# Quentin H. Gibson

1918–2011

BIOGRAPHICAL *Memoirs*

*A Biographical Memoir by*
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# QUENTIN HOWIESON **GIBSON**

*December 9, 1918–March 16, 2011*

Elected to the NAS, 1982

Photo courtesy of ASBMB

*By J. Woodland Hastings and John S. Olson*

Quentin Gibson[1] was a remarkable scientist, well known for his life-long research on the kinetics, intermediates and mechanism of oxygen, carbon monoxide and nitric oxide binding to hemoglobins. More than 200 of his 250 plus publications are concerned with hemoglobins and myoglobins, and his first paper was published while he was on the junior staff in medical school (1). Gibson's discoveries and conclusions about the function of hemoglobins are now textbook material for biochemistry, biophysics, and hematology classes.

Gibson is known even more widely for his Stopped Flow mixing apparatus (2), which allows kinetic measurements of reactions within 1-2 msec after mixing. His design, which resulted in more rapid and complete mixing, has stood the test of time and is used in almost all modern instruments(3). He also developed flash photolysis methods in conjunction with rapid mixing, which led to additional important discoveries in heme and flavo-protein kinetics.

Gibson's signature style was to work closely at the bench himself, often with a collaborator, of which there were an extraordinarily large number over his long career. The relationships formed during these collaborations were highly individual and intellectually intense. Truly brilliant and on some matters bitingly cynical, he could be characterized as somewhat reclusive, fiercely independent and highly principled, with disdain for matters ineffective, irrelevant, or outdated.

1. Portions of this memoir originally appeared, in slightly different format, in *Biographical Memoirs of the Royal Society* (6) and are reprinted with permission.

After his election as a Fellow of the Royal Society in 1969, Gibson was asked by the Society to prepare a biographical memoir of his colleague and friend F. J. W. Roughton (4). Annoyed, perhaps, by the fact that he knew little of Roughton's life outside the 20 years of their collaboration, he deposited a hand written account of his own life up to that time so as to spare the unlucky person charged with writing his own memoir the agony of excessive researching (5). In this memoir, some quotes from that account are extracted from the biographical memoir of Gibson for the Royal Society authored by Professors John Olson and Herbert (Freddie) Gutfreund (6). The Royal Society memoir should be consulted for its more comprehensive account of Gibson's life and career.

In addition to the Royal Society, Gibson was elected to the American Academy of Arts and Sciences in 1971 and the U.S. National Academy of Sciences in 1982, and received the Keilin Memorial Medalist Award and Lectureship in 1990. He was an associate editor of the *Journal of Biological Chemistry* from 1975 until 1994.

## Early life

Gibson's great-grandparents, according to his own handwritten memoir (5), included:

> *a Scot, Agnes Macintosh; Pooley, a Suffolk builder of slums in Ipswich; a Welsh farm manager who moved to East Anglia, and small farmers from the Monymusk district of Aberdeenshire, some of whom (called Troop) were reputed to have left Holland in discreditable circumstances (maritime robbery) some time earlier.*

The Gibsons moved from Northumberland to Edinburgh, where Quentin's great-grandfather and grandfather were watch and clockmakers, a business that effectively ended in the 1860's with the rise of the Swiss industry. His grandfather moved to London, where he worked for the St. Pancras and London County Town Councils. His father attended University College, where he was a student of Sir William Ramsay, who won the Nobel Prize for the discovery of the noble gases. During World War I, Quentin's father worked on the manufacture of explosives and shortly thereafter moved to Northern Ireland.

Quentin Howieson Gibson was born in Aberdeen, Scotland shortly after the conclusion of the First World War. The family then moved to Northern Ireland near Belfast, where his father was employed as Director of the Linen Industry Research Association. This position required living at the Institute, an estate in Lambeg, with ample acres for an only child to explore. His father bought him a chemistry set early on, encouraging him to carry out experiments guided by an excellent instruction book. Quentin's maternal

grandfather invented an improvement to the hydraulic ram, which he manufactured and sold. He later recalled that some of his fondest early memories included seeing the components of those rams being cast in gunmetal and bronze, and finished in a noisy, crowded machine shop (5,6).

Quentin attended a day school at nearby Lisburn, and then a boarding school near Kilkeel, where he found Latin and Greek studies unrewarding and discovered his dislike for team sports. He was then sent to Repton, a boarding school in England, where science teaching was quite good and he was fortunate to have a bright young mathematics master, P. S. Newell. There is a curious disconnect between Quentin's recollection that the "…school staff were generally dissatisfied with my progress…" and "I got all the form prizes each year. (5,6)"

After three years at Repton his father decided that Quentin should go to medical school. He entered Queen's University in Belfast in 1936, but lived at home in a somewhat difficult relationship with his mother, especially during the war years when his father was absent. He obtained his MB in 1941, an MD in 1944 and a PhD in 1947, and was appointed Lecturer there in the Department of Physiology in 1944. In 1947, he moved from Belfast to Sheffield as Lecturer in Physiology.

## Sheffield: Early interest in hemoglobin

By the time he arrived in Sheffield, Quentin's work was very much concerned with the biochemistry of heme proteins, largely in collaboration with the Professor of Biochemistry at Belfast, D. C. Harrison. Gibson's interest in this topic came from a serendipitous discovery by a Northern Ireland medical practitioner, Dr. James Deeny, who was keen on the idea that ascorbic acid had a powerful beneficial effect on chronic cardiac failure. Deeney found two "blue" (cyanotic) brothers, who he thought might be suffering from cardiac insufficiency. After providing injections of large amounts of vitamin C (ascorbic acid) for three weeks, Deeney succeeded in turning one of them pink with the other brother remaining as a "blue" control (7). However, much to Deeney's chagrin, the brothers had perfectly normal hearts when examined at Belfast Hospital. This case was the first report of familial methemoglobinemia in the British Isles.

Quentin learned about this report and set out to study how methemoglobin was reduced in normal cells and what was wrong with the cells of the patients (8). This collaboration continued with Harrison after his move to Sheffield, though his publications still only gave the Belfast address (9). This practice persisted as late as 1950 and created, understandably, difficulties with David Smyth, the head of his new department.

Gibson's work on methemoglobinanemia had established him as a major player in the hemoglobin field. Through the influence of his previous chief in the Belfast Physiology Department, Henry Barcroft, Quentin was invited to contribute to the Joseph Barcroft Memorial Symposium on hemoglobin research, which took place in Cambridge in June 1948. This meeting allowed him to meet and talk with leading scientists in the field, including Roughton in Cambridge and Rossi-Fanelli in Rome. These contacts eventually led to long-term collaborations after Quentin began to study ligand binding to hemoglobin using rapid mixing and flash photolysis techniques.

At the 1948 symposium Quentin also had an opportunity to observe Britton Chance's rapid flow apparatus, which had been left in Cambridge by Chance after making kinetic measurements of cytochromes with Keilin and Hartree at the Molteno Institute. Although temporarily discouraged by the complexity of Chance's equipment, it stimulated him to design and construct a mixing apparatus himself.

In his own account, Quentin writes that "I soon found out what was wrong with Chance's records: the deceleration in his method is too gradual. The mixture at the final point of observation is often at sub-turbulent velocity, resulting in inadequate mixing. (5)" Gibson perceived that the apparatus had to be constructed so as to result in complete mixing using an 8-jet tangential mixer made in Kel-F plastic, and then the turbulent flow had to be brought to a sudden stop, with no gradual deceleration and conversion to laminar flow, to obtain a time resolution of 2-3 msec.

In 1950 Quentin met Jane Pinsent, who had just come to Sheffield to work with microbiologist Sidney Elsden after a year in Van Neil's laboratory in Pacific Grove on a Commonwealth Fund Fellowship. Jane had completed her degree in biochemistry at Cambridge (with mentoring from Marjory Stephenson, the first female Fellow of the Royal Society) and then completed a PhD at the Lister Institute. In her thesis research, she discovered that selenium was required for growth of *E. coli* and that molybdenum was necessary for the formation of the enzyme formate dehydrogenase. Jane and Quentin were married in 1951.

In January 1951, Quentin wrote to J. F. W. Roughton, saying:

> *In the last few months I have been engaged in building a stopped-flow rapid reaction apparatus and naturally looked to the blood pigments as a means of testing it out. In this process one or two results have turned up,*

> *which may be of possible interest to you, although, of course, the data were not collected in a systematic manner. I thought it would be interesting to repeat the experiment of Legge & Roughton (1950). (6,10)*

Learning that the new results did not quite agree with his, Roughton invited Quentin to Cambridge for discussions that were the start of a close scientific friendship lasting until Roughton's death in 1972. A now classic paper gives details of that first apparatus and its use for the measurement of the rate of displacement of oxygen from hemoglobin by carbon monoxide (11).

Quentin later claimed too modestly that the "hard stop" for rapid mixing devices was one of his few original ideas. Further improvements of the Gibson apparatus included reduced reactant volumes, higher spectral resolution, and adaptation to fluorescence measurements, which led to wider biochemical applications (3). Quentin wrote in his recollections that he tried to get UNICAM, a Cambridge firm of instrument makers, to commercialize his instrument, but they passed on the opportunity, suggesting that there would be little demand (6). Quentin talked about this issue when I (W. J. Hastings) was on sabbatical in Sheffield in 1961-62. At that time he was taking steps to have the instrument constructed in the Sheffield machine shop and planned to market it himself. I urged him to abandon the idea, pointing out that he would likely get calls asking for help in trouble-shooting some problem or another from users near and far and, considering time zones, 24 hours a day.

> One hot and sunny day (very rare in Sheffield) …we were all sitting out on that bit of grass outside the lab door, at coffee time, and he admonished us in no uncertain terms and said it was like a beer-garden!!

Quentin did abandon the idea of his own company, and a commercial stopped-flow apparatus based on his design was produced soon thereafter by the Durrum Company in Palo Alto, CA, which sold about 500 in the 1960s and 1970s. Since that time, companies in Europe, Japan, and the United States have manufactured, with commercial success, stopped flow machines of essentially the basic Gibson design. Many major contributions to enzymology, molecular biology, and areas of chemical kinetics have resulted.

Quentin's interest in instrument development, data collection, and complex kinetic analyses continued throughout his scientific career, and he almost always had a lathe,

drill press and computer in or next to his office, and continued to refine and adapt the stopped-flow apparatus for different experiments. Part of the attraction of a new biochemical problem for Quentin was the challenge of developing the instrumental method to solve it.

At Sheffield, Quentin's research had become increasingly biochemical and widely recognized, and in 1955 he was appointed to succeed Hans Krebs, the Chair of Biochemistry, who had moved to Oxford. This gave Quentin his first (and last) experience as an administrator. Lorna Young, a technician in Gregorio Weber's lab, remembers him as "…quite a strict head of department…One hot and sunny day (very rare in Sheffield)…we were all sitting out on that bit of grass outside the lab door, at coffee time, and he admonished us in no uncertain terms and said it was like a beer-garden!! Unseemly behaviour for a University department!"

By the time I arrived in Sheffield in 1961, Quentin was openly annoyed by the unproductive duties required of him as department head, and critical of what he considered the ineptitude of the administrators with whom he had to deal. He once told me (tongue in cheek, surely) that his plan for retirement was to absent himself two years in advance


**Figure 1. Group photo of Sheffield Biochemistry Department members, with Krebs visiting.** (Gift from Graham Palmer, who was Vincent Massey's graduate student and is the fourth person from the right in the third row.)

of that date and take up other interests, being confident that no one would notice and his salary would continue to be paid.

Quentin's initial pleasure with being Head of Department related to colleagues. He was especially pleased with his interactions with Gregorio Weber, appointed by Krebs, and with Vincent Massey, who Gregorio persuaded to come to Sheffield in 1957, as well as with the numerous visiting foreign researchers who these and other faculty attracted.

But his frustrations, notably with the University's failure to create a chair for Weber, were more substantial than the pleasures and rewards. Discussing his appeal for the chair in a website tribute written about his relationship with Weber, he recalled that

> *...the Vice Chancellor J. M. Whittaker, known as 'Jolly Jack' in honor of his gloomy persona, advised me that it was useless to expect good people to stay in a third-rate University like Sheffield, saying that it can best be used as a stepping stone.*[2]

This matter contributed directly to the exodus of Biochemistry faculty from Sheffield in 1962-1963. Weber moved to the University of Illinois in Urbana, Quentin to the University of Pennsylvania, Massey to the University of Michigan, and Theo Hoffman to the University of Washington, Seattle. "Almost end of story," Quentin concluded, "Jolly Jack found a strong desire to return to research and resigned a few months later."

## University of Illinois

I first came to know Quentin Gibson when, in late January 1961, he came on sabbatical leave to the Biochemistry Division of the Chemistry Department at the University of Illinois in Urbana. His visit was on the invitation of the department chair, Irwin C. "Gunny" Gunsalus, who, in his relentless search for talent, had earlier enticed Gregorio Weber and Vincent Massey to come to Urbana as visiting Professors.

The Gibsons arrived at O'Hare airport in Chicago with four young children, the youngest only a few months old. I had volunteered to meet and drive them down, not knowing that my own fourth child would be born that afternoon. The skies were brilliantly red at sunset over the prairie that afternoon, and the very cold temperature was an appropriate, if chilling introduction for them.

2. http://www.cf.ac.uk/biosi/staffinfo/lloyd/weber/QH Gibson.html

In his wisdom, Gunny gave Quentin a laboratory having an inner door connecting with mine. Wandering in to chat, I saw that he was unpacking and assembling a piece of equipment. It was his stopped-flow apparatus, constructed in the Sheffield machine shop.

Without much knowledge of my research, Quentin asked if there was a reaction I would like to study using stopped-flow. Without hesitation I said that a study of the kinetics of the rapid autoxidation of reduced flavin would be of interest. In 1960, H. Gutfreund had shown that the reactions of reduced flavins with $O_2$ were fast (12), and I had found that the rapid mixing of reduced flavin and bacterial luciferase resulted in a single turnover reaction, evidently because any reduced flavin not captured by the enzyme in the first milli- or microseconds was rapidly autoxidized, so that each enzyme molecule experienced only a single turnover. But neither the rate nor the intermediates in the autoxidation were known; our work provided some of the first answers (13).

In May, wondering how we might continue with a study of the bacterial luciferase reaction itself, Quentin invited me to spend the following year in Sheffield. I was junior faculty and had been at Illinois only four years and, with PhD students underway, wondered if it made sense to be away for a year. Actually it would be 15 months, since I had already agreed to teach and assume the directorship of the physiology course at MBL in Woods Hole for the next six summers. I asked Gunny what I should do. “If your lab isn’t here when you return you’ll know it wasn’t worth it,” he opined.

The winter days were very short in Sheffield, and the smell of sulfur from burning soft coal permeated everything. I expressed a wish to be involved with teaching rather than only research, so Quentin arranged for me to be appointed to the faculty as a lecturer, and I taught a course in the spring. As a new faculty member I was required to meet with the aforementioned Vice Chancellor, “Jolly Jack” Whitaker. When I brought up the matter of inadequate support for the department he grumbled, complaining that Krebs had taken all the equipment with him.

With luciferase purified in Urbana, we turned to the study of its single turnover reaction. For the study of bioluminescence, a dark room was useful, which I found in adjunct departmental space, an abandoned cinema theater, the Scala. The fact that it had no heating turned out to be favorable, for with only a constant temperature bath I could carry out experiments at a low temperature without the need for cooling equipment. We were able to establish the existence of a long-lived oxygen-containing luciferase-flavin intermediate, whose reaction with aldehyde produced the luciferase-flavin excited state and light emission (14).

I returned to the USA in June 1962, while Quentin stayed in Sheffield until 1963 when, at the invitation of Britton Chance, he accepted a professorship at the University of Pennsylvania. His wife Jane was appointed assistant professor of microbiology.

During his time at Penn I traveled several times a year to do experiments with Quentin. On sabbatical leave in 1965, I came several times each week from my home in Princeton. Those were some of the most memorable and delightful times in my career. At the bench all day in a fully darkened room, we would orally compose a new sentence or two of a manuscript-to-be after each experimental run. Unfortunately we failed to tape-record the sessions. We continued working together during the summers in Woods Hole.

In Woods Hole Quentin acquired a wooden Cape Cod Knockabout sailboat named *Flamingo*, painted a brilliant pink, and sailing became something of a passion for him. Hans Kornberg, who was a student with Krebs at Sheffield in the early 1950's, remembers him from that time as "rather aloof." When Kornberg saw him again in Woods Hole, he recalls, "Only once was I invited to sail with Quentin in *Flamingo*—as you will remember, he liked to be out entirely on his own." So much so that on one occasion Quentin entered a race with no crew, contrary to rules, so was disqualified in spite of his good performance. *Flamingo* was transported to Ithaca where I last saw it in his barn.

Although Britton Chance had been very much a hero of Quentin, his time at Penn did not go well. As already noted, Chance was a pioneer in the field of rapid mixing techniques and, as it happened, had studied the kinetics of a bioluminescent system in one of his early experiments. This work and Chance's studies on cytochrome oxidase in mitochondria had surely been a part of the attraction for Quentin to take a position at Penn, but in the light of day, it was difficult for him to abide the way in which Chance administered the Johnson Foundation and did science, as well as the absence of a true intellectual relationship with Brit of the kind he had envisaged. There were other more personal problems, including issues around housing and commuting.

## Cornell

Although they initially tried to make the situation in Philadelphia work, it did not, so Quentin and Jane moved to Cornell in 1966, where they remained until retirement. As their eldest daughter Katharine quipped, "After 2.5 years of cosmopolitan living in metropolitan Philadelphia, they accepted positions at Cornell University in bucolic Ithaca, New York." For his part, Chance failed in his own personal memoir to

acknowledge the real importance of Quentin's contributions, diverting attention by citing instead his own use of the term "stop flow" in early publications (15).

Quentin's research activity became more intense and productive during his years at Cornell, but his health suffered. According to his personal reflections written for the Royal Society Archives in 1971 (6):

> *Work in the lab was pretty hectic between 1968 – 1971- lots of things took off. This time saw the end of the dimer hypothesis and work on the α-β chain difference, on probes of R-T transformations, and on a variety of chemically altered and mutant Hbs. There were too many people in the lab, and as I had always insisted on doing the kinetic experiments with my own hands, the load became too much…I had a pyloro-duodenal perforation and when that was followed by some radiological visible stenosis, I went to England for a pyloroplasty and secretomotor-vagotomy. As I write, the time has come to consider the rather dismal future. It is unlikely that my energy will ever return to that of 10 years ago or that I will be assailed by a stream of good ideas. So at last I must think of myself of middle aged. Though, of course, I do not feel any differently than I ever did. Looking back at this point in time my predominant feeling is that I was exceptionally lucky all along the line. I seem to have squeezed into things….*

Of course, there is a disconnect between "…the time has come to consider the rather dismal future." and "…I do not feel any differently than I ever did." In fact, he came to be highly productive with dozens of rewarding collaborations. Between 1970 and 2009 Quentin published about 150 substantial refereed papers, virtually all concerned with hemoglobin, the last one including almost all approaches in modern biophysics from molecular dynamics simulations, laser photolysis experiments, to time resolved X-ray crystallography with a library of recombinant Hbs. His contributions over the last 40 years of his life were, in a word, monumental.

During this same time period, Jane's career flourished at Cornell, where she was rapidly promoted to full professor in both microbiology and biochemistry. Jane was a world-recognized authority on the utilization of ammonia in the major groups of bacterial phototrophs and on anaerobic benzoic acid degradation in *Rhodopseudomonas palustris* and similar organisms. She was also an outstanding teacher at Cornell, and her dedication to developing new and exciting laboratory course experiments was legendary.

From 1975-1996 she taught the very popular Laboratory in Cell Biology, and was awarded the prestigious Edith Edgerton Career Teaching Award in 1994. With Quentin, she summered at MBL in Woods Hole, Massachusetts, where she taught the course in microbial diversity, while Quentin worked with Frank Cary on fish hemoglobins.

Quentin's laboratory at Cornell was indeed a hectic place after his move from Philadelphia. Between 1966 and 1980 Gibson's postdoctoral fellows included Richard DeSa, Larry Parkhurst, Mike Cusanovich, Robert Gray, Keith Moffat, Ronald MacQuarrie, Melissa MacDonald, Francis Cole, Francis Knowles, Charles Sawicki, and Roger Morris. Visiting scientists, both young and senior, came for shorter periods of time for collaborative kinetic studies, including Woody Hastings, Giuseppe Geraci, Robert Noble, Robert Cassoly, Maurizio Brunori, Ron Nagel, Frank Bunn, Austen Riggs, and Henry Kamin. During this period, Quentin also directed the Ph.D. thesis research of four graduate students, John Olson, Melvin Andersen, Edwin Moore, and Wilma Saffran.

Richard DeSa, a postdoctoral fellow in the 1960s, recalls their acquisition of a new PDP 8S mini-computer from Digital Corporation, which was purchased for online data collection:

> *After the excitement of unpacking…Quentin looked at me, and then the computer, and then back at me again…I looked at him and then the computer… With this shiny new toy sitting between us, Quentin spoke the classic words: 'What do we do now?'*

They proceeded to develop software for an acquisition system for stopped flow spectrophotometry, which became widely used thereafter both by Quentin and many other people around the world (16). Quentin remarked that one should not have to adapt the experiment to an existing instrument; the instrument should be built for or adapted to the experiment.

Quentin also made major developments in flash photolysis and its combination with stopped flow methods. George Porter, a professor of chemistry at Sheffield at the time and an expert on flash photolysis, provided him with significant advice in constructing high intensity Xe flash lamps. In his first experiments, Quentin measured time courses for the bimolecular rebinding of CO to hemoglobin after complete photo-dissociation of the HbCO complex. An analysis of the new results showed that immediately after dissociation of CO the free hemoglobin is transiently in a form that rebinds the ligand very rapidly, but then quickly (~5,000 $s^{-1}$) relaxes to the normal slowly reacting deoxy-

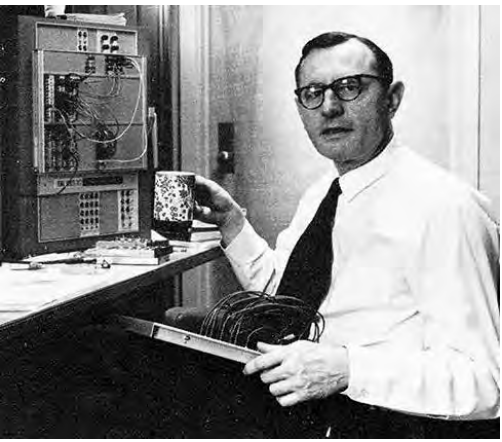

Figure 2. Quentin Gibson in front of one of his analogue computer modules in his office at Cornell University. ++This picture was taken when Quentin was elected to the Royal Society of London. (Picture was reproduced from H. Franklin Bunn and Bernard G. Forget, *Hemoglobin: Molecular, Genetic, and Clinical Aspects (1986)* W. B. Saunders Company, Philadelphia, p. 54, with permission from Elsevier.)

hemoglobin species that is seen in rapid mixing experiments (17).

In the late 1960s Quentin constructed flow-flash equipment in my laboratory at Harvard University and found that bacterial bioluminescence could be light-initiated (18). The intermediates were not characterized, but a trivial mechanism was ruled out. With his help I constructed a "double stopped flow" in which two reagents were mixed, then to that mixture a third reagent was added at an adjustable time interval shortly thereafter. The apparatus allowed us to determine how rapidly the calcium sensitive photoprotein aequorin is able to report the presence of calcium (19).

At Cornell, Quentin and his group published many new and clever kinetic experiments on ligand binding to hemoglobin. The results far outpaced their interpretations in terms of specific structures and chemical mechanisms. Many of the key kinetic features of $O_2$ binding to human hemoglobin were defined (20); the functional properties of dimers, tetramers, and the individual $\alpha$ and $\beta$ subunits were assigned (21,22); and the time dependences of proton release, organic phosphate dissociation, and changes in sulfhydryl reactivity with ligand binding were established (23,24).

Some of the initial ideas for mapping pathways for $O_2$ entry into globins and determining the factors governing iron reactivity were developed during this time period, using either large ligands or naturally occurring mutants and animal variants with substitutions at or near the heme pocket. In addition, the first ideas for looking at time-resolved motions of CO in hemoglobin crystals were conceived with Keith Moffat, who succeeded much later at the University of Chicago in obtaining the first "snapshots" of ligand movement in myoglobin by time-resolved X-ray crystallography (25).

In 1974 Quentin began the use of laser excitation to increase the time resolution of kinetic experiments with hemoglobin, initially to look at the speed of the transition between the low and high ligand-affinity states (20), and then some 10 years later to examine internal ligand motions (26). Over the next 30 years, Quentin applied these and other ideas to help determine, in structural detail, the paths, kinetics and factors that govern ligand binding to hemoglobins and myoglobins (27-29). In 2004, Quentin wrote a retrospective, which contains his personal reflections on his contributions to understanding ligand binding to hemoglobin (30).

One of the hallmarks of Quentin's research career, particularly at Cornell, was the large number of highly successful collaborations in which he took part. Tony Wilkinson, a collaborator from York University, remarked, that he had a great generosity of spirit, a trait often missing in ambitious and famous scientists. Visitors were invited to dinners with Jane at his home, a large farm house with barns on Slaterville Road, and then later at a smaller home on Game Farm Road. Lunch with visitors in the laboratory often involved David Wilson, Peter Hinkle and Leon Heppel, biochemistry professors in Quentin's department, and long walks around the beautiful Cornell campus afterwards.

While still at Sheffield, Quentin began a long and fruitful collaboration with Eraldo Antonini and then later Maurizio Brunori from the University of Rome. The initial work involved measurements of heme binding to apoglobins. The long term relationship was sealed when Quentin came to Rome in the early 1960s with a newly machined stopped flow spectrometer that he presented to the Antonini group as a gift. The initial studies were followed by years of both collaboration and competition on the role of ab dimers in cooperativity, differences between the a and b subunits of human hemoglobin, cytochrome c oxidase kinetics, and finally on the pathways for ligand movement within globins (31). This relationship remained very active even after the death of Antonini in 1983, and Maurizio Brunori was always a welcome visitor in Ithaca and Woods Hole.

The Rome connection also rekindled Quentin's interest in sailing. He sailed on the Mediterranean in Brunori's boat, which, ironically, was designed by Britton Chance's son. According to Brunori, the best times were sailing off Woods Hole in Quentin's Tartan 30 with Colin Greenwood, including a trip around Martha's Vineyard. Maurizio remembers taunting Quentin by remarking "I'm setting the sails as Brit would have demanded."

Other collaborations in Ithaca involved studies of hemoglobinopathies (i.e. Hbs Hiroshima, Bethesda, etc.) with Ronald Nagel and H. Frank Bunn at Albert Einstein

College of Medicine and Harvard Medical School, respectively, and Austen Riggs at the University of Texas. Gibson also worked with both Frank Carey at WHOI in Woods Hole and Robert Noble at SUNY at Buffalo on a variety of fish hemoglobins with his graduate students Mel Anderson and Wilma Saffran. In the 1980s, Quentin collaborated with Jonathan and Beatrice Wittenberg and Cyril Appleby on studies of plant leghemoglobins, and with Serge Vinogradov, Luc Moens, Maurizio Brunori, and Andrea Belli on a wide variety of invertebrate hemoglobins. He also was involved in a collaborative study of ligand binding to the homodimeric hemoglobin from the blood clam, *Scapharca inaequivalvis*. The latter work was initiated with Emilia Chiancone from the Rome group and then expanded to include William Royer from the University of Massachusetts Medical School at Worcester. Royer solved the crystal structures of wild type and mutant proteins in the middle 1990s, and together, they showed that the structural mechanism of cooperative $O_2$ binding involves conformational communication through ordered water molecules across an unusual hydrophilic subunit interface (32).

In 1984 Quentin and John Olson began to work together again, this time on the structural mechanisms of geminate rebinding and the effects of ligand size and reactivity on these processes. This collaboration with the Olson laboratory at Rice University would last for almost 20 years and result in 16 major publications on stereochemical interpretations of internal ligand recombination after short laser pulses (27,33), determinations of the relative reactivity of NO, $O_2$, and CO (26,34,35), and the use of site-directed mutagenesis to map pathways for ligand movement into globins (28). The work on site-directed mutants of myoglobins with Olson led to additional interactions with Kiyoshi Nagai and his students, Steve Sligar's group at the University of Illinois, Masao Ikeda-Saito at Case Western Reserve University, and Tony Wilkinson and his students and colleagues at the University of York.

Many larger lab groups had also become interested in geminate recombination, which involves internal ligand movements and rebinding immediately after photodissociation. The process is called "geminate" because the same ligand and iron atoms recombine internally. The new laser technology in the 1980s allowed visualization of true transition states for ligand binding that had previously only been implied in the theories of Eyring, Debye, and Smoluchowski. Unfazed by the competition, Quentin proceeded to build nano- (with Roger Morris) and picosecond (with Richard Blackmore) laser photolysis instruments. As with his stopped-flow apparatus and early photolysis devices, Quentin participated in the instrument construction, data collection, and analysis.

As Tony Wilkinson recalled from a visit in the early 1990s:

> *I particularly remember him turning to me after firing his laser and recording a rather baffling looking trace. When I asked him what it all meant, he replied 'Well I don't know, it's your sample Dr. Wilkinson!'*

Many others had heard that same response.

In the spring of 1987, Quentin was diagnosed with a large solid abdominal lymphoma. He chose to be treated in Ithaca, began a debilitating regime of chemotherapy, and started to talk of giving up science and donating his equipment to collaborators. John Olson remembers a conversation in late November 1987, after the treatment regime had been completed. Quentin was still in low spirits and only reluctantly revealed the details of the doctor's report. The tumor had disappeared, no metastasis had been detected, and he was given a clean bill of health. John asked why he sounded so depressed. Quentin's response:, "Now I have to write another NIH grant to keep going." He did indeed write two more successful grants and remained active for another 20 years.

Figure 3. Group picture from the 1988 Asilomar Meeting on $O_2$ Binding Proteins. Second row, left to right: Quentin Gibson (Cornell), John Olson (Rice), Kiyoshi Nagai (MRC, Cambridge), Jeremy Tame (MRC, Cambridge), Nai-Teng Yu (Georgia Tech), Steven Sligar (University of Illinois). First row, left to right: David Shih (Oregon HSU), Jean-Paul Renaud (MRC, Cambridge), Barry Springer (University of Illinois), Karen Egeberg (University of Illinois), Shun-Hua Lin (Georgia Tech). (Photograph was given to JSO by Kiyoshi Nagai after learning of Quentin's passing in March 2011.)

The collaborations with Rice University had expanded by 1988 when John Olson and his colleagues began generating large libraries of mutant myoglobins and hemoglobins. These active site variants allowed a direct connection to be made between rate parameters

derived from kinetic mechanisms and specific features in the three dimensional structures of the globins, which were determined either at Rice University by George N. Phillips, Jr. or at York University by Tony Wilkinson. Similar combined structural-kinetic studies were carried out with Emilia Chiacone and William Royer on the dimeric clam hemoglobin from *Scapharca inaequivalvis*.

The results of these combined mutagenesis and laser photolysis studies led Quentin and others to conclude that simple consecutive chemical reaction schemes do not provide a satisfactory interpretation of geminate recombination. These ultrafast processes involve chemical barriers to bond formation, diffusive processes for ligand movement, rotations of amino acid side chains, and tertiary structure expansions. Quentin had been impressed by the molecular dynamics simulations of ligand exit from Mb presented by Ron Elber and Martin Karplus, at the 1988 Asilomar Meeting (36). When Elber moved to the University of Illinois, Chicago, he began to work with Quentin and Olson on ligand migration in Mb mutants that dramatically alter geminate recombination. Quentin was so intrigued with these simulations that he asked Elber to help him set up software and computational equipment in Ithaca, and their close collaboration continued until Quentin's final paper(29).

## Winters in Houston

In 1996, the Gibsons formally retired from Cornell University, left Ithaca, and moved into a house they had purchased some years before near Dartmouth University in Hanover, NH. Their daughter, Ursula, was a professor of physics and lived nearby with her husband and three children. However, Quentin still wanted to keep working and called John Olson, asking if he could move his equipment to Houston and spend the mild winters there doing experiments.

Rice University enthusiastically appointed him as a Distinguished Faculty Fellow. Literally everything in Quentin's laboratory was moved to Houston, and Jeff Nichols helped get the equipment and machine shop working at Rice University within a matter of months, leading to a long term working relationship that continued after Quentin decided to stay year around in New Hampshire in 2001 and Nichols moved to Massachusetts to take a faculty position.

Among other accomplishments in Houston, Gibson, Olson, and his graduate student Emily Scott mapped experimentally the pathway for ligand movement into and out of sperm whale myoglobin using a library of over 90 different mutants (28). They

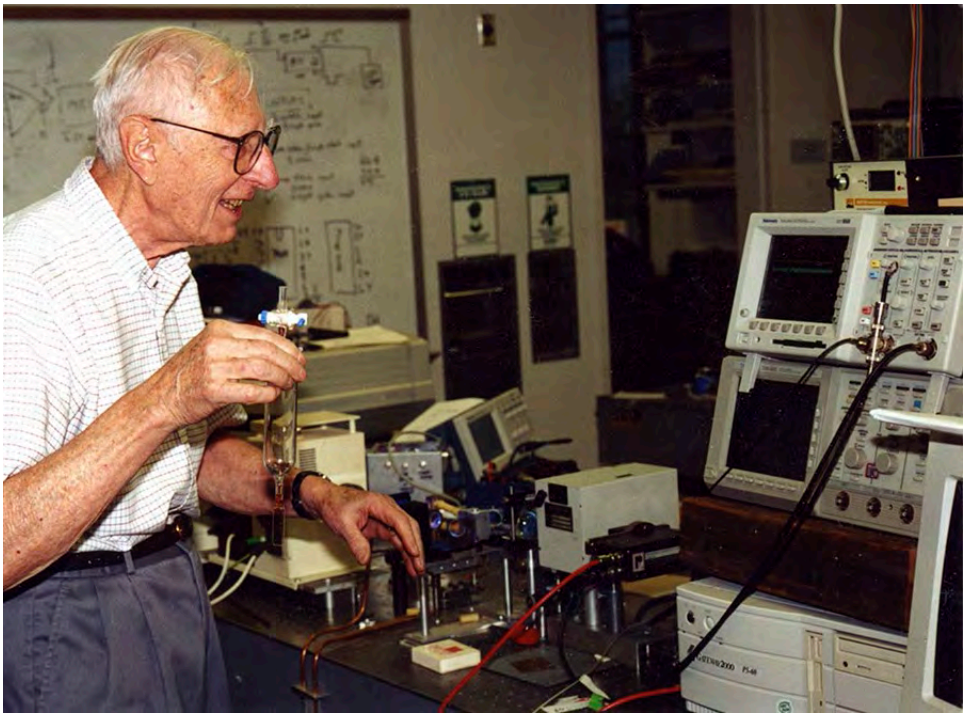

Figure 4. Gibson in January 2001 performing some of the last geminate recombination experiments in Houston for the Mb pathway mapping work. (Photograph taken by Jeff Nichols for JSO in January 2001.)

concluded that, in the wild-type protein, photodissociated ligands can reside in internal cavities and may rebind internally. However, the fraction escaping to solvent is governed only by movement through a channel created by outward rotation of the distal histidine at the E7 helical position, an idea that was originally proposed by Perutz some 50 years previously. These results contradicted prevailing ideas based on molecular dynamics simulations but, like all of Quentin's work, have stood the test of time and been verified experimentally for both myoglobins and hemoglobins.

## Retirement

In 2001 Quentin and Jane decided that it was time to retire permanently. Quentin had provided many words of wisdom at Rice. His best advice was a sign on his door

that advised students to "Learn to Complain without Suffering." He would also chide colleagues about becoming "science managers" and insisted that it was absolutely essential to actually do experiments "or you will eventually become obsolete and have to quit," advice that Quentin clearly followed in his own career.

After moving back to New Hampshire, Quentin continued work with Bill Royer's group in Worcester MA, which was only a few hours' drive from Hanover. He set up a kinetics laboratory and continued experiments for several more years. Toward the end Jeff Nichols, who was by then on the faculty at Worcester State University, ran the experiments and sent the kinetic traces to Quentin immediately by email. Between 2001 and 2009, Quentin published four more large papers based on original data, and maintained his computational activities with Ron Elber.

Figure 5. Quentin Gibson at age 91 holding his honorary degree from the University of Sheffield at The Kendal at Hanover, NH with his daughters, from left to right Emma, Ursula, and Katharine. December 2010. (Photograph taken by Staff at the Kendal for the Gibson daughters and is reproduced with their permission.)

Quentin's last paper contained ultrafast kinetic data that he and Nichols had collected, time resolved X-ray crystallography by Royer and his students, site-direct mutagenesis studies, and MD simulations, all of which showed that, as with Mb, ligands enter and leave *Scapharca* Hb through the distal histidine channel (29). This paper was a fitting end to a remarkably distinguished career, which started before the primary sequence of hemoglobin was known and ended with a detailed structural picture of how $O_2$ migrates into the globin active site and combines with the iron atom.

In 2010 the faculty of the University of Sheffield voted to award Quentin an honorary Doctorate of Science and established an eponymous chair in his honor for his work at Sheffield from 1947 to 1963 and his lifetime of scientific achievements. Professor

David Hornby from the University of Sheffield travelled to Hanover in December of 2010 and presented Quentin with the award in person. Quentin's career had begun with his appointment in the physiology department at the University of Sheffield in 1948 and ended with an honorary degree and a chair named for him in 2010 by the same university.

Quentin's scientific accomplishments were truly ground breaking in the fields of rapid reaction measurements and ligand binding to heme proteins. He taught his students and colleagues how to do science and not just "manage" it. Quentin felt strongly that experiments should be done every day if progress was to be made. When collaborators came to his laboratory, they usually left in a state of exhaustion with literally hundreds of time courses to analyze. His work on hemoglobin progressed from empirically determined association and dissociation rate constants measured on millisecond time scales in the 1950s to the determination of specific structural pathways and iron bond formation parameters on picosecond and nanosecond time scales in the 1990s. Even more remarkably, Quentin was physically involved in making almost all the measurements, normally using instruments that he and his students constructed with their own hands. As Tony Wilkinson wrote in late spring of 2011, Quentin was "a wonderful character, out of a mold that has long since been cast aside."

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The frontispiece photograph was originally published in the June 2011 *ASBMB Today* Retrospective for Quentin H. Gibson and is reprinted with permission from the American Society for Biochemistry and Molecular Biology.

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