Robert Josephs

I did my PhD with Bill Harrington at Johns Hopkins. The topic was the assembly of muscle thick filaments. This was just after Hugh Huxley came out with his GREAT '63 paper on EM of muscle structure. I did ultracentrifuge experiments on thick filament assembly and determined some thermodynamic quantities. But I always felt that EM was really the way to go. I remember Bill telling me that every paper I would write will have errors in it no matter how carefully I would try to avoid them. (I didn't realize he was right until much later). He added I had to accept that fact and to never try to bluster my way through but rather to admit it when I was wrong. Good advice.

Because of my interest in EM I got a fellowship to work with Hugh. That was the period when the MRC was the place to go especially for structural work. Nobel prize winners walked the halls just like ordinary mortals. I arrived in January and immediately after arriving I made my way to a bed and breakfast in Cambridge to sleep off the trip. I awoke around 4AM believing I was going to freeze to death. In England, at that time, the heat was turned off at night and things got really cold especially for a greener like me.

I met Hugh at the lab and quickly discovered I was totally ignorant of the math and computer techniques used in Structural Biology. It seemed that everybody else at the MRC was aware of my ignorance as well. And they did not hide their disdain for me and my ignorance. I found working on muscle very frustrating and after a while began working on glutamic dehydrogenase (GDH). I thought the work Aaron and David were doing was what I really wanted to get into. The GDH project was a path to learn the discipline. I recall Aaron telling me that I should not expect to publish my work in JMB because, JMB being sort of a house Journal, the MRC had to keep up standards. How's that for setting your mood?

I worked my backside off learning the structural stuff and discovered it was not as difficult as I had thought. It was more difficult. But it was also fascinating. I read every paper Aaron wrote and was amazed at the clarity of his expression and the range of his competence. But being at the bottom of the pile took a toll. And I had a girlfriend in Israel.

Heini Eisenberg was working on GDH and I visited him at the Institute. We agreed that I could come there when I finished my work at Cambridge. The fellowship was a 3 year grant so I left Cambridge after about 2 years. When I arrived in Israel I was astonished at the primitive EM facilities at the Institute and that the 'owners' of the facilities had such a 'lock' on their access. I also started to write up the GDH work I had done at Cambridge. Aaron had offered me some suggestions but, in his typical way, they were far from clear. Sort of like "read chapter 4 in Jones and you will see how to analyze the diffraction data".

Evidently I did a good job on the writeup because after I sent it in to JMB Aaron sent me a nice letter saying the paper "was a model of how such a paper should be written". That single letter made up for all of the frustration of the time I spent in England. In fact on several of Aaron's visits to Israel he came, unannounced, to the Institute looking for me. I recall on the first occasion he visited someone told me "Aaron Klug is here looking for you".

Stu Edelstein came to the Institute on a sabbatical and got me interested in Sickle cell hemoglobin. Initially the project looked like an easy target. Just get the pictures, analyze them and publish. Initially it worked out that way. But my (Stu was a coauthor) work sharply conflicted with work John Finch and Max had previously published. The problem that posed was mainly that I had such a high regard for both of them I was baffled about the discordant results. I wrote it up and got it published in JMB (recall Bill Harrington's admonition). Max and John agreed that my data and its analysis was correct and no one ever figured out why their micrographs produced a different structure. Their interpretation of their data was absolutely correct but perhaps the preparation procedure favored a different polymorph. In any event the structures they observed were not to my knowledge observed again. Sort of like quantum mechanics.

I found life in Israel to be emotionally very rewarding but economically difficult. I had a car but had to sell it because it was too expensive to keep. I was a po boy. In 1976 or thereabouts Paul Sigler came to the Institute on a sabbatical. He was interested in sickle hemoglobin and the U of C was applying

for a big grant on HbS. Paul and I got friendly and he offered to try to get me a position at the U of C. He succeeded. I had tenure at the Institute and did not have tenure at the U of C but decided to stay in Chicago anyway and take a chance.

I continued working on sickle hemoglobin. A year or two later Stu published a structure for HbS fibers which differed from our first work. His structure involved some very complicated pertubations of our earlier model. His analysis failed to deal with a variety of unusual features of the fiber structure. I disagreed with him and pushed for a model which was more closely related the crystal structure Warner Love had published. Many people agreed that the model I proposed made more sense. In the end working with Bridget Carragher and Dave Bluemke (both brilliant graduate students) we (Dave, Bridget, Mike Potel - Dave's and Bridget's former advisor- and I) came to the conclusion that Stu was correct in spite of the shortcomings in his analysis. (Chalk up another one for Bill's advice). The odd thing was that when I published the work showing Stu's model was the correct structure people told me "Great work! We knew you were right all along". It was as if they never read either Stu's or my earlier papers.

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