A tribute to Annemarie Weber (1923–2012)

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Annemarie Weber, Alpbach conference, 1974

Dr. Annemarie Weber died on July 5th, 2012 in Philadelphia before being able to reach her beloved summer home in Woods Hole, Massachusetts. She obtained her MD at the University of Tübingen, Germany in 1950 but did not practice medicine. Instead, she followed her father's (Professor Hans H. Weber) footsteps in investigating the myosin ATPase mechanism of muscle contraction (Weber and Hasselbach 1954) but soon made her own niche in elucidating the role the divalent metal ions in the regulation of ATPase activity. After postdoctoral periods at University College, London and Harvard Medical School, she established her independent research in the Department of Neurology at Columbia University. Here she determined the critical roles of Ca^{2+} and Mg^{2+} in the control of actomyosin ATPase (Weber 1959; Herz et al. 1969) and

showed the role of the “relaxing factor”—a suspension of sarcoplasmic reticulum fragments—as a pump to reduce the free Ca^{2+} concentration (Weber et al. 1966). As summarized in a review of Annemarie's contributions (Franzini-Armstrong 1998), the field was fraught with difficulties because the concentration of contaminating Ca^{2+} in glassware and research grade chemicals was sufficient to activate actomyosin ATPase. In addition, there was no gel electrophoresis to check on the protein composition of preparations, so that actin preparations came with unknown amounts of contaminating tropomyosin and troponin (the latter had not been identified in the early period of her work). To add to these complications, if the [ATP] was in excess of $[\text{Mg}^{2+}]$, then the free ATP would chelate some of the Ca^{2+} required to activate the regulatory proteins and Ca^{2+} ATP itself is an inhibitor of the actin-activated ATPase, but an activator of the basal myosin ATPase. Furthermore, it turned out that the regulatory mechanism involved the loss of inhibition by troponin, so that poor preparations of regulated actomyosin showed higher ATPase activity, which worked against the tradition of biochemists to aim for the highest specific activity. By careful use of EDTA and EGTA chelators to control the free divalent metal ion concentration, Annemarie elucidated the distinct roles of Ca^{2+} and Mg^{2+} ions (Weber and Winicur 1961).

Annemarie became Professor of Biochemistry at St Louis University Medical School, Missouri in the late 60's; then moved to The University of Pennsylvania School of Medicine in 1972 where she continued to explore the regulation of actin through cooperative interactions of tropomyosin (Bremel and Weber 1972). In later years, her attention turned to the regulation of actin polymerization and she had another period of producing highly-cited publications (Weber et al. 1994; Gregorio et al. 1995).

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Towards the end of her career, she expended much energy in revamping medical school teaching and became a popular lecturer. This was recognized by the Berwick award in 1985 and the University's Provost Award in 2001 from her Institute in response to student feedback. Reading through old papers and analyzing citations, however, can only form part of a tribute to Annemarie. She was a unique character in the muscle field, which is perhaps best illustrated by some personal memories.

Andrew Szent-Györgyi writes We knew of Annemarie before we really met her. Her father, Hans H. Weber, visited Albert Szent-Györgyi in Szeged and returned greatly impressed. Both of these scientists were strongly against Hitler and did their best to save the Jews. In these difficult times, Albert and Hans helped a number of Jewish scientists leave Hitler's Germany to establish for themselves new lives in new lands. These efforts to help Jewish scientists did not go unnoticed by the German authorities. Hans Weber, who was greatly respected for his science and his character, was thus exiled to the north of Germany to what is now part of Poland. By this time Annemarie, who had obtained her medical diploma and was conscripted into the army, was also helping her father. Fortunately, she was transferred very close to her father. When the German army began to collapse, they were able to escape and live in the same place, Dortmund. When the Allied bombing created deadly fires, the only means of escape was between and through the flames. Father and daughter covered themselves with wet blankets, which allowed enough protection to cross the fires. An incredible performance! The activities of the two Webers at considerable danger to themselves were not forgotten by those German Jews and others who had been saved by colleagues. This explains the open arms they extended towards the Webers, leading to international visits and new scientific collaborations.

It was very important for Annemarie to work independently from her father, and prove to him that her work and that of her students produced convincing results. She demonstrated that the presence of Mg^{2+} was required for contraction. It turned out that Setsuro Ebashi did not realize the importance of Mg^{2+} until he heard of Annemarie's comments. Ebashi asked her permission to use it in his studies. Annemarie did not object and a new friendship was developed.

I was delighted when she accepted my invitation to become an instructor with me in the Physiology Course that initially started in the stinky old wooden building in 1968, while the new Jacques Loeb Building was under construction, at the Marine Biological Laboratory, Woods Hole. She worked extremely hard and was extremely helpful. She both lectured and was capable of discussing problems. As Jim Sellers wrote to me about Annemarie, "I don't think that I could get anything past her. She really

taught me the value of doing rigorous controls and the idea that you have to be willing to prove yourself wrong if you really want the right answer."

Annemarie was strict and at the same time extremely friendly with both colleagues and students. As a teacher at the University of Pennsylvania Medical School, her high personal and professional standards became renowned. She taught students who were interested in Medical Research. She developed a text that gave them the current important information in lively lectures. Nonetheless, she insisted on maintaining quality. Hugh Huxley and I went to visit her at her retirement celebration, and were greatly impressed with all the students who gathered in her honor and appreciation of her style of instruction.

Annemarie and I became good friends during our times in Woods Hole. This started when she volunteered to help me and my wife, Eva Szentkiralyi, clean after the flood of Hurricane Carol in 1954, which distributed a lot of gasoline from floating gas tanks. When Eva became ill with cancer, Annemarie was a great companion and offered great comfort. When Annemarie found out about her own cancer about 20 years later, she was helped by a number of good friends including my second wife, Ursula whom she called regularly both in Woods Hole and from her house in Marion Pennsylvania.

We will all be missing Annemarie, her enthusiasms, her joy in learning, and her cheer.

Clive Bagshaw writes Annemarie welcomed me into her laboratory as a post-doctoral researcher at the University of Pennsylvania in 1974, which included the possibility to collaborate with the magnetic resonance group run by Mildred Cohn. I was interested in the possibility of using Mn^{2+} as a structural probe and paramagnetic substitute for Mg^{2+} in the myosin ATPase reaction. At the first group meeting, I presented my initial results, which produced the response from Annemarie "Where are the gels and what was the $K^+(EDTA)ase$ rate?". The latter, although not physiologically relevant, was a useful assay as the rate was much greater than the basal Mg^{2+} ATPase rate but sensitive to inhibition due to sulphydryl oxidation. Having not run a gel since my undergraduate days, I took a deep breath and responded that I checked the quality of the myosin S1 preparation from the % enhancement of tryptophan fluorescence, a direct measure of the the $M^{**}.MgADP.Pi$ complex. A prolonged silence followed. The following week I was exempted from gel inspections and given the freedom to develop my own program in collaboration with George Reed, who introduced me to the electron paramagnetic resonance. That is not to say Annemarie was detached from the project—group meetings were still a grilling, but Annemarie almost invariably introduced humor into her quizzing. She believed that the "uncertainty principle" should remain in the field of quantum mechanics

and if she detected a “may be” in a conclusion she suggested you go back and repeat the experiment. As it turned out, Mn^{2+} bound not only to the nucleotide at myosin active site but also the regulatory light chain Ca^{2+}/Mg^{2+} site, so I was soon running gels routinely to quantify the light chain composition of myosin subfragments.

Annemarie was not impressed with technology for technology's sake. She would not be bamboozled by instrumental jargon and had a knack of bringing conference speakers down to ground level by asking fundamental questions about the biochemistry. Whenever a question started with the endearment “Hey Sweetie ...” you knew the speaker was in for a tough time. I am sure this “back to basics” approach accounted for her success as a teacher. She confided that she deliberately kept a small laboratory so she would be close to the action and could focus on one problem at a time. She also said that as she grew older she became more aware that science is done by scientists and that personalities played a big role in its progress. Annemarie was generous with her time and hospitality. She also initiated my visits to Woods Hole, which led to my move into researching the molluscan myosin regulatory system pioneered in Andrew Szent-Györgyi's laboratory. I will miss her greatly.

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