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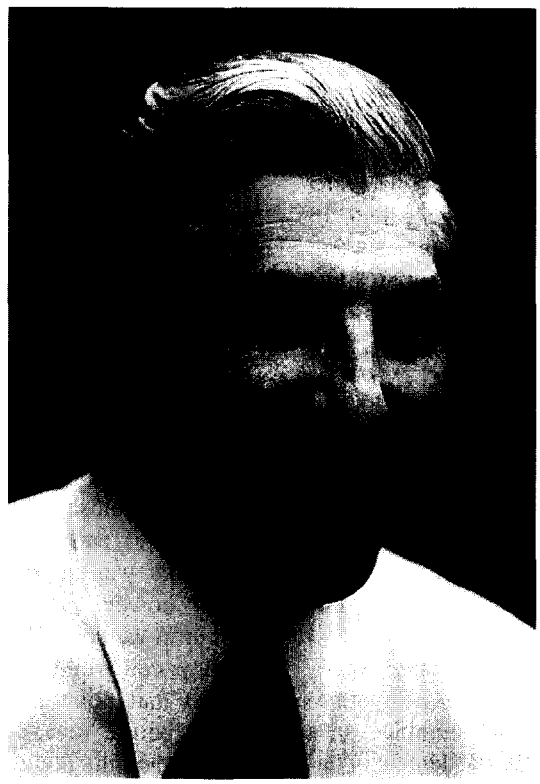
Remembrances of Bill Harrington



In the following pages some of us who knew Bill well in various stages of his life reminisce about him and the science that we shared with him. Obviously these reminiscences would have been much longer if we had been able to invite all Bill's friends to share their memories of Bill in these pages. Unfortunately, journal limitations have prevented this, but we hope that some of these vignettes will recall for others of you equivalent happy times with Bill in one or more of these contexts, and will serve to remind us all of the humanity and dreams that underlie all good scientific endeavors. Bill had more than his share of such humanity, and many of the best features of each of us were formed in part by our contacts with him. These remembrances, as well as the scientific papers that follow, are offered in commemoration of Bill's human qualities, which left such an impression on all those who were privileged to know him.

Howie Schachman remembers Bill as a graduate student.....

Within a few weeks following my arrival at the University of California with the prestigious title, Instructor in Biochemistry and Assistant Research Biochemist in the Virus Laboratory, I met an engag-

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ing, enthusiastic graduate student who was interviewing faculty members in Berkeley before deciding what type of research he would like to do for his PhD degree. Bill Harrington exhibited impeccable judgment, even at that very early stage, and I became the lucky faculty member with my first graduate student only a few weeks after launching my own uncertain career. We were of comparable age, liked and respected each other enormously and worked harmoniously in scientific pursuits while forging a close friendship that involved our families and continues to this day even after his untimely death.

It did not take long to discover that Bill was bright, asked good questions, dissected and challenged the answers, and was amazingly effective at the laboratory bench. He was intrigued with my newly acquired Model E ultracentrifuge which, of course, I considered 'out of this world' when compared to the older air-driven instrument that I had used for my own Ph.D. research.

Bill joined me in the efforts to unravel aspects of the structure of tobacco mosaic virus (TMV) by studying its breakdown in mildly alkaline solutions. We worked together constantly and contributed to a single notebook. Who did which experiment was easily recognized by the difference in handwriting. Progress was great, the research was exciting, and it seemed desirable to diverge so that Bill would follow the alkaline degradation and I would examine the dissociation of TMV by detergents like sodium dodecyl sulfate (SDS). Thus we began doing experiments in parallel. He was finding a series of intermediates depending upon the pH and I stumbled on a single intermediate about 60–70% the length of intact TMV. This occurred at a certain SDS concentration and seemed to be a stable particle. To prove that it was indeed a stable discrete entity we did some reconstruction experiments by mixing it with an equal amount of intact TMV and looking in the ultracentrifuge at the two discrete sharp boundaries. They were there all right, but there was always more of the slower species than we expected on the basis of the initial concentrations. Could the SDS come off the short particle and then degrade the intact TMV to the same intermediate?

A few additional experiments convinced us that the answer was "NO" and that we were dealing with an ultracentrifuge anomaly that occurs with mixtures of macromolecules. From that time on, Bill and I turned all our attention to the analysis of mixtures in the ultracentrifuge and the newly described Johnston–Ogston effect. All experiments were discussed jointly ahead of time, predictions made and bets placed on the expected outcomes. Each night I would drive past Bill's apartment and we went back to the lab together. The bets involved the purchase of the midnight snack of coffee and pie or a hamburger. In my exalted position on the faculty, my income was only slightly greater than Bill's, so the outcome of the bets did not place either of us in a financial bind.

In short order, based on the Johnston–Ogston paper and our independent formulation, we knew that we had to make a boundary in the middle of the ultracentrifuge cell by layering a solution of the faster species (TMV) over a more dense solution containing TMV and a more slowly sedimenting component. We used bushy stunt virus (BSV) as the slower species. We each became proficient in this but, of course, after the cell was placed in the rotor we had to turn it through 90° to couple the rotor to the vertical shaft. Actually, we started the rotor spinning as the vacuum chamber was closing. Much to our astonishment we did get some reasonable boundaries and enough preliminary data to realize that this was an endeavor worth pursuing. It was clear, however, that we would not really be successful until we could form the boundary in the ultracentrifuge cell while the rotor was spinning.

At that point I contacted Ed Pickels at Spinco (long before it was a division of Beckman Instruments) and the outcome of that collaboration was the synthetic boundary cell and a paper in *Proceedings of the National Academy of Science of the United States of America* describing it and some applications. With this new toy we were like a couple of kids in a candy store, doing experiments that could not be done before. We measured backward flow of solution in the cell due to the transport of macromolecules toward the periphery. We formed boundaries between H_2O and a 1% sucrose solution and measured the sedimentation coefficient of sucrose. Most importantly, we measured the sedimentation coefficient of a slowly migrating species in the presence of the faster component. This was the parameter we required to test the theory for the sedimentation

of mixtures. Based on all of that activity, Bill and I published a general paper dealing with different applications of the synthetic boundary cell. This paper later served as the seed for a series of detailed applications of the synthetic boundary cell by others in my laboratory after Bill departed for postdoctoral fellowships in Cambridge, England and the Carlsberg Laboratory in Copenhagen.

Before he left, Bill did unravel many significant facets of the alkaline degradation of TMV and he clarified puzzling aspects of the effect of temperature by demonstrating that some of the observed products were the result of reassociation reactions rather than the dissociation process. Ironically, additional research that Bill did with a pH-stat was never published, even though it was ahead of its time. Bill knew that it was incomplete and his standards were so high that it was relegated to the unpublished file.

Life with Bill Harrington was always challenging, exciting and fun. We were more like fellow graduate students than student and mentor. Throughout my own professional life Bill provided sound, constructive, and wise counsel on all types of matters — scientific, personal and political. His career progressed from one success to another, and the many friends he made in the course of his professional activities also became my friends, thereby enriching my own life. What more can one expect from ones first graduate student?

John Schellman writes about Bill as a fellow postdoc at the Carlsberg Laboratory.....

The Carlsberg Laboratory was a splendid place to work and became even more so in 1954 when Bill Harrington arrived, fresh from England, with Inge, Susan, Eric and Peter (the latter born just months before in Cambridge). Though he had had a good year at Cambridge, questions associated with the structure and assembly of TMV virus, his thesis topic with Howard Schachman, were uppermost in his mind. In fact this interest in large structural assemblies was to persist for the rest of his scientific life. His spirits soared on his very first tour of the laboratory when he found a Beckman Analytical Ultracentrifuge, in excellent condition, which was only occasionally used by others. With the approval of Linderstrøm-Lang he took possession immediately. In his pocket was the synthetic boundary cell that was soon to prove so important to us all in the study of small proteins and isolated peptide chains.

At that time the stage was set for exciting progress in protein science and there was no better place to be than at the Carlsberg Laboratory. Sanger had completed the sequence of the A and B chains of insulin and the positions of the disulfide links had just been disclosed. The α-helix was an established structure, but no one knew quite what to do with it for globular proteins. Kauzmann had just published his extensive studies on the kinetics of unfolding of proteins. Linderstrom-Lang had just developed his method for the hydrogen exchange of proteins. I had begun studies on the optical rotatory dispersion of proteins, which provided signatures for protein structures in solutions. Jacobsen, Neurath and Ottesen had established the methodology of limited proteolysis. Finally Anfinsen had arrived in the laboratory with the sequence of ribonuclease and 5–10 g of the protein, highly purified by the standards of the time. This liberated us from the durance of work with β-lactoglobulin, hemoglobin, ovalbumin and serum albumin, all of which had disadvantages.

Against this background, and under the inspiring leadership of Linderstrom-Lang, the laboratory was undertaking a broad range of studies in limited proteolysis, peptide and protein conformation, the relation of enzymatic activity to structure, stability of helices and proteins, and the accessibility of protein amide hydrogen atoms to exchange. In some ways this was the beginning of modern protein physical chemistry. For most of the people involved, this was the most exciting scientific period of their careers because of the very rapid production of results that were genuinely novel and because of the continual changing and flowering of ideas.

Bill quickly moved to a central position in all these activities, partly because of the major contributions he was able to make with his expertise in sedimentation and viscosity, but mainly because of his outstanding qualities as a collaborator. All those who have worked with him know his special style: relaxed but intense, humorous but serious. There was nothing like a scientific discussion with Bill, who would stop in the middle of a walk, a meal, a stairway or a crowded sidewalk and continue only after a troubling point had been clarified. His open

and inquisitive manner stimulated lengthy and enthusiastic discussion, even in those of us who normally tended to be somewhat quiet or non-communicative. This was, in fact, one of his most outstanding qualities: this ability to bring out the best in students, collaborators and colleagues.

Pete von Hippel remembers early research collaborations with Bill.....

My first memories of Bill invoke an overwhelming sense of joy and laughter. Bill was, and remained all his life, great fun to be with, and though our interactions and later collaborations were filled with exciting scientific questions, they also always retained an element of pure, unadulterated joy that is too often missing in these serious and competitive times. Bill could see the amusing side of almost anything, and delighted in describing scientific concepts in unusual and humorous phrases.

We first met in 1957; Bill was a research scientist in Chris Anfinsen's laboratory at NIH and I was across the street at the Naval Medical Research Institute as a postdoctoral fellow with Manuel Morales. Manuel and most of my other close colleagues soon left as a result of a shake-up in the management of NMRI, leaving me in de facto charge of several laboratories and considerable scientific resources. (I was an active duty naval officer at the time, and thus not free to leave.) Bill and I soon found common scientific interests, and began to collaborate on the use of proteolytic enzymes as probes of the secondary structure of fibrous proteins, particularly collagen and myosin, and our life-long friendship began. Bill's family and mine soon became friends as well. I particularly remember Bill's young son Peter from this period. Peter became entranced with my naval uniform and when I stopped off at the Harrington house to visit on the way home he would parade around proudly, wearing my uniform cap and a long red tie that nearly touched the floor.

Bill and I got particularly excited about trying to understand how collagen helices reform on cooling solutions of denatured collagen chains, and influenced by the successes of the Pauling school of modeling fibrous proteins on the basis of limited crystallographic information and simple stereochemical ideas, we constructed and argued about wonderful models of the nucleation and growth of collagen coiled-coils. When our ideas got too outrageous Bill would draw himself up to his full height and intone in a mock-serious voice: "Now see here, Paaater....". We would then burst out laughing and start over.

I remember a delightful two-week period that we spent together at Dartmouth Medical School after I had moved there in late 1959. We were trying to finish a piece of joint work on the formation of collagen helices using optical rotatory dispersion measurements. We went back to the lab together every night and took turns staring into the Rudolph spectropolarimeter with its clicking prism until neither of us could see straight. One of my wife's patients had given her a two-pound jar of Russian caviar, and when we got home each night we would sit and eat caviar and discuss the day's experiments until we fell asleep. Bill vowed that he would stay until the experiments were finished or the caviar ran out — not surprisingly the latter happened first.

In later years our scientific paths diverged, but our friendship did not. At least once each year we got together in Baltimore, in Eugene, or at a scientific meeting. We always had dinner together and sat and talked until the scowls of the waiters became too pronounced to ignore. We thought a great deal about the analogies between proteins sliding on DNA and myosin heads perhaps sliding on actin, and planned to write a paper together on the subject if we ever succeeded in understanding it. After each such meeting we exchanged thick packets of notes and reprints.

I was planning a trip to Baltimore in the fall of 1992 and would, of course, stay with the Harringtons. A week before my visit Bill died. I stayed with Inge anyway, and we sat in the kitchen and ate sandwiches and talked about Bill.

Of course Bill lives on in all of us, and memories of him sustain us, but his death left a huge void. Each of us might define this void differently, but for me it represents the loss of a component of joy and fun from my life that I sorely miss.

Walter Englander and Parker Small write of Bill as an early postdoctoral mentor.....

When Bill Harrington went to work at the NIH, he looked for some postdocs to work with and he

found us, or maybe we found him. One could not have found more naive, inexperienced workers. We knew little about science, and next to nothing about proteins, the field in which Bill was already a master craftsman. He was in complete control of what was then often referred to as the armamentarium of protein biochemistry, the wide collection of physical chemical approaches that had been developed to deal with the emerging field of protein structure in solution. Unlike many others, Bill was a generalist, equally at home with all the tools of the trade — analytical centrifugation, optical rotatory dispersion, viscosity, diffusion, light scattering, spectral and enzymological and related methods. We were exposed to all this, and to a particular style of working and thinking and living with science that has helped to shape the rest of our lives. Bill related to his science and to people in a deeply sensitive and giving way. He just was not concerned about how inexpert we were.

Bill's lab and his approach to science were somewhat different from the standards of the time, and were remarkably different from the standards of today. The hiring issue was only one example. His emphasis was on science for the sake of science and was not focused on publication, advancement, or career. Bill just did not think in terms of his own self interest. One of us did a project on the molecular weight of myosin, an interesting issue at the time, having to do with the fundamental substructure of that major protein. It was something Bill really cared about. It was done in Bill's lab. It was a good piece of work, correct to 1% as it turned out. But Bill did not put his name on it. He wanted us to have it for ourselves. Bill really cared about understanding nature; he was essentially unconcerned with the publications race.

Bill illuminated his lessons in a characteristically memorable way. Were you worried about getting due credit for your most recent great idea? Do not worry about it. If it's the only idea you ever have, it will not do you much good anyway. But if you are truly clever you will have plenty more, so get to work on them! What is the measure of a productive scientist? One *good* paper a year.

We entered Bill's lab relatively early in his career, but by that time he had already risen to considerable prominence. A scan of *Advances in Protein Chemistry*, perhaps the leading organ of the time in the protein world, shows that his work was heavily cited. Citations to his work appear in a large majority of the articles, which covered a broad field. You will not see that happening today. It was a great lab to be in. The illustrious scientists of the time dropped in for a visit. There was intensity, but there was also a lot of laughter. Bill's spirit and enthusiasm were infectious. The lab was part of a section at the NIH that was staffed by a most unusual mix of people, from which there arose two Nobel prizes and an assortment of other impressive careers. The impact of all that on two neophyte scientists is hard to overestimate.

It is clear that the whole course of both our scientific careers was set by the science and the style that permeated Bill's work and his lab at the time. He taught us how to do science, ranging up to thinking about how proteins might do all the things that make life possible and down to how to worry about cleaning the glassware to ensure good clean experimentation. We hope that the environment that we have managed to create for our own students has approached in some measure the devotion to and pleasure in science that was characteristic of the environment that Bill created for us.

Julien Davis remembers Bill as a recent scientific collaborator and mentor.....

Bill Harrington was by nature a scientific iconoclast with a deep awareness of the power of biophysical and biophysical-chemical methods for solving biological problems. My first contact with his work and appreciation of these qualities came indirectly from his publications on myosin thick filament assembly. In the early seventies I was at Bristol University in the Molecular Enzymology Laboratory, developing pressure-jump equipment for kinetic studies on protein self-assembly. Myosin thick filaments formed in vitro from purified subunits served as my test system for the pressure-jump, and Bill's papers with his colleagues Morris Burke, Jamie Godfrey, Sylvia Himmelfarb, Bob Josephs and Emil Reisler lay dog-eared on my desk.

A particular quality of the work intrigued me — those detailed and elegant biophysical studies were on a class of short, irregular myosin filaments formed

by dialysis at pH 8.0 and shunned by microscopists. Only one other group experimented briefly with this morphological class of filaments; the majority used filaments prepared at an acceptable pH of 7.0 with smooth surfaces and lengths similar to that of native thick filaments in muscle. Yet only pH 8.0 filaments behaved as a model tractable self-assembly system in the ultracentrifuge. As was often the case, Bill was right. Only later was it appreciated that salt bridges are central to myosin assembly and that an adjustment of the pH to 8.0 at 5°C is required to maintain the physiological charge balance, and also that an artifactual layer of myosin over the surfaces of pH 7.0 filaments gave them their smooth appearance.

Bill's favorite, often recounted, experiment of the time was performed in collaboration with Morris Burke. Steel and brass models of myosin dimers of different geometry were assembled and spun in a vat of water to determine their rotary friction. These precise data were compared with the hydrodynamic properties of the myosin dimer in the ultracentrifuge. The illuminating link that these experiments provided between a macroscopic structure and protein murk clearly had great appeal to Bill. My work on pH 8.0 filaments evolved from a test system into a detailed kinetics and structural study on myosin thick filament assembly and length-regulation that led to the characterization of the first example of an unusual class of protein self-assembly mechanism in which the emergent properties of the growing polymer serve to direct the assembly of identical subunits.

Bill's interests changed, and the role of the hinge region of the myosin rod in muscle contraction assumed center stage; it was then that we met. With my first sabbatical due in 1982–1983, it seemed appropriate to add muscle function to my researches. The dual role of the hinge in assembly (as part of the tail of the myosin molecule that forms the backbone of the thick filament) and in contraction (as a segment of α-helical coiled coil of low stability that might generate tension in muscle) held considerable appeal. My wife and I arrived in the States (our first visit) with great trepidation from two months of lab and conference hopping in Europe, anticipating that all would be over after a brief shoot-out. We rented a house next to Bill and Inge and had to frequently pinch ourselves to remember that the New World of excellent wine, music, art, science and friendship which we shared with our neighbors was very real and precious.

It was a heady time. Bill, in a theoretical paper, showed that the renowned Huxley–Simmons T_1/T_2 recovery of tension following a small step-change in muscle length could equally well arise from a helix–coil transition in the hinge region, establishing the mechanism as a plausible alternative to the then current dogma. In the laboratory Soren Hvidt, Trudy Karr, Peter Knight, Steven Lovell, Michael Rodgers, Kazuo Sutoh and Hitoshi Ueno all contributed to a host of interesting experiments related to the function and properties of the hinge.

Two years later I resigned my faculty position at the Witwatersrand University and joined Bill, leaving a then unattractive South Africa behind. I continued to use the laser temperature-jump apparatus for muscle fibers that I had built during my sabbatical, and showed that fibers heated above physiological temperatures in the absence of chemical energy contract much like fibers under normal physiological conditions, as clearly predicted by the helix–coil transition model. Over time it became increasingly apparent from aspects of these and other experiments that tension generation is associated with the myosin head and not the hinge, but many ideas, like the indirect coupling of tension generation to the chemistry of the actomyosin ATPase, live on. I greatly miss the energetic discourse, gentle humor and friendship of a fellow traveler dedicated to working on the scientific edge. His many contributions to science and his impact as an individual will resonate far into the future.

Maurice Bessman writes of Bill as a departmental colleague.....

Bill Harrington was recruited by William D. McElroy to bring physical biochemistry to the McCollum–Pratt Institute and to broaden the scope of a department that was top heavy in enzymologists unraveling the pathways of intermediary metabolism. I remember Bill's interview seminar well — not the substantive issues of his research, but his erudite presentation and the distinct impression that here was someone who would add some 'class' to our faculty. And I was right. From the outset it was clear

that Bill's focus was always on the science and not on the scientist. He seemed to get as much pleasure out of someone else's elegant experiments as he did from the beautiful work emanating from his own laboratory. He was always fair in acknowledging contributions of others, and I never heard him use the word 'competitor.' He viewed his group as part of an international team bent on elucidating the basic processes of muscular contraction; he was respected for this broad view and often asked to give lectures at meetings summing up the current status of the field.

His fairness and wise counsel were also recognized by his students and postdocs, who often referred to him as 'Uncle Bill.' In discussions at faculty meetings he was the 'conscience' of the group, not always voicing what the faculty wanted to hear, but reducing the arguments to human considerations as well as pragmatic solutions.

Several years ago, Bill, then our chairman, decided that he had been at the helm long enough, and we were forced to seek a new chair. We decided that we would choose someone from within the department rather than search outside. This was a particularly sensitive era in the history of Biology at Johns Hopkins, because the traditional strengths and focus of the Department of Biology over the past 20 years were now in transition, and the new chair could have a strong impact on its direction. Each faction within the department would have liked to be represented by a chair sympathetic to its perception of modern biology. How to choose from within and avoid the polarization of individual groups, and potential embarrassment of unsuccessful candidates?

It was decided that all full professors would be eligible, and that a closed vote by the whole department would elect the new chair. In the event that the candidate-elect declined the position. the second highest vote-getter would be elected and perhaps the third. But who could be trusted to tally the vote? Who would follow through on the wishes of the department independent of his own views. Why, Bill Harrington of course. Without hesitation, we agreed that Bill would tally the votes and follow the prescribed procedure. To this day no one but Bill knows whether the resulting chair was the first, second, or third choice. But we all are certain that Bill Harrington deserved our trust.

And now, three years after he left us, his slot in the department has not been filled. In fact, there has not been a concerted effort to find someone to replace him. Perhaps we are all reluctant to set ourselves an impossible task!