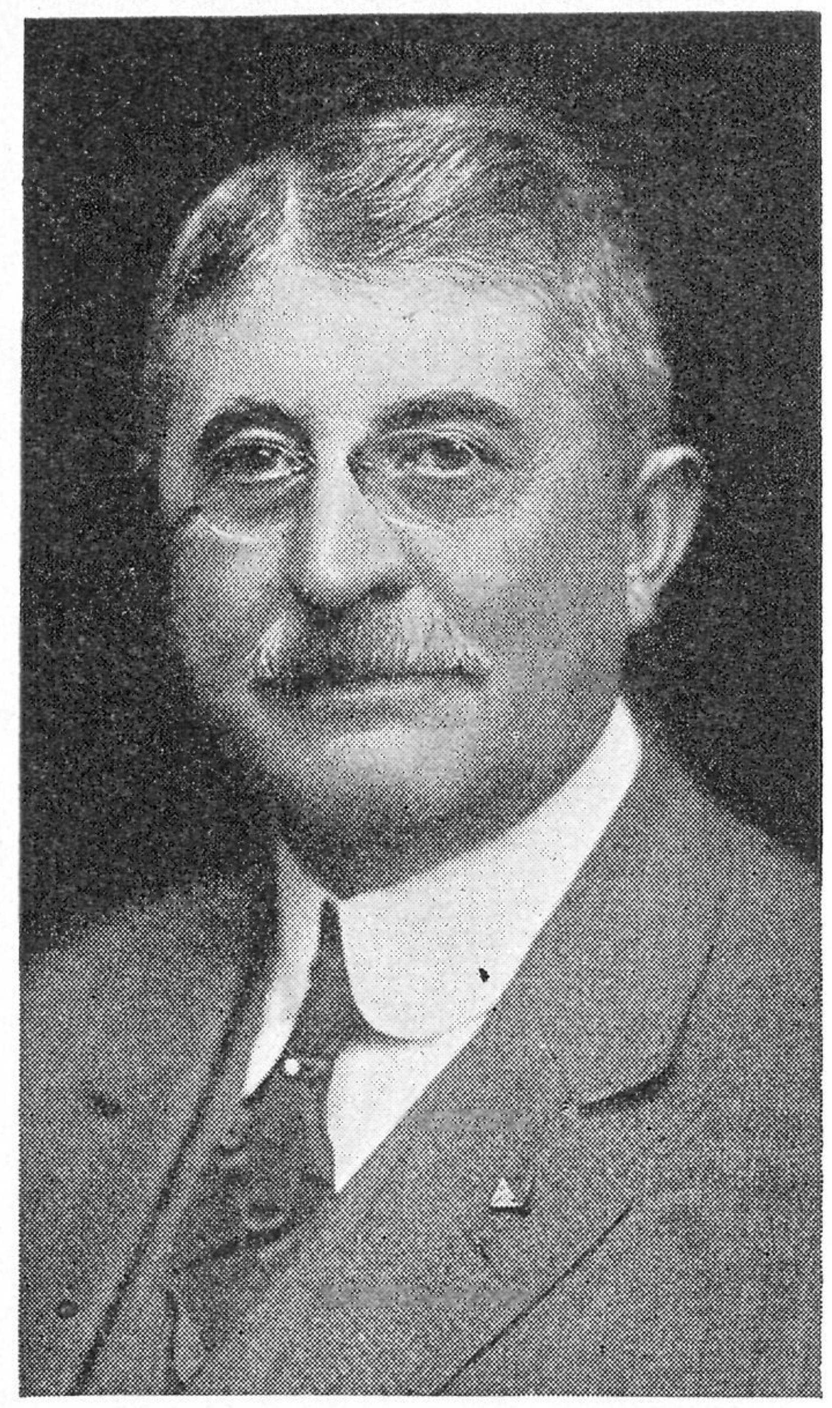

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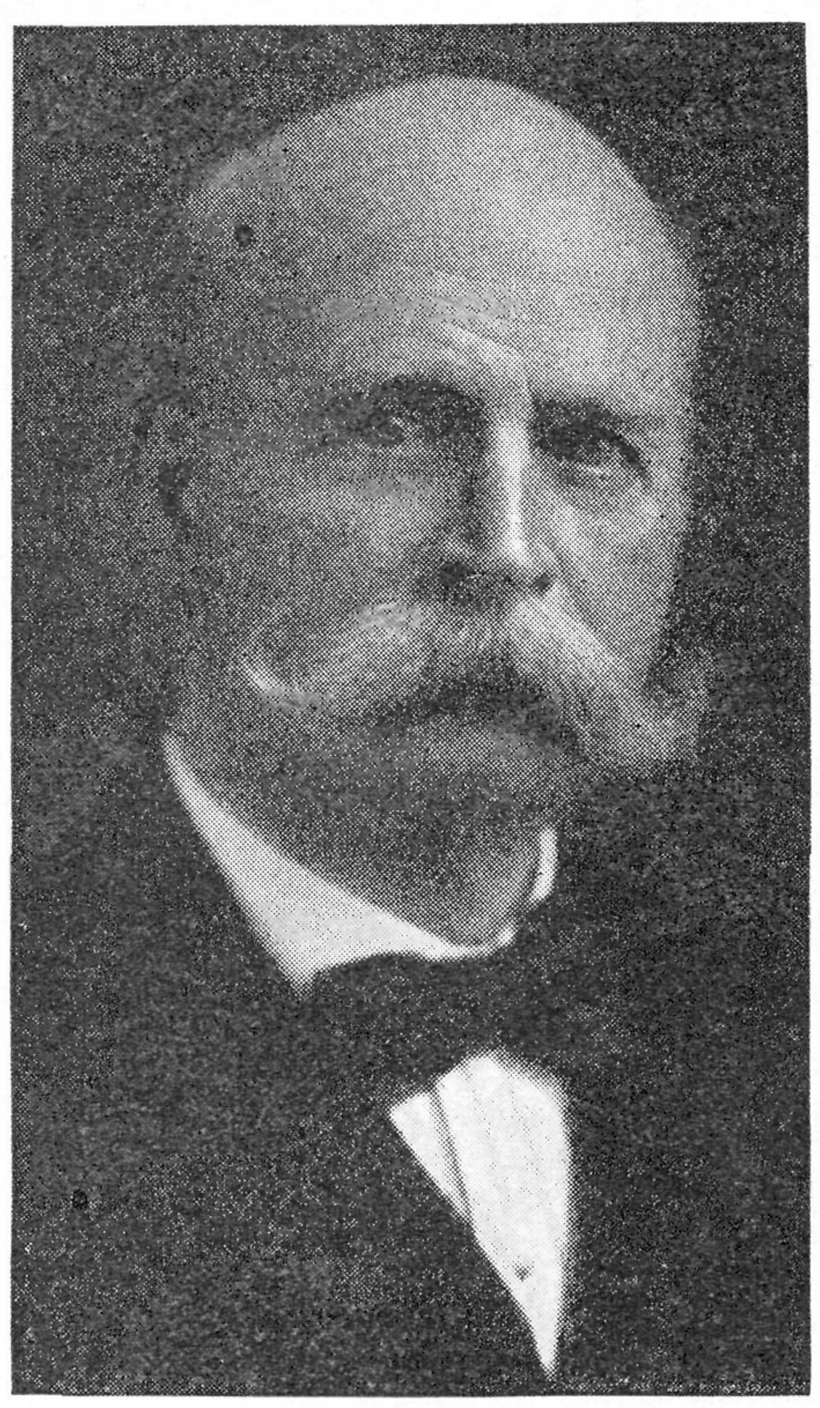

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EDWARD G. LOVE
(1850–1919)
Treasurer 1917–1919

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JOHN E. TEEPLE
(1874–)
Treasurer, 1919–