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JAMES LAWDER GAMBLE

1883—1959

A Biographical Memoir by
ROBERT F. LOEB

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Biographical Memoir

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July 18, 1883–May 28, 1959

BY ROBERT F. LOEB

JAMES LAWDER GAMBLE, a member of the National Academy of Sciences, elected in 1945, died on May 28, 1959 of a cerebral hemorrhage. With the death of Dr. Gamble, there passed from our midst one of that small group of pioneers in this country, trained in clinical medicine, but with the vision to recognize that not only practical benefits to man's welfare but also many of the fundamental problems of biology are to find their solution in the study of man in health and disease. The group of leaders represented by Dr. Gamble took the plunge of turning back to the biochemical laboratory for training in depth to prepare themselves for the quantitative attack on problems inviting solution through these approaches. This type of training is not only profitable but also fashionable today. Opportunities for the preparation of young clinicians for careers centering about human biology (more frequently and perhaps restrictively termed clinical investigation) are ample. But in the early days Gamble's excursion into basic science, beginning with the study of microchemical methodologies in the laboratory of Otto Folin, was sufficiently unconventional to be looked upon as "strange." The trail blazed by Gamble had a profound influence not only upon his own pupils but also upon succeeding crops of graduates in medicine.

The son of a gentleman farmer who migrated to the blue grass region of Kentucky for reasons of health, James Lawder Gamble was born on July 18, 1883 in Millersburg, Bourbon County. His primary education began in the Millersburg Female College, an institution

in which boys were enrolled over the years of innocence. From the pangs of his valedictory at the age of twelve there stemmed, perhaps, his lifelong anxieties and feelings of inadequacy as related to public appearances, yet the clarity and grace so characteristic of his lectures reveal no evidence of this early tribulation.

As early evidence of his versatility he was undaunted by his abrupt transfer from the atmosphere of the Female College to the Millersburg Military Institute. There, under a retired colonel who loved his Greek and Latin, he was given a substantial old-fashioned schooling which enabled him on graduation to pass entrance examinations for Harvard without difficulty. Then, because of parental apprehension that the rigors of the Boston climate might prove damaging to his health, a thesis refuted by the record, he entered Stanford University in 1901, and enrolled in the premedical course. Like many others with notable records of achievement, Gamble "drifted" into medicine without any particular conscious motivation and with the natural assumption that he would devote his life to the practice of medicine. After losing a year in college because of typhoid fever, Gamble graduated from Stanford in 1906, with the assistance of the earthquake which came in the spring of that year and eliminated the ordeal of final examinations.

Now strong enough to endure the New England climate, Gamble entered Harvard Medical School, from which he graduated in 1910. He completed a two-year medical internship at the Massachusetts General Hospital and, following a six-month service at the Children's Hospital in Boston in 1913, he went abroad to visit the famous European clinics. This journey proved to be the turning point in Gamble's career, for he was deeply impressed with what appeared to be effective attempts to study disease in man by the quantitative techniques of the biochemist and physiologist, cumbersome though they were at that time.

Upon his return to this country he took advantage of his financial independence which, with characteristic modesty, he always looked upon as a significant factor in his career. Gamble's sincere and sus-

tained scientific interest and his drive never succumbed to the temptations of dilettantism, so often the hazard of security. He went to work in the laboratory of Folin where simple chemical procedures were being developed which were readily applicable to the study of metabolic processes in man. He also acquired the technique of indirect calorimetry under Francis Benedict.

With these methods at his disposal, Gamble returned to the Massachusetts General Hospital where, in the small chemistry laboratory of those days, he began his career as an investigator under the aegis of Dr. Fritz Talbot. His first undertaking was to study in infants the effect of varying protein intakes upon the partition of nitrogen end-products in the urine, as Folin had done in adults. He also collaborated with J. H. Means and Walter W. Palmer in his first publication entitled, "Basal Metabolism and Creatinine Elimination." While carrying out these studies there entered into Gamble's life a profound influence which turned out to be the directing force of his career as an investigator. His roommate and intimate friend Palmer was at work in the same laboratory under the direction of Professor L. J. Henderson with whom he had embarked upon fundamental studies of acid-base and osmotic pressure regulation of the body by the kidney. In frequent visits to the laboratory, Henderson's catalytic propensities began to act not only on the substrate of Palmer but also on that of Gamble. Stimulated to seek further training in biological chemistry, Gamble soon asked Henderson for counsel. Henderson characteristically replied, "Come to Cambridge on Saturday mornings and quiz my students in Chemistry 15." Gamble accepted the challenge and fortified himself by reading fifty pages of Abderhalden each week in preparation. Perhaps nothing beyond discipline emerged from this experience, but his close contact with Professor Henderson continued to stimulate his imagination in problems of electrolyte physiology.

In 1914 rumors reached Boston that there had come into being at Johns Hopkins the first full-time department of pediatrics, well equipped with splendid laboratories for investigation. John Howland directed this new venture at Hopkins, and associated with him were

Drs. Edwards A. Park and W. McKim Marriott. This group was later augmented by the advent of Alfred Shohl and Benjamin Kramer, who in the course of his studies developed techniques which in subsequent years proved invaluable. Dr. Gamble visited Hopkins and was invited to join the group by Dr. Howland. He accepted and moved to Baltimore in January of 1915 and was assigned to the out-patient department for half of his time, free, however, to carry on his research in the other half. His entire teaching assignment consisted of two lectures a year on the food requirements of infants. The first of these lectures, Dr. Gamble confesses, he memorized so effectively and delivered with such fluency that, to Dr. Howland's great merriment, his material ran out in twenty-five minutes and he had to dismiss the class.

Six months after his arrival in Baltimore, Dr. Gamble made the important decision to abandon a career in clinical medicine. Thus, the influence of L. J. Henderson continued to play a guiding role in his life. Dr. Howland accepted Gamble's decision with reluctance and misgiving, fearful that he would be lost in a "no man's land" between clinical medicine and the fundamental sciences. Subsequent events bear witness to the fact that this "no man's land" has happily become a densely populated terrain. It was something of a shock to Howland that Gamble exhibited no interest in academic advancement but was content to dedicate his life, "to the study of disease by means of chemistry." Indeed, Howland continued to have misgivings about Gamble's wisdom and his future, despite the deep and abiding friendship which had developed between them. But from then on, relieved of routine clinical assignments and unencumbered by administrative responsibility, Gamble was free to follow his curiosity and imagination into many problems of fundamental importance. He always exhibited a propensity for quiet contemplation and early developed the capacity to design simple experiments which yielded definitive answers. He worked with his own hands and rarely with technical assistance—an invaluable approach all too often neglected today. He was deliberate in publication. However, his continued measured pace insured that each of his works reflected clarity of expression,

a rare sense of proportion, a capacity for self-criticism and discipline and, with all, a disarming modesty.

During the First World War Dr. Gamble returned for a time to clinical medicine. He served as *médecin-chef* of the Sanatorium Édouard Trudeau, this being the name of a small American hospital for women refugees from the devastated region of France which he set up in a dilapidated chateau near Versailles. Here he cared for some ninety women patients and also looked after several hundred undernourished children housed in barracks built in the handsome park surrounding the chateau. This was his one and only experience as an administrator, but on reflection in later years he remembered it with pleasure and much amusement.

Shortly after Dr. Gamble's return to Baltimore in 1919, Dr. Howland developed a deep interest in the treatment of epilepsy by the ketosis of starvation. Alert to the possibilities which this therapeutic regimen offered for the exploration of the responses and defenses of the body in acidosis, Gamble went to work with his two Canadian collaborators, Graham Ross and F. F. Tisdall. The design of this study was simple. Since there was no food intake or feces it depended only on measurements from daily urine collections and from the blood plasma. The execution of the experiment was laborious and extended over a period of nearly two years, and the analytical determinations were tedious beyond words, but rarely have data been subjected to more original deductive reasoning. The results are best summarized in Gamble's own words.

"1. The data display in operation the two adjustable components of the acid-base construction of urine (titrable acidity and ammonia production) which Henderson and Palmer described and which permit the removal of anion excess within the prescribed limits for urine acidity without expenditure of fixed base beyond the quantity which properly presents for removal."

2. They show "the determining role of fixed base in sustaining the osmolar value of the body fluids because of the adjustability of the total cation-anion equality."

3. They show further "the relation of volume of the body fluids to fixed base content on the premise of preservation of the normal osmolar value with the corollary that, so long as the kidney is operating accurately, loss (or gain) of water and electrolytes will be parallel. On this basis the data were used to allocate losses of water from the body fluid compartments from measurements of outgo of intracellular and of extracellular base."

This study of fasting children, begun in 1919, was finally published in 1923 and is a notable classic. Perhaps more significant than the contribution which these experiments made to our knowledge of electrolyte physiology was their influence on clinical research. At a time when most clinical investigation consisted of the recording of endless observations based on some new method, Gamble planned a crucial experiment to elucidate basic problems of function and applied chemical methods to this end. These experiments constituted a pioneer approach to the interpretation of quantitative description in terms of the mechanisms involved. Meaning received the primary emphasis. It was thrilling for a small but sympathetic group of colleagues to see something happening to figures other than tabulation, to see them come to life and illuminate the processes of the acid-base equilibrium. The general design of the experiments devised by Gamble continues to be the pattern for most studies dealing with electrolyte and water metabolism today. Even the expression of data by simple graphic means, now known as "Gambelian diagrams" or "Gamblegrams," has been generally adopted and is a blessing for students, teachers, and investigators alike.

In 1922, on the invitation of Dr. Oscar Schloss, Professor of Pediatrics at Harvard, Dr. Gamble decided to return to the scene of his early training as an Assistant Professor. Opportunities were presented to develop his own laboratory, hopes of a metabolic ward at the Children's Hospital were raised, and Schloss was wholly sympathetic to Gamble's interest. Dr. Gamble was appointed a full Professor and Chairman of the Department in 1932. In 1950 he became an Emeritus Professor, but continued to hold the post of Director of the Metabolic

Research Laboratory at the Children's Hospital, and continued active investigation.

Beginning with Dr. Allan Butler, his first protégé in Boston, there passed through Dr. Gamble's laboratory a steady stream of embryonic investigators, matured by an indoctrination into scientific critique and enriched by their association with him. His pupils not only shared his laboratory, they also enjoyed the warm hospitality of the Gamble family in Brookline, at the farm in Taunton, and in the summer home in Maine where they found that their host was equally accomplished at golf and sailing. Dr. Gamble proved to be a master of leisure as he was a master of science, and he showed the same versatility, ingenuity, and generosity in planning his play as in planning his work. The archives of the Gamble family contain for the delight of generations to come the films of the Arthurian romances adapted and directed and filmed by Dr. Gamble with his children as the actors. During these theatricals the household was in a gentle uproar and bore with the commandeering of its most prized possessions if it would thereby enhance the Lady Guinevere's charms or cause more to tremble at Merlin's magic.

It is beyond the scope of this sketch of Dr. Gamble to recount his many contributions to medical science enumerated in his bibliography. Nevertheless, it is impossible to resist the temptation to review briefly the "Life Raft" studies carried out during the Second World War with Dr. Allan Butler. As in the studies on fasting epileptic children, Gamble seized upon a problem of practical importance to explore and delineate certain basic physiological principles. The gravity of the problem of castaways, particularly in the Pacific area, needs no amplification. As Dr. Gamble has set down in his Harvey Lecture, "These studies were undertaken before the merciful invention of methods of obtaining [drinking] water from sea water. Their premise was, therefore, a limited weight allowance for food and water per man per day. Since survival for fasting is several times longer than for thirsting, the physiological benefits of food, under the circumstances of a restricted over-all allowance for both food

and water, must be appraised in terms of cost to the water balance of the body. The obviously indicated first step in this study was to define the minimal water requirement in the state of fasting. The second step was to observe, in subsequent experiments, the alteration of this requirement produced by the intake of a given kind of food." With the problems thus clearly stated, Gamble, Butler, and their associates carried out their studies with simplicity of design, a nicety of precision, and thoroughness, again reminiscent of the studies on the acidosis of starvation. The two physiological questions posed were answered. The unique suitability of glucose, the inutility of protein and the fallacy of providing fat in an emergency ration of limited weight in which water must have priority were clearly demonstrated.

Dr. Gamble's contributions have happily been recognized and appreciated throughout the world, as forcefully evidenced by his having been the recipient of honorary degrees from the University of Zürich, from Yale University, and from the University of Chicago. He served as Editor-in-Chief of the *Journal of Clinical Investigation* for a number of years and served it well. He was honored not only by membership in the National Academy of Sciences but also by other scientific bodies too numerous to mention. He served as President of the American Pediatric Society in 1945. Among many lectureships may be cited that of the Harvey Society, the Thayer Lectures at Johns Hopkins and the Lane Lectures at Stanford. He was the recipient of the Kober Medal of the Association of American Physicians, the Moxon Medal of the Royal College of Physicians of London, and the John Howland Medal of the American Pediatric Society.

In the presentation of the Kober Medal to Dr. Gamble in 1951, it was fittingly stated, "I wish that it had more sides than two; one for the loyal friend, one for the talented wise human being, one for the inspiring leader of young investigators, one for the warm and entertaining host, and above all, one for the scientist who has contributed as much to the philosophy of his disciplines as to its fund of knowledge."

CURRICULUM VITAE

EDUCATION

A. B., Stanford University, 1906
 M. D., Harvard University, 1910
 Intern, Massachusetts General Hospital, 1910-12
 Intern, Children's Hospital, Boston, 1912-13
 Clinical Studies in Vienna, 1913
 Metabolism Studies, Massachusetts General Hospital, 1914

ACADEMIC POSITIONS

Johns Hopkins Medical School, Associate in Pediatrics, 1915-18
 Instructor, 1918-22
 Harvard Medical School, Assistant Professor of Pediatrics, 1922-25
 Associate Professor, 1925-32
 Professor, 1932-50
 Chairman of Department, 1946-50
 Professor Emeritus, 1950-59
 Children's Hospital, Boston, Physician and Chief of Metabolism Division,
 1933-1953
 Consulting Physician (Metabolism), 1953-1959

SCIENTIFIC SOCIETIES

Association of American Physicians
 American Society for Clinical Investigation
 American Pediatric Society. President 1945
 Pediatric Research Society
 American Academy of Pediatrics
 Société de Pédiatrie de Paris
 British Pediatric Association
 American Society of Biological Chemists
 The American Institute of Nutrition
 American Academy of Arts and Sciences
 National Academy of Sciences
 Editor, The Journal of Clinical Investigation, 1944-47
 American Red Cross Physician in France, 1917-19
 With A. M. Butler, carried out studies on life raft ration for OSRD, 1942-

LECTURESHIPS

Thayer Lectures, John Hopkins Medical School, 1937
The Harvey Society of New York, 1947
Lane Medical Lectures, Stanford Medical School, 1949
Chapin Oration, Rhode Island Medical Society, 1950
Robert J. Terry Lecture, Washington University Medical School, 1952

HONORARY DEGREES

S. M., Yale, 1930
M. D., Zürich, 1950
Sc.D., Chicago, 1952

AWARDS

Borden Award, American Academy of Pediatrics, 1946
Chapin Award, Rhode Island Medical Society, 1950
Kober Medal, Association of American Physicians, 1951
Moxon Medal, Royal College of Physicians, London, 1954
John Howland Medal and Award, American Pediatric Society, 1955

KEY TO ABBREVIATIONS

- Am. J. Dis. Child.=American Journal of Diseases of Children
 Am. J. Physiol.=American Journal of Physiology
 Am. Med. Assoc. J. Dis. Child.=American Medical Association Journal of Diseases of Children
 Arch. Neurol. Psychiat.=Archives of Neurology and Psychiatry
 Boston Med. Surg. J.=Boston Medical and Surgical Journal
 Bull. Johns Hopkins Hosp.=Bulletin of the Johns Hopkins Hospital
 Harvard Med. Alum. Bull.=Harvard Medical School Alumni Bulletin
 Internat. Clinics=International Clinics
 J. Am. Med. Assoc.=Journal of the American Medical Association
 J. Biol. Chem.=Journal of Biological Chemistry
 J. Clin. Invest.=Journal of Clinical Investigation
 J. Exp. Med.=Journal of Experimental Medicine
 J. Mich. Med. Soc.=Journal of Michigan State Medical Society
 J. Pediat.=The Journal of Pediatrics
 New Eng. J. Med.=New England Journal of Medicine
 Proc. Am. Phil. Soc.=Proceedings of the American Philosophical Society
 Proc. Soc. Exp. Biol. Med.=Proceedings of Society for Experimental Biology and Medicine
 R. I. Med. J.=Rhode Island Medical Journal
 Trans. Am. Pediat. Soc.=Transactions of the American Pediatric Society
 Trans. Assoc. Am. Physicians=Transactions of the Association of American Physicians

BIBLIOGRAPHY

1914

With J. H. Means and W. W. Palmer. Basal Metabolism and Creatinine Elimination. *J. Biol. Chem.*, 19:239.

1916

Ammonia and Urea Content of Infant's Stools. *Am. J. Dis. Child.*, 12:333.

1917

With F. B. Talbot. The Protein Metabolism of an Infant. *Am. J. Dis. Child.*, 13:362.

1919

With S. Goldschmidt. A Study of Creatinuria in Infants. I. Relation of

Creatinuria to Acidosis. The Elimination of Ingested Creatine and Creatinine. *J. Biol. Chem.*, 40:199.

With S. Goldschmidt. A Study of Creatinuria in Infants. II. Relation of Protein Intake to Urinary Creatine. *J. Biol. Chem.*, 40:215.

1920

With K. D. Blackfan. Evidence Indicating a Synthesis of Cholesterol by Infants. *J. Biol. Chem.*, 42:401.

Carbonic Acid and Bicarbonate in Urine. *J. Biol. Chem.*, 51:295.

1922

With S. G. Ross and F. F. Tisdall. A Study of Acidosis Due to Ketone Acids. *Trans. Am. Pediat. Soc.*, 34:289.

1923

The Manner of the Therapeutic Action of Substances Producing Hydrochloric Acid. *Trans. Am. Pediat. Soc.*, 35:208.

With S. G. Ross. Studies of Tetany. I. The Effect of Calcium Chloride Ingestion on the Acid-base Metabolism of Infants. *Am. J. Dis. Child.*, 25:455.

With S. G. Ross. Studies of Tetany. II. The Effect of Ingestion of Hydrochloric Acid Producing Substances on the Acid-base Metabolism of an Infant and the Probable Manner of Their Action in the Treatment of Tetany. *Am. J. Dis. Child.*, 25:470.

With S. G. Ross and F. F. Tisdall. The Metabolism of Fixed Base During Fasting. *J. Biol. Chem.*, 57:633.

1925

With K. D. Blackfan and B. Hamilton. A Study of the Diuretic Action of Acid-producing Salt. *J. Clin. Invest.*, 1:359.

With S. G. Ross. The Factors in Dehydration Following Pyloric Obstruction. *J. Clin. Invest.*, 1:403.

With M. A. McIver. A Study of the Effects of Pyloric Obstruction in Rabbits. *J. Clin. Invest.*, 1:531.

1926

With M. A. McIver. Fixed Base in Gastric Juice. *Proc. Soc. Exp. Biol. Med.*, 23:439.

1927

The Chemistry Findings in Rickets. *Boston Med. Surg. J.*, 197:373.

With B. Hamilton. The Acid-base Composition of Urine from an Epileptic Child. *Bull. Johns Hopkins Hosp.*, 41:398.

1928

No Child Need Have Rickets. In: *Chemistry in Medicine* (N. Y., The Chemical Foundation), p. 145.

With M. A. McIver. Body Fluid Changes Due to Upper Intestinal Obstruction. *J. Am. Med. Assoc.*, 91:1589.

With M. A. McIver. Acid-base Composition of Gastric Secretions. *J. Exp. Med.*, 48:837.

With M. A. McIver. Acid-base Composition of Pancreatic Juice and Bile. *J. Exp. Med.*, 48:849.

With M. A. McIver. Body Fluid Changes Due to Continued Loss of External Secretion of the Pancreas. *J. Exp. Med.*, 48:859.

Acidosis and Alkalosis. *New Eng. J. Med.*, 199:1318.

1929

Dehydration. *New Eng. J. Med.*, 201:909.

With M. C. Putnam and C. F. McKhann. The Optimal Water Requirement in Renal Function. I. Measurements of Water Drinking by Rats According to Increments and of Several Salts in the Food. *Am. J. Physiol.*, 88:571.

With K. D. Blackfan. The Treatment of Acidosis and Alkalosis. In: the George Blumer Edition of Billings-Forchheimer's *Therapeutics of Internal Diseases—Supplement* (N. Y., Appleton), Chapter 29.

1930

Epilepsy. Evidences of Body Fluid Volume Disturbances. *Arch. Neurol. Psychiat.*, 23:915.

With T. G. H. Drake and C. F. McKhann. Total Water and Chloride Content of Dehydrated Rats. *J. Exp. Med.*, 51:867.

With T. G. H. Drake and P. Marsh. The Alkalosis of Vomiting and the Acidosis of Advanced Renal Disease. *Am. J. Dis. Child.*, 40:705.

1933

With A. M. Butler and C. F. McKhann. Intracellular Fluid Loss in Diarrheal Disease. *J. Pediat.*, 3:84.

1934

With C. F. McKhann and A. M. Butler. Economy of Water in Renal Function Referable to Urea. *Am. J. Physiol.*, 109:139.

1936

Extracellular Body Fluid. *Internat. Clinics*, 2:184.

Extracellular Fluid and Its Maintenance. *New Eng. J. Med.*, 215:1150.

1937

I. Extracellular Fluid and Its Vicissitudes. II. Renal Defense of Extracellular Fluid. Thayer Lectures. *Bull. Johns Hopkins Hosp.*, 61:151, 174.

1942

The Story of an Education. Memorial Exercises for Kenneth D. Blackfan. *Harvard Med. Alum. Bull.*, 16(suppl. 1).

Pathogenesis of Acidosis and Alkalosis. *J. Mich. Med. Soc.*, 41:210.

1944

Water Requirements of Castaways. *Proc. Am. Phil. Soc.*, 88:151.

With A. M. Butler. Measurement of Renal Water Requirement. *Trans. Assoc. Am. Physicians*, 58:157.

1945

Random Thoughts on the Position of Pediatrics. (President's Address to the Annual Meeting of the American Pediatric Society.) *Am. J. Dis. Child.*, 69:1.

With K. R. Fahey, J. Appleton, and E. A. MacLahlan. Congenital Alkalosis with Diarrhea. *J. Pediat.*, 26:509.

1947

Physiological Information from Studies on the Life Raft Ration. The Harvey Lectures, ser. 42, 1946-1947, p. 247.

Deficits in Diarrhea. *J. Pediat.*, 30:488.

With W. M. Wallace. Diarrheal Dehydration. Charts printed for exhibit Fifth Intern. Pediatric Congress. Boston, Spaulding-Moss.

1950

Body Fluids and the Rationale of Fluid Therapy. Ninth Annual Charles V. Chapin Oration. *R. I. Med. J.*, 33:403.

Presentation of the Kober Medal to Dr. Edwards A. Park. *Trans. Assoc. Am. Physicians*, 63:21.

1951

Acceptance of the Kober Medal by J. L. Gamble. *Trans. Assoc. Am. Physicians*, 64:36.

With W. M. Wallace, L. Eliel, M. A. Holliday, M. Cushman, J. Appleton, A. Stenberg, and J. Piotti. Effects of Large Loads of Electrolytes. *Pediatrics*, 7:305.

Background of Work on Survival Rations. Activities Report by the Research and Devel. Associates, Food and Container Institute, 3:137.

Companionship of Water and Electrolytes in the Organization of Body Fluids. Lane Medical Lectures. Stanford, Calif., Stanford University Press. Vol. 5, No. 1.

1953

Early History of Fluid Replacement Therapy. Annual Robert J. Terry Lecture, Washington Univ. Medical School. *Pediatrics*, 11:554.

1954

The Hospital for Sick Children, Great Ormond St., London, and the Children's Hospital in Boston. *Harvard Med. Alum. Bull.*, 28:9.

Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. A Lecture Syllabus, 6th ed. Cambridge, Mass., Harvard University Press.

1955

Acceptance of the John Howland Medal and Award of the American Pediatric Society. *Am. Med. Assoc. J. Dis. Child.*, 90:483.