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HISTORICAL

Martin Gibbs and the peaceful uses of nuclear radiation, ^{14}C

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Abstract This abstract is a prologue to this paper. Prior to his health failing, Martin Gibbs began writing remembrances of his education and beginning a science career, particularly on the peaceful uses of nuclear radiation, at the U.S. Brookhaven National Laboratory (BNL), Camp Upton, NY. Two years before his death Martin provided one of us (Govindjee) a draft text narrating his science beginnings in anticipation of publication in *Photosynthesis Research*. Govindjee edited his draft and returned it to him. Later, when it became difficult for him to complete it, he phoned Govindjee and expressed the desire that Govindjee publish this story, provided he kept it close to his original. Certain parts of Martin's narrations have appeared without references (Gibbs 1999). The Gibbs family made a similar request since the narrations contained numerous early personal accounts. Clanton Black recently presented an elegant tribute on Martin Gibbs and his entire science career (Black 2008). Clanton was given the draft, which he and Govindjee then agreed to finish. This chronicle is their effort to place Gibbs's narrations about his education and his maturation scientifically, in context with the beginnings of biological chemistry work with carbon-14 at the BNL (see Gibbs 1999). Further, these events are placed in context with those times of newly discovered radioisotopes which became available as part of the intensive nuclear research of World War II (WW II). Carbon-14, discovered during WW II nuclear research in 1940, was extremely useful and quickly led to the rapid discovery of new carbon metabolism pathways and biochemical cycles, e.g., photosynthetic carbon assimilation, within a decade after WW II.

Keywords Asymmetric glucose labeling · Brookhaven 1950 Conference on CO_2 assimilation · Brookhaven National Lab (Camp Upton) · ^{14}C-labeled sugars · First Gatlinburg Photosynthesis Conference · Hexose monophosphate pathway in plants · Hill reaction · Photophosphorylation · Photosynthesis

Abbreviations

BNL	Brookhaven National Laboratory
EMP	Embden, Meyerhof, and Parnas
HMP	Hexose mono phosphate
WW II	World War II

Youth and college (1922–1943)

Martin Gibbs was born in Philadelphia in 1922; his youth was shaped and dominated by the decade of the Great Depression. Assessing options after graduation from an all male high school in February 1940, he decided that he wanted to study chemistry in college. Due to financial constraints, institutional choices had to be located nearby to his parents. In 1940, between high school and fall entry into the Philadelphia College of Pharmacy and Science (now the University of Sciences in Philadelphia), he was hired in a bookbinding shop, where his job was to spread

Honoring Martin Gibbs (1922–2006).

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glue on the spine of book covers (with no notion of a future career engaged in editing and publishing); by a local supermarket, where he apprenticed as a butcher; and finally in that summer by the Pennsylvania Railroad, where he secured an evening position that he held for three years while he was an undergraduate student.

At college, he followed a traditional course of study in chemistry. However, he did include general biology, pharmacognosy, and botany as electives. His pharmacognosy instructor, Edmund MacLaughlin, emphasized the history of drugs, taught him how to make herbarium specimens, and how to identify important medicinal plants. Gibbs's interest in biology, particularly in plant sciences, became strong when he met Theodore Phillip Haas, a former curator of the Munich-Nymphenburg Botanical Institute and instructor in Botany, who conducted weekend field excursions through the parks of Philadelphia and introduced him to the principles of plant systematics and comparative morphology. America was in a decade-long deep economic depression and research budgets were low, especially at his school, being mostly a teaching institution. Nonetheless, Nathan Rubin, the professor of organic chemistry encouraged his lab initiative and secured some funding for independent study. Under his immediate guidance, Gibbs received some laboratory training in synthetic organic chemistry.

Graduate school at the University of Illinois at Urbana-Champaign (1943–1947)

Just prior to college graduation, Gibbs attended the 1943 meeting of the American Chemical Society where, following registration at the placement center and subsequent interviews, he accepted without hesitation a teaching assistantship (12 weekly hours of laboratory instruction in general and analytical chemistry, with an additional eight hours given to paper grading and tutorials for the grand sum of $750 per annum) in the highly regarded Department of Chemistry at the University of Illinois at Urbana-Champaign (UIUC). His first courses, all taught by members of the National Academy of Sciences (USA), were general biochemistry and laboratory (William C. Rose), vitamins and hormones (Herbert E. Carter), organic chemistry (Reynold C. Fuson), and physical chemistry (Frederic T. Wall). As the year progressed, Gibbs's interest in chemistry waned which led to the decision to major in the application of chemistry to botany. But the biochemistry faculty, a division of the Chemistry Department, had scant interest in plants; thus he transferred into the Department of Botany as a technical assistant in the laboratory of F. Lyle Wynd.

Wynd had moved to Urbana in 1938 when there was very little money available in the department budget for research facilities, equipment, and stipends; he had known W. Richard Graham of the Cerophyll Laboratories, Inc. (American Dairies, Inc.) and was able to interest him in providing financial support for the Wynd laboratory. Unusual then, the grant supplied money for equipment, supplies, travel, and graduate student stipends. The Cerophyll fund enabled Wynd to convert the Botany Annex of the UIUC, a turn-of-the-century two-story residence, into a spacious laboratory facility reasonably equipped for applying chemistry to the problems of botanical physiology and biochemistry (Fig. 1). With Graham as mediator, Wynd succeeded in getting additional funding including graduate student stipends from the King Ranch in Texas. Gibbs fulfilled his obligation to the donor (W. Richard Graham) and to Wynd by ashing endless samples of grasses followed by mineral content analyses using techniques developed by Ray Noggle (Noggle 1945), the senior student occupant of the Botany Annex (Fig. 2). Ray distributed the plant specimens and in turn Gibbs gave the data to him. In addition to Ray and Gibbs, the group included three undergraduates, one of whom arranged a "blind" date with her roommate, Karen Kvale, who, after a career as a flight attendant, later became the wife of Gibbs in 1950. Gibbs took the usual courses in botany (taxonomy, genetics, ecology, morphology), as required by the departmental program. It was only in Wynd's physiology course that Gibbs learned about photosynthesis, focusing upon the effects of light, CO_2, temperature, water, and mineral content on the process. The formaldehyde theory of CO_2 conversion to glucose proposed in 1870, without experimental proof, was highlighted (Pfeffer 1900).

After one year of employment in the Annex under the guidance of Wynd and Noggle and completion of course work in botany, chemistry, and agronomy, Gibbs

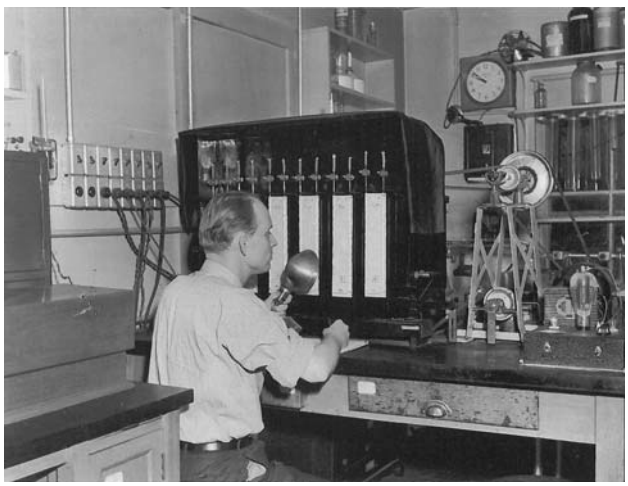

Fig. 1 Laboratory constructed for F. Lyle Wynd in the Botany Annex at the University of Illinois, Urbana, Illinois, ~1940. Photo provided by Govindjee

Fig. 2 Ray Noggle at the Charles F. Kettering Laboratory, Yellow Springs, Ohio, ~1953. Photo provided by Clanton Black

approached Wynd with a thesis proposal. He learned that Wynd was soon going to move to Michigan State University as Head of their Botany Department, but Wynd advised Gibbs to remain in Urbana; this was "totally unexpected and devastating" to Gibbs. He was a third year graduate student in Botany, but without a "thesis father," without financial support, and without a departmental mentor. However, fortunately, the role of a mentor was taken by Harry Fuller, the other senior plant physiologist; he was an outstanding teacher and a gifted writer, and when he accepted to act as advisor of Gibbs this satisfied the graduate college requirement. In addition, the financial support problem was also, unexpectedly, solved for Gibbs: Cerophyll and King Ranch monies remaining in the coffers of the Botany Department were turned over to E.E. DeTurk, an eminent authority on soil fertility in the Department of Agronomy (see DeTurk 1948). DeTurk offered and Gibbs accepted immediately a two-year half-time appointment in the Department of Agronomy, while retaining graduate status within the Department of Botany. The research project, '*the effect of soil type on the chemical composition of common grasses*,' was analogous to the one directed by Wynd and Noggle, but with one major difference: Gibbs had to be responsible for the growth of the plant specimens in the field plots of the Dixon Springs Experiment Station near Vienna, Illinois. Vienna was 200 miles away, and Gibbs did not have a license to drive, but his colleagues in Agronomy gave him their unselfish support in transporting him to the site. Further, Fuller negotiated with the Department and helped Gibbs to retain space in the Botany Annex. Gibbs became the sole occupant of the Annex with approval of the Department to utilize the facility for his obligation to DeTurk and for his future undefined thesis research.

With financial and space predicaments solved, Gibbs attended to the thesis. Ray's doctoral research (Noggle 1945) dealt with ploidy in plants, and with the analytical procedures that Gibbs had mastered coupled to lecture materials in the morphology course of John T. Buchholtz (see Buchholz 1939), a thesis outline for Gibbs was approved by Harry Fuller. Buchholz, the 1941 President of the Botanical Society of America, had been a summer investigator in the Department of Genetics, Cold Spring Harbor, New York, where he had published with the distinguished geneticist Albert F. Blakeslee (see Satina and Blakeslee 1941). Gibbs's Ph.D. topic focused on the chemical changes occurring during the growth of diploid and tetraploid *Datura stramonium* (Jimson weed) (Gibbs 1948). Gibbs writes, "Comparison was made on both physiological and chronological ages of the plants because the diploids took 35 days and the tetraploids needed an additional 15 days to complete the vegetative phase of growth. The slower rate of development explained most of the differences in the chemical composition of the two tissues of equal chronological age. Blakeslee supplied the seeds and Buchholz advised the plan of research." Several years later, soon after Gibbs settled into his post graduation position at Brookhaven National Laboratory (BNL), he traveled to Northampton, MA, where Blakeslee held a part-time position at Smith College, to personally thank Blakeslee for his support. Mrs. Blakeslee invited Gibbs to spend the evening in their comfortable home rather than the Northampton Inn. Gibbs recalls that he never had an opportunity to visit Buchholz. Mrs. Blakeslee was killed in an automobile accident in April 1951 and Blakeslee died six weeks later.

The appointment of Gibbs in the Department of Agronomy at the University of Illinois terminated in May 1947. With that deadline looming before him, he gave final reports to DeTurk and to the dissertation committee. Prior to the thesis defense examination, Gibbs sent a brief communication with results taken from the project with DeTurk to *Plant Physiology*, his first and only manuscript accepted as submitted (Gibbs 1947).[1] Following his successful defense of thesis there was a lunch arranged by the two botanical members of the committee (Harry Fuller and Oswald Tippo). Gibbs remembered it as:

> …memorable since the event was the single informal occasion that I experienced with faculty during four years in graduate school. After my departure from the Botany Annex, James Nance, Robert Emerson,[2]

[1] It was serendipitous that the article was on *Panium antidotale*, a warm season grass from the King Ranch, because it employs C_4 photosynthesis, unknown then, which Gibbs persistently challenged during the 1970s and 1980s. In fact Gibbs's data on leaf mineral content is in agreement with a character of C_4 plants known today, namely the efficient use of mineral nutrients in photosynthesis and growth (Black 1973; Brown 1978; Gerwick and Black 1979; Moore and Black 1979).

[2] Both Robert Emerson and Eugene Rabinowitch later were Ph.D. thesis advisors of one of us (Govindjee) during the late 1950s.

Eugene Rabinowitch and distinguished Historical Corner Editor Govindjee (of *Photosynthesis Research*) occupied or stored material therein.

This venerable structure (photo in Black 2008) was demolished in July 1988, and it was replaced by a parking lot albeit paved. Gibbs wrote "C'est la vie in academe."

Life after Ph.D.

Attempts by Gibbs to secure a postgraduate position, without professional input, were a trying and emotionally draining experience. He made use of two primary outlets, placement agencies and journals. Applications directed to private industry, agricultural experiment stations, and academic institutions were denied. There was total rejection, but an intriguing pattern emerged from the replies. Based solely upon his résumé and reference letters, the industrial managers concluded that Gibbs was best qualified for a teaching slot while the academic department heads advised a career in research. Downhearted, Gibbs turned to Robert Emerson (see Rabinowitch 1961), a new arrival in the Department of Botany. This resulted in letters to Ray Dawson (Columbia), David Goddard (Pennsylvania), and Kenneth Thimann (Harvard). None had funds to support a postgraduate student, but Thimann urged submission of a résumé to the BNL, scheduled for activation in July 1947. In June of 1947, Gibbs returned to his parents' home with an advanced degree but without employment.

It was his habit, when he was an undergraduate in Philadelphia, to reserve two weeks in August for solo bicycle tours through New England and Eastern Canada via the America Youth Hostel network. On the 1947 trip, he collected all his mail addressed to *General Delivery, Boston Post Office*, on August 12. Enclosed in the packet was an interview invitation from the Brookhaven Director of Personnel. Events moved rapidly. The week following, he sat opposite Dr. Robert A. Patterson, a nuclear physicist. After 30 min of chitchat and without meeting a member of the Biology Department including the Chairman, Gibbs accepted a position with little discussion other than salary ($4,000 per annum). Patterson emphasized that the aim of the Laboratory was to support the Associated Universities in the uses of radiation as research tools and to discover new peaceful uses for nuclear radiation. The sole recommendatory letter was supplied by Kenneth Thimann to whom he had sent his thesis. The two met the following years on the Harvard campus when Gibbs was invited to present an informal talk to Thimann's laboratory group. "Dining in a faculty home that evening was a novelty," recalled Martin Gibbs.

The discovery of Carbon-14 and other radioisotopes of elements essential for life

Societal awareness, indeed fascination, yet trepidation with nuclear radiation skyrocketed after the unparalleled release of energy by the atomic bomb explosions of WW II. When Gibbs was completing graduate school, as a derivative of the Manhattan bomb project, the United States Atomic Energy Commission was establishing large civilian linked National Laboratories, e.g., BNL with the Associated Universities, to study and foster the peaceful uses of nuclear radiation and to allay public health concerns regarding nuclear radiation. Historically, basic discoveries and understandings of nuclear physics and chemistry of the atom that were initiated in the late 1800s and early 1900s formed a firm basis for the intensive nuclear studies of the 1930s and 1940s (Romer 1970). In 1913, F. Soddy proposed the name *isotopes* to designate varieties of chemically identical atoms, which however differed from one another in atomic weight and sometimes also in radioactivity (Soddy 1913–1914). Soddy realized, while he was working with pure substances, that they seemed identical, but they had 2 different molecular weights! Out of such investigations came the discovery of radioisotopes of elements, which are essential for living creatures.

A central part of biological chemistry is organic and requires large quantities of crucial elements, particularly carbon, nitrogen, phosphorus, and sulfur. Intensive efforts of nuclear physicists resulted in the discovery of active radioisotopes of sulfur, ^{35}S, in 1935 (Amaldi et al. 1935); phosphorous, ^{32}P, in 1936 (Anderson 1936); and carbon, ^{14}C, in 1940 (Ruben and Kamen 1940; Kamen and Ruben 1940). In 1938, two young energetic scientists, Samuel Ruben and Martin Kamen, began working together in the WW II war effort at the Berkeley Radiation Laboratory. Their discovery of carbon-14 in 1940 is a fascinating story of determination, failures, persistence, serendipity, and their sagacity (Ruben and Kamen 1941; Kamen 1963). Nuclear research during the 1930s and the huge Manhattan Project efforts of the 1940s resulted in the construction of powerful atom bombardment sources such as cyclotrons and nuclear reactors with uranium piles; these greatly enhanced the discovery of radioisotopes and allowed the production of isotopes in amounts needed in research and commerce. Thus, for the first time an absolute bonanza of radioactive tracers for biological and chemical studies became available as WW II ended.

Radioisotopes rapidly became one of the most potent and dependable tools of biological chemistry and physiology, indeed of science. In biochemical research, for example, sulfur-35 was used by S. Ochoa and others in studying the biochemistry of Coenzyme A; it carries acyl groups by forming the stable C–S bond that is used in the

oxidative tricarboxylic acid cycle, lipid metabolism, and membrane biosynthesis. Phosphorus-32 likely is the most versatile radiotracer and is intensively used today, e.g., in discovering unknown RNA functions such as those of microRNAs in the regulation of gene expressions (see Special Report Section of Science; Riddihough et al. 2008). Photophosphorylation was observed in 1954 in photosynthetic bacteria (Frenkel 1954) and in oxygenic photosynthesis (Arnon et al. 1954); phosphorus-32 was used in the chloroplast studies to measure ATP formation. Without question, radiotracers are one of our most incisive and useful tools in scientific research and in the development of ever-growing varieties of isotope applications in medicine and commerce (see Kamen 1957). Thus, isotopes are invaluable tools that are universally applied in many scientific fields of study and work, e.g., in biology, medicine, geology, archeology, anthropology, astronomy, and many other applied fields. *One cannot imagine the status of biological and chemical knowledge today without radioisotopes as tracer tools in countless investigations.*

Camp Upton, New York

Brookhaven National Laboratory is situated on Long Island roughly equal distance between New York City and Mantauk Point, near the towns of Patchogue and Yaphank. The Camp (Fig. 3) was a US Army induction center in the two World Wars. Gibbs recalls, "Possibly its best-known inductee was Sergeant Irving Berlin who composed musicals about Army life with an all soldier cast including Yip Yip Yaphank." This 1918 show featured the song "God Bless America," now considered by some as an alternate to the US national anthem. The Camp, deactivated in 1946, was transferred to the US Atomic Energy Commission (now Department of Energy, DOE), which in turn contracted it in March 1947 to Associated Universities, Inc., a consortium of nine major northeastern universities (Columbia, Cornell, Harvard, Johns Hopkins, Massachusetts Institute of Technology (MIT), Princeton, University of Pennsylvania, University of Rochester, and Yale). The availability of radioactive isotopes and sensitive methods to detect nuclear radiation were very enticing products of the nuclear research efforts just prior to and during WW II. Radiation research had an almost exotic pull with active researchers such that radiotracers and nuclear sources quickly found routes into research laboratories. The BNL in fact was formed by an Association of Universities in response to visions about the peaceful uses of newly available radioisotopes and growing concerns about human safety and possible biological damages from nuclear radiations.

When Gibbs arrived at the BNL on September 2, 1947, the biologists (about ten) were squeezed into a World War I (designated T or temporary) barrack used earlier by Army inductees (Fig. 4). The central library had a few holdings, and construction of a biology facility was scheduled in the spring of the following year. Food service in the sole eatery concluded with Friday lunch. Without transportation, Gibbs wrote, "I remained on site with provisions stored in the departmental refrigerator."

The first meeting of Gibbs with the then Department Chairman, Leslie Nims, a mammalian physiologist and a transferee from Yale, was postponed for at least two weeks. Gibbs took advantage of the delay, as he stated, "to snoop"; he came across a professional infrastructure including glassblowers, machinists, and instrumentation personnel. When he finally met Leslie Nims in his office, he was informed that a part of the laboratories' efforts was to find and develop "peaceful uses for radiation," and one function of the Brookhaven personnel was to supply ^{14}C-labeled compounds to the research community of Associated

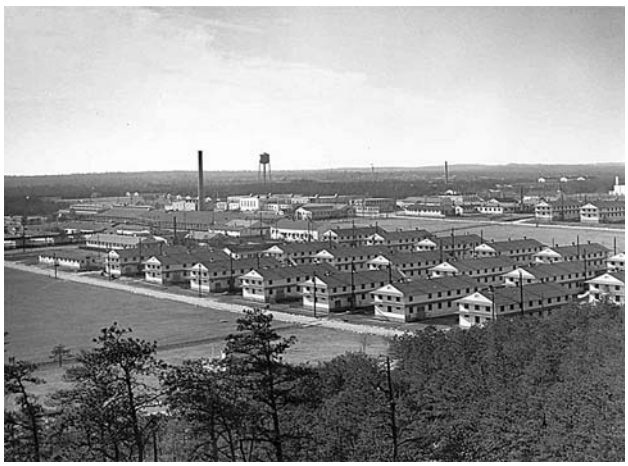

Fig. 3 World War II time barracks and buildings at Camp Upton, NY. Photo courtesy of the Brookhaven National Laboratory

Fig. 4 US Army inductees inside of a barrack at Camp Upton (date unknown). Photo courtesy of the Brookhaven National Laboratory

Universities, Inc. There was a demand, Nims said, for radioactive simple sugars. Gibbs had not expected assignment to a dedicated project, but "the experience, without realization then, set the direction of my research program at Brookhaven and my career subsequently." Inasmuch as barium carbonate was the sole carbon-14 compound (available from the nuclear reactors at the Oak Ridge National Laboratory) and Gibbs was the token botanist, *photosynthesis in leafy material seemed the practical approach*.

Gibbs recalled, "The winter of 1947–1948 was spent commuting to the nearest suitable library (New York City), designing of the photosynthesis chamber and vacuum line apparatus, locating and renting off-site greenhouse space in Bellport about ten miles from the lab site, observing daily the construction of research space in the adjoining barrack which was equipped with a one-bucket-a-day coal stove and evacuation chute (slide way) from the upper level, gaining the confidence of the service cops and lastly, the hiring of two technicians." All personnel were subjected to a lengthy security clearance procedure; thus, it "was not uncommon for the technicians to seek other employment after waiting up to two months for the decision." As far as Gibbs was concerned, his permanent employment was dependent upon the clearance procedure, which, he learned later, involved University of Illinois faculty and his Philadelphia boyhood acquaintances.

Two remarkable colleagues, Robert Steele and J. Raymond Klein, were particularly helpful to Martin Gibbs, "a newly minted doctoral graduate." Under the mentorship of Steele, his officemate from the University of Wisconsin, he was introduced to the techniques of assessing radioactivity in ^{14}C as a perceptible solid, barium carbonate, or as a gas (CO_2) involving vacuum line methodology (Fig. 5). The 'unflappable' Klein had volunteered to monitor the mechanics of assembling the raw data, obtained by Gibbs, into polished manuscripts and coached Gibbs; Klein also taught Gibbs how to react and respond to editorial critiques. Gibbs wrote, "Klein recognized and demonstrated repeatedly a sympathetic and tolerant attitude toward my youthful anxiety but never once faltered or wavered in his tutorage." After a few manuscripts of Gibbs were accepted for publication, he eventually realized his own responsibilities.

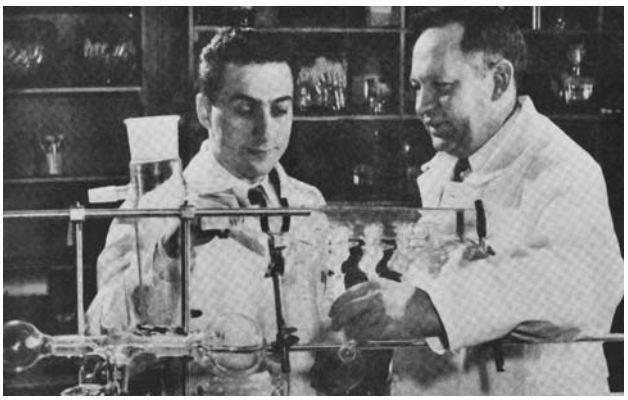

Fig. 5 Scientists working with a gas vacuum apparatus constructed to measure $^{14}CO_2$ as a gas ~1948. Photo courtesy of the Brookhaven National Laboratory

In the spring of 1948, a workable laboratory was in place to assemble the various parts of a procedure to yield uniformly labeled ^{14}C sucrose, glucose, and fructose biosynthetically. After Gibbs had studied the available literature, he decided to use leaves from rhizome-generated *Canna indicus*, which accumulate high levels of sucrose with respect to starch and the two components of the disaccharide. Key to success of Gibbs was his reading of a paper from the laboratory of Melvin Calvin and Andy Benson wherein ion-exchange columns were described to remove organic acids and other contaminating materials of an ionic nature (Benson and Calvin 1947; also see Benson 2002). Of the end products, the monosaccharides were fermented out with *Sacchromyces globosus* and the disaccharide was crystallized by the addition of absolute alcohol. Monosaccharides were derived from sucrose by enzymic hydrolysis followed by preparative paper chromatography (Udenfriend and Gibbs 1949).

While considering the journal outlet for publishing their method, Gibbs felt scooped by the Berkeley 'quartet' of Putman et al. (1948). Gibbs wrote, "One author was the distinguished, white-haired Canadian plant physiologist, Gleb Krotkov (Fig. 6), who, earlier enroute to a sabbatical

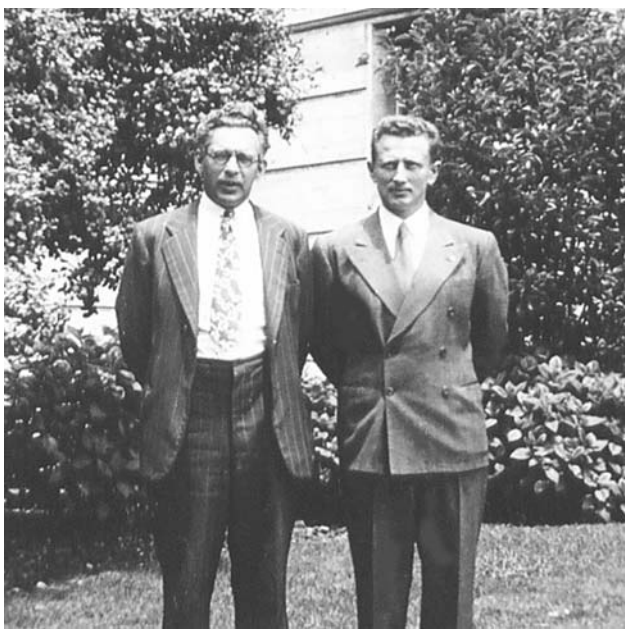

Fig. 6 Gleb Krotkov (left) and Daniel Arnon. Photo taken in California while Krotkov was on sabbatical leave at University of California at Berkeley, ~1947. The determined nature of both persons is depicted well in this picture. Photo courtesy of the Krotkov family and Connie Nozzolillo

leave at the University of California at Berkeley, came without fanfare into the Botany Annex while I was a student. How disappointing for him when he became aware that I, a third year graduate student, was the only occupant. Gleb and I became fast friends, and indeed, my family spent one summer in his Kingston home near the campus of Queen's University where I and others supervised two energetic Australian graduate students, Robert Smillie and Kenneth Scott, with questionable success."

The method for producing ^{14}C-labeled sugars, devised by Gibbs, remained unpublished until Editor E.G. Ball requested its inclusion in *Volume 2* of *Biochemical Preparations* (Gibbs et al. 1952). Gibbs conjectured that the eminent biochemist, D.D. Van Slyke, Associate Director of Brookhaven, a member of the publication Advisory Board, had a hand in it. Gibbs felt highly gratified when his procedure was verified at the University of Illinois at Urbana-Champaign, in the laboratory of his former teacher, Herb E. Carter.

Beyond a source of ^{14}C-labeled sugars

A gratis supplier (Martin Gibbs) of photosynthetically ^{14}C-tagged sugars had its rewards. Samples were exchanged for glucose chemically synthesized with isotope in C-1 (aldehyde), C-2, or C-6 position. Many senior investigators were recipients of the BNL radiocarbon-tagged sugars; this led to invitations to Gibbs to cutting-edge laboratories in the northeastern states of USA. Of equal value was the earned credibility and recognition by BNL departmental administration resulting in generous funding to Gibbs to equip his laboratory, to attend professional meetings, and the chance to organize the first BNL Biology Department Conference (Gibbs 1950).

Critical to his first venture into isotopic tracer methodology was the confrontation he witnessed between Melvin Calvin–Andy Benson and Hans Gaffron–Allan Brown at the American Association of Advancement of Science meeting in December 1948 (Benson 2002) that focused on the first product of photosynthetic CO_2 fixation. The Berkeley group provided proof that glycerate-3-P was that compound.

Gibbs reminisced:

> A more personal take-home lesson was the conclusion that elucidation of the complex carbon reduction cycle would be accomplished not by classically educated botanists but by organic chemists and enzymologists who could characterize the products isolated from intact cells or formed by purified enzymes. I had neither skill.

Martin Gibbs opted to study the distribution of labeled carbon within the glucose molecule to elucidate the pathway by which glucose was formed (Wood et al. 1945). Using this procedure, Aronoff et al. (1947) had reported an unequal labeling pattern of ^{14}C (61% in C-3, C-4; 24% in C-2, C-5; 15% in C-1, C-6) in barley hexoses extracted after a brief (30 s) period of photosynthesis. True to his character, Gibbs honestly confessed:

> My entry into photosynthesis was a solid blunder. I (Gibbs 1949) reported a conflicting distribution, namely C-1, C-6, had the highest specific radioactivity in glucose synthesizing sunflower leaves after one hour of photosynthesis. An explanation for the discrepancy was published immediately by Vittorio et al. (1950) who demonstrated convincingly that my faulty data resulted from the extended exposure time whereby the central carbon atoms of early synthesized uniformly labeled glucose were diluted by respiratory $^{12}CO_2$ over the long period of an hour.

It became clear to Gibbs that an evaluation of research options was inescapable. His preference was metabolic events in plants but his apparent lack of chemical and biochemical training to pursue meaningful experimentation in botanical physiology or specifically in photosynthesis was apparent to him. BNL had not established a sabbatical program. Funding for personnel other than the lab technicians was not in the offing. After much library time and consultation with senior staff members (particularly Robert Steele and J. Raymond Klein), Gibbs was determined to study carbohydrate dissimilatory pathways using the specifically labeled glucoses traded for his photosynthetically prepared sugars. Toward that end, he employed a technician with credentials in microbiology, and convinced the department to purchase basic equipment including an autoclave and a few incubators. *Lactobacillus casei*, a homofermentative lactic acid bacterium, which had been used to determine ^{14}C-labeling patters in glucoses synthesized in mammals and plants, was selected as the first organism to be analyzed. The conventional and perhaps sole route catalyzing glucose catabolism to lactic acid was thought to encompass reaction sequences formulated by Embden, Meyerhof, and Parnas (EMP) using yeast and mammalian preparations; this is also termed glycolysis (Bonner 1950). In this pathway, the methyl, alpha, and carboxyl carbons of the three-carbon acid were derived exclusively from C-1, C-6; C-2, C-5; and C-3, C-4 of glucose, respectively. Gibbs's chemical degradation of the *L. casei* lactic acid gave relative isotopic concentrations not totally consistent with the conventional pathway. To account for randomization of 3% of glucose C-1 into the carboxyl position and lesser amounts of glucose C-3 and C-4 into the alpha and methyl carbons of the three-carbon acid, a symmetrical intermediate, dihydroxyacetone, was proposed (Gibbs et al. 1950; Gibbs 1951). However, a

symmetrical compound was not a satisfactory explanation for isotopic labeling in the middle carbon of lactic acid. Reacting glucose in strong alkali was known to yield lactic acid, with dihydroxyacetone as a possible intermediate (Evans 1942). Thus, Gibbs et al. (1950) tested the proposal by incubating glucose 1-^{14}C in the presence of 3 N KOH and found equal isotopic distribution between carboxyl and methyl carbons of the purified lactic acid, indicating a symmetrical molecule in the chemical transformation. It must have been a happy feeling for Gibbs.

Gibbs wrote:

> When I assess the developmental status of my career, three years after graduation with a classical botanical curriculum, absence of postdoctoral training, the isolation of Brookhaven National Laboratory, and my ignorance of the sensitivity of isotopic tracer techniques, I was unprepared to accommodate the obviousness of the *L. casei* fermentative data. From an earlier event I can recall vividly a botanical member of my dissertation committee objecting with sarcasm to the seating of a biochemical representative in my doctoral committee. The compromise was an analytical chemist. However within two to three years, the anomalous bacterial results would be explained by two yet to be elucidated carbohydrate catabolic pathways.

The 1950 BNL Biology Conference on "CO_2 Assimilation Reactions in Biological Systems"

Organizing the first Biological Conference at BNL was a very fortunate career direction-setting event early in Gibbs's career. On June 7 and 8, 1950, about 65 prominent scientists attended the conference on the application of radiotracers, carbon-14, in biology. Many eminent scientists participated, e.g., 3 persons were or later became Nobel awardees: Otto Meyerhof (1922), Severo Ochoa (1959), and C·B. Anfinsen (1972). Notable plant scientist participants included Richard Byerrum, Ray Dawson, Robert Emerson, Solon Gordon, J. Horsfall, Gleb Krotkov, Alan Mehler, Jack Myers, Ray Noggle, and Hubert B. Vickery. There Gibbs became acquainted with numerous scientists who became lifelong professional and personal colleagues. Organizing this Conference and meeting established scientists was a heady career boost for Gibbs just 3 years past graduate school.

The introductory speaker was Harland G. Wood who was the co-discoverer of heterotrophic CO_2 fixation in non-photosynthetic bacteria and then in animals.

The following introductory comments of Wood (1950) have timeless applications:

> This, apparently, is the first full-scale symposium devoted exclusively to CO_2 fixation. It is exactly 15 years since the first paper on heterotrophic fixation of CO_2 was presented, and I wish to make a few comments about this early work before we get down to the more detailed business of this symposium. The paper was entitled "The Utilization of CO_2 in the Dissimilation of Glycerol by the Propionic Acid Bacteria" (Wood and Werkman 1935). It was read at a meeting of the North Central Branch of the Society of American Bacteriologists in Minneapolis in June 1935. As I recall, it provoked little or no comment. The general attitude seemed to be "the observation is interesting, if true, but it must be a peculiar characteristic of the propionic acid bacteria."
>
> It is difficult at this time to realize what a change in thinking this and subsequent observations on CO_2 fixation have evoked. The idea was firmly entrenched and accepted at that time that CO_2 was utilized only by photosynthetic plants and certain autotrophic bacteria that had the peculiar ability to grow on a completely inorganic medium. Some idea of the firmness of this opinion may be obtained by recalling that all the mechanisms of carbohydrates metabolism assumed that CO_2 which was formed was completely inert.
>
> ***This account is worth telling because it illustrates how difficult it is to cast aside accepted ideas and how conformity blinds one's thinking. It should give heart to the young graduate student who may have some unconventional ideas, and also it should cause some of us older heads to pause before discouraging some of the unconventional experiments that the less experienced worker may propose.***
> **[Bolded and italicized by CCB and G].**

Ten presentations were given at this 1950 conference by Harland Wood, Severo Ochoa, Merton Utter, Stanley Carson, Eric Conn & Birgit Vennesland, Robert Stutz, two by Sam Aronoff & Leo Vernon, Andy Benson, and Martin Gibbs. The conference session chairmen were Drs. Harland Wood and Severo Ochoa. Gibbs edited the proceedings and the U.S. Atomic Energy Commission printed and distributed them for the '*grand price of 45 cents per copy*.'

Introduction and evolution of the term "Photosynthesis"

In a paper read to the Botanical Section of the American Association for the Advancement of Science at its Madison, Wisconsin, meeting in August 1893, Charles Reid Barnes (1893) proposed the term "photosynthesis" as one

of the alternates to describe the process whereby all green plants form carbohydrates from CO_2 and water with the elimination of O_2, i.e., photosynthetic carbon assimilation. The alternate term was "photosyntax" which Barnes had earlier favored. "Photosynthesis" (and certainly "Photosyntax") was not favored by the established laboratories of Europe (Pfeffer 1900), perhaps because Barnes was a teacher rather than a researcher. "Carbon assimilation" was the term used in Europe up to the late 1930s when CO_2 fixation was discovered in heterotrophic bacteria using carbon isotope, ^{13}C (Wood and Werkman 1935). Then with the discovery of CO_2 fixation in animal cell extracts (Wood et al. 1945), the phrase "photosynthetic carbon assimilation" came into common use, as distinct from, e.g., heterotrophic carbon assimilation.

In his formidable plant physiology text, used by Gibbs as a graduate student, Edwin C. Miller (1938) gave full credit to Barnes for introducing the word 'Photosynthesis' even though it was an alternative word. Howard Gest (on pp. 39–42 in Govindjee et al. 2005) has presented a complete story of the term. Charles A. Shull, the prominent leader of the American Society of Plant Physiologists (see Hanson 1989) and the first editor of the journal *Plant Physiology* (1926–1945), memorialized his professor by establishing the Charles Reid Barnes Life Membership awarded annually by that Society since 1926. Herman A. Spoehr (1928), Frederick F. Blackman (1934), Cornelis B. van Niel (1952), Hubert B. Vickery (1956), Walter E. Loomis (1957), C. Stacy French (1971), Jack E. Myers (1974), William A. Arnold (1975), Samuel G. Wildman (1979), Daniel I. Arnon (1982), Martin Gibbs (1984), André T. Jagendorf (1989), Olle Bjorkman (2001), and Harry Y. Yamamoto (2003) have been eminent awardees for their contributions to photosynthesis.

What follows is how Gibbs became identified with photosynthesis and carbon metabolism early in the third quarter of the 20th century through the use of ^{14}C. In retrospect, it is remarkable that Gibbs applied photosynthesis as a "tool" to make labeled sugars even though the biochemical pathways photosynthesis uses to make sugar were unknown!

A "Real Introduction" to photosynthesis, the 1st Gatlinburg conference, 1952

Gibbs was invited to the 1952 Conference on Photosynthesis in Gatlinburg, Tennessee, October 28–November 1 by Sterling B. Hendricks on behalf of his organizing committee (Melvin Calvin, C. Stacy French, Hans Gaffron, Sterling B. Hendricks, and N. Edward Tolbert, listed alphabetically) to participate in a conference on photosynthesis "for the purpose of examining those aspects of the subject which appear to be limiting further understanding." The meeting was supported by the National Science Foundation, the Atomic Energy Commission (now Department of Energy, DOE), and the Office of Naval Research (ONR). The Gatlinburg gathering was the first held on this topic in the United States with international representation. Inasmuch as the proceedings were not published, and the meeting has historical importance, some details are included. The group photograph of this conference (see Fig. 7) was earlier published on p. vii in Govindjee et al. (2005). [The 2nd Gatlinburg conference proceedings were, however, published (Gaffron et al. 1957; see pp. 1249–1262 in Govindjee et al. 2005, concerning this and other conferences).]

Gibbs recalls, "The 4-day program afforded one half-day discussion of six areas of research and an additional uncommitted day. For each session, an Introductory Speaker presented some aspects of the subject while a Chair kept the ball rolling and became a primary contributor when discussion lagged." The program, based on earlier discussions with Martin Gibbs and Eugene Rabinowitch, was as follows.

Day one

Molecular Structure of Chlorophyll and Related Pigmenting, Questions of photochemistry, Molecular Spectra of Chlorophyll
Speaker: John R. Platt
Chair: Robert S. Livingston

Fluorescence: Transfer of Excitation Energy between Various Molecules
Speaker: E.C. Wassink
Chair: Eugene Rabinowitch

Day two

Transfer of Electronic Excitation to Free Energy; Maximum Efficiency; Quantum Requirement
Speaker: F·S. Brackett
Chair: Bessel Kok

Oxidation-reduction; Hill Reaction; Organization of the Plastid from the Point of View of Reactions
Speaker: Robert Hill
Chair: C. Stacy French

Day three

Path of Carbon During its Photosynthetic Assimilation
Speaker: Melvin Calvin
Chair: Farrington Daniels

Biochemical Energy Transfer in Photosynthesis; Characterization of the Biochemical Reducing Pool
Speaker: Hans Gaffron
Chair: Martin Kamen

All the attendees were housed in the Mountain View Hotel, 60 miles from Knoxville, TN, reached by hotel

Fig. 7 Participants at the 1st Gatlinburg (Tennessee) Photosynthesis Conference 1952 From left to right: ***Sitting*** (front row): Rufus Lumry, Jerome Rosenberg, Eugene Rabinowitch, Farrington Daniels, (gap), Leo P. Vernon, Martin Kamen, Henry Linschitz, Sam Granick, unidentified, T. Tanada, C. Yachan (unsure), Wolf Vishniac, Howard Gest, unidentified, Larry R. Blinks, and Paul Rothemund. ***Standing***: M. Keyes (unsure), Lou Levin, E. Kelly (unsure), Bernie Strehler (behind Kelly), Al Frenkel, Andy Benson, Robin Hill (from the UK, hiding behind Aronoff), Sam Aronoff, Al Bassham, William Stepka (partially hidden), Alan Mehler, John Weigl, Hans Gaffron (wearing glasses), E.M. Redding (behind Gaffron), R. Bandurski, Allan Brown, Howard Skipper (head only), Dean Burk, Melvin Calvin (head only), Lou N. M. Duysens (from the Netherlands, in dark suit), Birgit Vennesland (only partially visible), Robert Emerson (head only, behind Duysens), Jack Myers, E.D. McAlister (on the right of Myers), N. Uri (in front of McAlister), G.R. Noggle (right of Uri), C. Stacey French (behind Noggle), E.W. Fager (right behind French), A.H. Corwin (right of French), Barry Commoner (wearing glasses), John R. Platt (behind Commoner), Gus Dorough (right of Platt), R. Burris (next to Commoner), James H·C. Smith (right of Burris), unidentified (behind Smith), R.B. Withrow (right of Smith), **Marty Gibbs** (open jacket; with a tie), Earl Jacobs (slightly behind Gibbs), N. Ed Tolbert (right of Gibbs), A. Stanley Holt (slightly behind Tolbert), Sterling Hendricks (right of Tolbert), P. Zill (in bow tie),V.T. Riley (behind Zill), D. Goddard (dark suit), Norman Good (right of Goddard), unidentified (slightly behind and left of Good), unidentified (slightly to the right back), unidentified (bow tie, right of Good), Bill Arnold (smoking a pipe), William McElroy (bow tie), Bessel Kok (from the Netherlands, in glasses and tie), Dan Arnon (double-breasted jacket), Alexander Hollaender, and E.C. Wassink (from the Netherlands). ***On the balcony*:** unidentified (hidden), Mrs. Weigl, Mrs. Strehler (standing, in white top), B. Kok's child (sitting), Mrs. M. Calvin, Mrs. B. Kok (sitting on ledge), unidentified, unidentified, and unidentified man (standing). Photograph courtesy of Andy Benson; names of persons were put together by Govindjee from lists provided by Benson. *Original source of photo*: ORNLNewsPhoto#21292. Reproduced from Govindjee et al. (2005, p. 4)

limousine (Cadillac convertibles). The organizers were presumably unaware that public sale of alcoholic beverages was banned within the community. To correct this oversight, Martin Kamen, Howard Gest, and Martin Gibbs, with sponsorship by the hotel administrator, "were deputized by many of the attendees to meet covertly in Gatlinburg each evening with the local moonshine distributor to exchange $15 for three pints of a fluid guaranteed to be aged at least 90 days. Inspection of bottle residue indicated that a wooden vat was, indeed, a likely site of maturation."

Gibbs's primary interest was in the final three half-day sessions. Robert Hill, who always referred to the photochemical liberation of oxygen by isolated chloroplasts not as the Hill reaction but as the chloroplast reaction, made a lasting impression on Gibbs. The man cornered the market with humility. Melvin Calvin, a superb lecturer and clearly a distinguished academic teacher, proposed a photosynthetic carbon reduction pathway now accepted as the Calvin–Benson–Bassham cycle in essentially its present form (Bassham et al. 1954; see A.A. Benson and J.A. Bassham on pp. 793–813 and 815–832, respectively in Govindjee et al. 2005).

According to Gibbs' narration, "Hans Gaffron had an uneasy assignment since substantive biochemical information on the nature of the photosynthetic reduction was lacking." Invoking the principles of "unity in biochemistry" and "comparative biochemistry" Gibbs had concluded that if glycerate-3-P was the first stable product of CO_2 fixation, then it followed that reduction to glyceraldehyde-3-P was catalyzed by glycerate-3-P kinase and glyceraldehyde-3-P dehydrogenase; the kinase required ATP and the dehydrogenase NAD(P)H as cofactors. To this end, Gibbs revealed there the contents of an "in press" manuscript (Gibbs 1952) (Fig. 8). In his work, Gibbs had prepared extracts from roots, stems, and leaves of pea plants that catalyzed the oxidation of glyceraldehyde-3-P with NAD(P). Inasmuch as there appeared to be two oxidative enzymes in green stem and leaf preparations, one requiring NADPH and the other NADH while the root enzyme functioned solely with NADH, Gibbs speculated that the

Fig. 8 Martin Gibbs using a battery powered hand-operated Beckman DU Spectrophotometer, ~1950 at the Brookhaven Lab. Photo courtesy of the Brookhaven National Laboratory

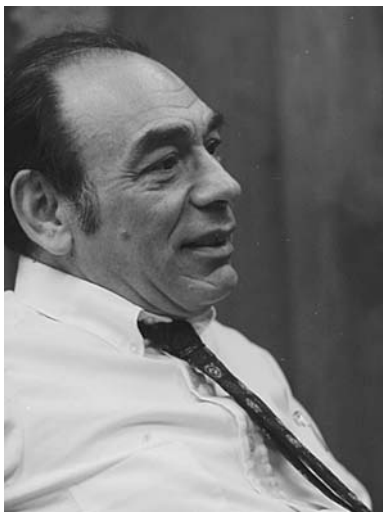

Fig. 9 Tony San Pietro at the Charles F. Kettering Laboratory in 1973. Photo provided by Steve Dunbar from the now inoperative Charles F. Kettering Laboratory

"NADP-linked enzyme participated only in photosynthesis, that is in the conversion of phosphoglycerate to triose phosphate, whereas the other dehydrogenase is concerned in glucose metabolism. And NADP reduced by glucose-6-P dehydrogenase in extracts of green stem and leaf could be reoxidized with glycerate-3-P in the presence of ATP."

Gibbs found differences in the properties of the glyceraldehyde-3-P dehydrogenases obtained from root and leaf extracts to be puzzling. While both extracts oxidized glyceraldehyde-3-P with NAD as a cofactor, the leaf preparation had an additional oxidizing enzyme linked to NADP. The rate of NADP oxidation, in some extracts, was accelerated by arsenate suggesting the presence of two enzymes, classical glyceraldehyde-3-P enzyme dependent upon inorganic phosphate or arsenate and another catalyzing the reduction of NADP and not requiring the additional cofactor. This perplexing question was resolved about 20 years later when Grahame Kelly, a doctoral student of John F. Turner, arrived in Gibbs's lab. To this end, Kelly characterized a nonreversible NADP-linked glyceraldehyde-3-P dehydrogenase which oxidized glyceraldehyde-3-P directly to glycerate-3-P, bypassing glycerate-1,3-diP (Kelly and Gibbs 1973). Inasmuch as the nonreversible enzyme, in contrast to the reversible one, is localized outside the chloroplast, it could function in a shuttle mechanism for the transfer of photosynthetically reduced NADP from organelle to cytoplasm (Latzko and Gibbs 1968; Kelly and Gibbs 1973; McGowan and Gibbs 1974).

Definitive proof that illuminated chloroplasts accumulated reduced pyridine nucleotides was first demonstrated by San Pietro and Lang (1956). Figure 9 shows a photograph of Tony San Pietro (see his personal perspective: San Pietro 2008). Confirmation of a chloroplast electron transfer sequence, coupled to ATP formation, was documented by Daniel Arnon et al. (1958) (see Arnon in Fig. 6, shown earlier). The presence of glucose-6-P dehydrogenase indicated that the direct hexose monophosphate oxidation pathway pioneered in mammalian and bacterial cells by Dickens (1938) and Warburg and Christian (1939a, b) might function in plants. However studies by Gibbs on this pathway, optional to classical glycolysis, were delayed until an on-site greenhouse was constructed.

Brookhaven National Laboratory announces a program to support visitors

In 1949, a program was established at the Laboratory to attract postdoctoral students for periods of up to three years and summer visitations by undergraduates and distinguished investigators ostensively for training in the emerging technology based on isotopic tracer methodology. Generous stipends and reasonable family accommodations bolstered responses. For Gibbs, personally, a reverse flow of information was set into effect—the visitors became his mentors. Finally, the isolation he had felt at the University of Illinois in Urbana and at Camp Upton was no longer there.

The first postdoctoral associate of Gibbs, supported by the new program, was Ralph DeMoss (Fig. 10); he later chaired the Department of Microbiology, at the University of Illinois at Urbana-Champaign. In his doctoral research with the prominent microbiologist and biochemist Irwin C. (Gunny) Gunsalus, Ralph had documented in *Leuconostoc mesenteroides* a fermentative pattern with a stoichiometry of one mole each of CO_2, ethanol, and lactic acid per mole of glucose metabolized. Furthermore, the bacterium was found to possess growth characteristics indicative of a fermentative reaction sequence differing from glycolysis via the EMP

Fig. 10 Ralph DeMoss, who taught Gibbs microbiology while conducting research at Brookhaven as Gibbs's first postdoctoral student. Photo courtesy of the Department of Microbiology, University of Illinois at Urbana-Champaign

pathway (Bonner 1950), the only established pathway of glucose dissimilation (DeMoss et al. 1951). Under DeMoss's guidance, the basic instrumentation required to conduct meaningful microbial and plant biochemical investigations was assembled. Based on their enzymic and isotopic experiments, they confirmed the earlier proposal, of Gibbs, that a new pathway for ethanol formation existed in *Leuconostoc* (Gibbs and DeMoss 1951).

When Gunny came to Brookhaven the following summer, he and Gibbs could show that *Leuconostoc mesenteroides* fermented glucose via a novel sequence: CO_2 was derived form carbon 1; the methyl and carbinol carbons of ethanol from C-2 and C-3 in that order; and the carboxyl-, alpha-, and beta-carbons of lactic acid from C-4, C-5, and C-6 (Gunsalus and Gibbs 1952). Figure 11 shows a photograph of Gunny, who had also taught, in 1957, Advanced Biochemistry to one of us (Govindjee). Clearly, to account for the data, the anaerobic breakdown of glucose involved at least a portion of the oxidative pentose-P pathway (also termed the direct oxidation pathway or the hexose monophosphate shunt pathway). Of equal importance for the determination of isotopic carbon patterns in carbohydrates, this degradative sequence yielded each carbon atom of glucose separately, a decided advantage over *L. caseii*.

Gibbs and DeMoss (1954) went on to determine that *Pseudomonas lindneri*, which ferments glucose and fructose by a stoichiometry similar to yeast, used a catabolic pathway unlike that of yeast or *Leuconostoc*. Analysis of their tracer data indicated a mechanism similar to the aerobic pathway of glucose oxidation by *Pseudomonas saccharophila* (Entner and Doudoroff 1952). Thus, in a brief span of three years, based on radio isotopic tracer methodology, DeMoss and Gibbs had found two novel pathways of microbial fermentation.

Fig. 11 Irwin C. (Gunny) Gunsalus at the University of Illinois at Urbana-Champaign, ~1990. Photo provided by Govindjee

In addition to Gunny, other 'boys of summer' (in the words of Gibbs 2003) were Harry Beevers, Vincent W. Cochrane, Howard Gest, G. Robert Greenburg, and Bernard L. Horecker (see Gest and Gibbs 1952; Gibbs et al. 1954), undergraduates from northeastern institutions, Henry Linschitz and Jerome Schiff, colleagues to be on the Brandeis campus, and André Jagendorf, with whom Gibbs held many productive discussions on photosynthesis while lunching in the beautiful greenery surrounding the Biology building. So enchanted were Horecker and Beevers by *Leuconostoc*, the result was their composing a ditty to the tune of "Clementine" (see Black 2008):

Leuconostoc in the sidearm
Glucose in the outer well;
Tip it in with phosphate buffer,
Carbon-1 comes off like hell.
Refrain
To the counter, to the counter
To the counter like a shot.
Turn the switch on, see the lights flash
Is it cold or is it hot?

The fermentative reaction was carried out in a Warburg vessel fitted with side arms which carried cell suspension and buffer. The evolved CO_2 was trapped in alkali in a compartment in the center of the vessel. The lights of an ancient binary scaler counting by tens flashed out the level of radioactivity. Additional ditty verses were contributed by Mary Stiller.

The direct oxidation (hexose monophosphate) pathway in higher plants

In a brief communication, Gibbs (1952) noted that the extracts prepared from the roots and leaves of peas

contained the enzyme, glucose-6-P dehydrogenase, indicating that a pathway, alternate to EMP, characterized in yeast, animal tissue, and microorganisms and termed the "Hexose monophosphate (HMP) shunt" may also be operating in higher plants. Two other research groups (Axelrod et al. 1953; Barnett et al. 1953) also made vital contributions toward elucidating this alternate carbohydrate degradatory pathway.

Gibbs had postponed a return to this respiratory pathway due to involvement with microbial fermentation but more importantly due to the then commercial unavailability of substrates and cofactors. While they purchased fructose 1, 6-diphosphate, fructose 6-P and ATP and NAD from Schwarz Laboratories, glucose 6-P, and gluconate 6-P were prepared in the lab by them, laboriously by the methods of Seegmiller and Horecker (1951). Basic to characterizing the HMP shunt was NADP, which had to be procured the old fashioned way—"trash can chemistry." The 30 gallon metal trash can container was an 'honorable tool' (in the words of Gibbs) in a 1950 lab. The starting ingredient was 20 kg or more of beef liver taken from immediately slain animals in the slaughterhouses of Manhattan and transported frozen in liquid N_2. Since the yield was in the order of 300 mg (about 30% purity, but free of NAD), the slaughterhouse was seen not infrequently. Gibbs said 'Hallelujah,' when NADP (80%) appeared in the Sigma Chemical Co. catalog.

The HMP shunt was evaluated using spectrophotometry (Beckman DU, shown earlier in Fig. 8) and manometrically (Warburg apparatus) in cell-free extracts of pea leaves and roots (Gibbs 1954; Gibbs and Beevers 1955). Gibbs and coworkers observed that both preparations could catalyze the conversion of glucose-6-P to ribose-5-P via gluconate-6-P with NADP as cofactor and with the elimination of CO_2. That both cell-free extracts supported O_2 consumption with ribose-5-P, but not ribonic acid-5-P, indicated return of the pentose-P into the metabolic mainstream of the EMP pathway, a result consistent with other findings (Gibbs and Horecker 1954; Gibbs et al. 1955). Enzymic studies with many tissues had made possible the formulation of a cyclic sequence of events whose operation might, of itself, account for the total oxidation of glucose-6-P (and glucose) to CO_2 and would, at the least, produce metabolites, which are also intermediates in the classical glycolytic pathway (Horecker 1951) without the mediation of the mitochondrial-bound citric acid cycle. Couri and Racker (1959) were the first to reconstitute a multienzymic preparation confirming this oxidative pentose-P pathway, which is the cytoplasmic counterpart to the chloroplastic photosynthetic reductive pentose-P cycle of Calvin, Benson, and Bassham. Later Chen and Gibbs (1991) presented isotopic evidence that the cyclic oxidation pathway operates in intact chloroplasts of the green alga *Chlamydomonas reinhardtii*.

When Harry Beevers came for two summer visits to BNL, there was ample evidence for the operation of the EMP glycolysis (Bonner 1950; Stumpf 1952) and of the direct oxidative sequence of reactions in plant materials. However, no evidence concerning the relative importance of alternatives in plant respiration had been offered. Martin Gibbs and his coworkers undertook an intensive investigation to obtain evidence on this point. They made use of an isotopic procedure introduced by Bloom et al. (1953), designated as the C-6/C-1 ratio. In this procedure, plant tissues were incubated with glucose-1-^{14}C and glucose-6-^{14}C and yields of $^{14}CO_2$ were determined at timed intervals. Thus if comparable samples of tissues were respiring equally on the two sugars, respectively, the ratio of 1 was taken as an indicator of total metabolism by EMP. If, on the contrary, a glucose molecule was metabolized by way of the oxidative pathway, CO_2 from glucose-1-^{14}C would be expected to be initially higher in ^{14}C than that from glucose-6-^{14}C since C-1 of the glucose molecule is the first one to be converted to CO_2. Clearly a ratio less than unity would implicate the participation of the direct oxidation pathway. Of the dozen tissues tested only corn roots tested for EMP, which confirmed an earlier finding that in this juvenile material classical glycolysis was the sole route (Beever and Gibbs 1954), and the other tissues had a substantial fraction (25–50%) of the glucose respired via the direct oxidation pathway.

There was preliminary evidence, obtained from experiments with a wide variety of plant parts of different ages, that in juvenile and undifferentiated tissues, generally, the EMP sequence is of major importance, but that as the tissue ages, the direct oxidation pathway comes to play an increasingly important role. In a sequel manuscript, Gibbs and Beevers (1955), working with various plant tissues (stem, root, leaf, cotyledon, hypocotyl and coleoptile), confirmed that the participation of the direct oxidation pathway was increasingly pronounced during differentiation and aging.

The 8th International Congress of Botany, Paris, France, 1954

Martin Gibbs received an invitation to participate in the 1954 Botanical Congress in Paris (France). He immediately made a request for travel abroad, subject to clearance by the security division of the Atomic Energy Commission office on the Brookhaven site; it was approved. Gibbs recalled:

> McCarthyism persisted then and security personnel while in the main thoughtful and polite, nonetheless, could be pesky and testy. In-office interrogation without forewarning was direct and approached an

impasse when I refused to comply with an impossible and inclusive request of the birthdates and places not only of my parents and siblings but also of uncles, aunts, and cousins. And for good measure, the interrogator tossed in the entire family of my wife. However, compared to a 50-minute informal interview including stenotypist held in November 1954 concerning an uncle retired honorably from the military and with pension resulting from wounds in World War I, who allegedly was observed reading the Communist *Daily Worker*, the one in March was less alarming.

Prior to the Botanical Congress, Gibbs scheduled an ambitions itinerary. His first stop was King's College in New Castle (UK), where he had an enjoyable day with Meirion Thomas, the thesis professor of Harry Beevers, and Stanley Ransom, who had coauthored with Thomas a most readable and useful plant physiology/biochemistry text. After a day with Robert Hill in Cambridge, Gibbs was invited to the country home of Frank Dickens who had confirmed and extended the reports of Otto Warburg on the direct oxidation pathway in mammalian tissue (Dickens 1938). Gibbs crossed the English Channel, where he received a warm welcome and a lecture invitation from the famed Dutch microbiologist, Albert Jan Kluver, in Delft. Kluver possessed the attributes to charm even the most casual visitor. At the Congress, Gibbs became friends with Bessel Kok, in whose laboratory he later would spend two summers. Also in Paris, Gibbs was introduced to A. Moyse, Chair of the Photosynthesis Section of the Botanical Congress, who would later guide Gibbs's nomination through the French Academy of Sciences and remain a lifelong friend. After the Botanical Congress ended, Gibbs went to Munich (Germany) where he was hosted by Feodor Lynen who, in 1953, with Severo Ochoa had used Gibbs's laboratory to prepare highly enriched radioactive sulfur-35 for incorporation into coenzyme A. Sitting in the audience at the Department of Biochemistry, University of Munich, where Gibbs presented a lecture, was Otto Kandler, an accomplished microbiologist; he invited Gibbs for lunch with his wife, in their apartment strategically located in the Botanical Garden at the University. At that time, they decided upon a collaborative study focused on the carbon labeling pathways in photosynthetically synthesized sugars using *L. mesenteroides* rather than *L. casei* as the degradative microorganism.

Asymmetric ^{14}C distribution patterns in glucose

Otto Kandler aided by a grant from the Rockefeller Foundation arrived in 1955 at BNL to carry out the collaborative project Gibbs had discussed with him in Munich the previous year. Ably assisted by Gertrude, his wife, and Jerome Schiff, a 'summer boy,' Kandler and Gibbs determined the ^{14}C labeling patterns of glucoses isolated from the green alga *Chlorella*, tobacco, sunflower, and *Canna* that had photoassimilated $^{14}CO_2$ for short time periods. In their first report, Kandler and Gibbs (1956) observed that glucoses from glucose-P and uridinediphosphate glucose were associated with the photosynthetic cycle. In a follow-up paper, Gibbs and Kandler (1957) observed the end products of the cycle, sucrose and starch, when degraded by fermentation with *L. mesenteroides.* All the glucoses possessed an asymmetrical distribution of ^{14}C. The ratio of C-3 to C-1 (aldehyde carbon) and/or C-2 was less than that of C-4 to C-5 and/or C-6. An average of four glucose degradations from one sample in which the activity of the various carbon atoms are expressed in percentage of the total glucose molecule was: C-1(7.9%), C-2(7.6%), C-3(33.8%), C-4(42.5%), C-5(3.5%), and C-6 (4.7%). The asymmetric labeling of glucose was not expected and became known as the "Gibbs effect" (Stiller 1962).

To account for the labeling pattern, Kandler and Gibbs (1956) proposed a "dilution and exchange pathway." This pathway involved a slight modification of the photosynthetic carbon reduction cycle proposed by the Berkeley lab (Bassham et al. 1954; Bassham and Calvin 1957; Bassham 1963).

The dilution and exchange scheme, according to the narrative of Martin Gibbs, was as follows:

1. "Conversion of asymmetrically labeled ribulose-1-5-diphosphate (Bassham and Calvin 1957) into two moles of glycerate-3-P followed by conversion into one mole each of glyceraldehyde-3-P and dihydroxyacetone-P. The values assigned to the carbon compounds were considered arbitrary. In this formulation CO_2 had been assigned the highest number since the CO_2-acceptor had presumably been diluted by endogenous material.
2. The isotopically labeled dihydroxyacetone-P could be diluted by a pool of inactive dihyroxyacetone-P derived from endogenous lipid. Dilution prior to condensation would produce an asymmetrically labeled fructose-P molecule.
3. A rapid exchange catalyzed by transketolase between the "active glycolaldehyde" moiety of fructose-6-P with sedoheptulose-7-P and a pentulose-P. The result of the exchange was an increase tracer in C-1 and C-2 of the hexose-P molecule".

The weakest point in this pathway was the source of unlabeled dihydroxyacetone-P in cells. A possible explanation to account for the higher label in C-4 than in C-3 was an incomplete equilibration of label between the two triose phosphates so that specific activity of

glyceraldehyde-P is higher than that of dihydroxyacetone-P (Bassham and Calvin 1957; Bassham 1963). This seems quite unlikely considering the high activity of triose phosphate isomerases.

Kandler and Gibbs (1956; also see Gibbs and Kandler 1957) set forth "the direct reduction pathway" as another interpretation of asymmetry. It would produce an asymmetrically labeled hexose in the following manner: (1) addition of CO_2 to C-4 of ribulose-1-5-diphosphate, (2) a reduction of this primary addition compound by reductant generated in the light, (3) a rearrangement in which the new carbon atom becomes C-4 of hexose, and (4) lack of reductant results in the primary addition product being split into two molecules of glycerate-3-P. In a later publication, Kandler (1957) suggested a polyhydroxyacid as a hypothetical intermediate between the carboxylation product of ribulose-1-5-diphosphate and fructose-1-6-diphosphate. Direct reduction would maintain C-4 with the highest label.

Gibbs's speculation, in his narrative, was that an Archaeon enzyme glyceraldehyde-3-P dehydrogenase coupled to ferredoxin, found in a primitive photosynthetic cell, could affect the light-driven conversion of –COOH to –CHO eliminating the requirement of PGA-Kinase, NADPH, and ATP (see Mukund and Adams 1995). Possibly a similar enzyme or a variant also could be involved in the reduction of the intermediary proposal by Kandler (1957).

Asymmetric hexose labeling, dubbed the "Gibbs Effect" (Stiller 1962), had been quoted as an argument against the correctness of the Calvin-Benson-Bassham cycle, elucidated by the Berkeley lab. The rapid movements of triose phosphates, in and out of plastids, are now well documented as a clear explanation for the asymmetric labeling of hexoses during photosynthesis (Black 2008). Thus, in the fifty years since its publication, no convincing kinetic, chemical, and enzymic observations have been reported to challenge the validity of the established Calvin-Benson-Bassham cycle. Melvin Calvin received the Nobel Prize in Chemistry, in 1961, for their discoveries at Berkeley. The asymmetrical labeling, observed by Kandler and Gibbs (1956), was the result of "isotopic equilibrium effects" and is not an indicator of any modification of the original cycle presented by Bassham et al. (1954).

Termination of Gibbs's job at BNL

In 1952, the Director of BNL announced a policy establishing a tenure structure patterned upon but not identical to that in effect in the consortium of universities which operated the lab. A few senior biologists were awarded tenure, while the overwhelming majority was presented with an obscure and undefined permanence. Engrossed in an ongoing, actively enlarging research program which resulted in a reasonable number of full-length manuscripts in peer-reviewed journals, Gibbs concluded, at that time, that tenure would be won.

Leslie Nims, the founding Departmental Chair, resigned from his position in the fall of 1954. A biophysicist was his replacement. Reflecting upon that swap in the departmental leadership, Gibbs sensed then that his final years at BNL had begun. Determined that a vigorous and thriving program in plant/microbial physiology and biochemistry with emphasis on photosynthesis persist after his possible departure from the Brookhaven Lab, Gibbs grasped the opportunity to encourage Rufus Clinton Fuller to join BNL. This was possible because of the elegant seminar visit of Fuller, who was then a member of the Calvin lab (Fig. 12). After a long talk that day with the Chair Howard Curtis, discussions with Dan and Marion Koshland, and Gibbs's enthusiastic endorsement, Fuller agreed to an appointment, and he set up a lab at Brookhaven in early 1955. (See Fuller1999 for his personal perspective.)

Fuller and Gibbs became colleagues and fast friends, a relationship that was maintained throughout Gibbs's life. Fuller's knowledge of events in the Calvin lab was extremely valuable during Gibbs's collaboration with Otto Kandler and additionally Fuller assisted Gibbs with experimental procedures. A combination of Fuller's expertise and skills with the analysis of ribulose-1-5-diP carboxylase, gained from Andy Benson's imaginative insight and tutelage (Quayle et al. 1954), and that of Gibbs with NAD(P) glyceraldehyde-3-P dehydrogenase was key to their success in studies on in vivo regulation of enzyme synthesis and structural development of the chloroplast (Fuller and Gibbs 1956, 1959). Louise Anderson who earned her doctoral degree in Gibbs's lab at Cornell was later Fuller's postdoctoral student. Further, Gibbs served as the biochemistry representative on Samuel F. Conti's

Fig. 12 Martin Gibbs (left) introducing R. Clint Fuller at a Brookhaven Lab seminar. Photo courtesy of Clint Fuller via Martin Gibbs

Cornell doctoral committee; Conti was another Fuller postdoctoral associate. Fuller and Conti eventually became staff members on the University of Massachusetts-Amherst campus; the former was Chair of Biochemistry, the latter a Professor in the Department of Microbiology and subsequently Fuller's Provost.

Shortly after the departure of Otto Kandler in 1955, Gibbs was terminated by the Chair with the provision of a final year. Donald D. Van Slyke, Director of the Division of Biology and Medicine, added a second year. A stroke of good luck rescued Gibbs's family (then 4) and his career. Harold Williams, Head of the Department of Biochemistry, College of Agriculture at Cornell University, enjoying a sabbatical semester with Robert Steele, offered a position of Associate Professor, with tenure, to Gibbs. In 1956, after many productive and exciting years, dedicated entirely to a research program with a generous operating budget, ample equipment, and most importantly no administrative assignments, during which Gibbs edited a Conference book (Gibbs 1950) and was a coauthor of 33 full-length manuscripts in peer-reviewed publications, the Gibbs family packed the station wagon and motored to Ithaca, high above Cayuga's waters. Gibbs reviewed and interpreted the BNL work and related metabolic research on plant carbon metabolism soon after arriving at Cornell (Gibbs 1959). His BNL laboratory, carved out of a bowling alley in the Camp Upton post exchange building, has been well occupied by Clint Fuller, Robert Smillie, Harold Siegleman and then Geoffrey Hind. On return to Brookhaven in 1997 to celebrate its 50th anniversary, Martin Gibbs was gratified that his ancient refrigerator still circulated coolant.

Epilogue

The work of Martin Gibbs at the BNL, applying ^{14}C as a tool to produce ^{14}C-labeled biochemicals, and the development of tracer measurement methodologies produced specifically labeled sugars which were distributed worldwide. The discovery of new biochemical processes in living creatures was greatly enhanced by that epic decade of radiotracer work that indeed discovered "peaceful uses of nuclear radiation"! Thereby Gibbs fulfilled the dictum, "He saw a need and filled it"! Gibbs's subsequent career and life as educator, mentor, editor, father and husband simply followed the same principle (Black 2008).

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