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John Ferry—the most important man I never knew

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In my third year of graduate school at the University of Wisconsin, I was heavily invested in proteins, mostly urinary proteins. I had become very adept at measuring them quantitatively, found several new factors affecting the excretion thereof, mastered some of the renal clearance calculations much beloved by physiologists, and even done a few paper electrophoresis runs on an apparatus made from a plastic fishing tackle box. Furthermore, I had thoroughly enjoyed Mark Stahmann's course in protein biochemistry, despite the facts that he was not one of the great orators of the western world (actually, he tended to mumble) and that his handwriting was impenetrable. Nonetheless, I realized that I had barely scratched the surface of understanding proteins as macromolecules.

Therefore, when it came time to register for classes for the next semester, I scanned the course catalogue for something to help me. There I found it (eureka!): John Ferry was offering a course in polymer chemistry. What could be more perfect! Proteins are polymers, I reasoned, so who could object to my hiking from the Biochemistry Department (which was in the College of Agriculture in those days) over to the Chemistry Department (College of Letters and Sciences) a couple of times a week to sit at the feet of the great man? The answer was my major professor, Carl Baumann, a nutritional biochemist.

He frowned, he scowled, he clenched his teeth, he turned magenta. "No," he pronounced, "that's out of your field!" Stunned, I was trying to think of a reply that would not cost me my degree, when he continued with what was undoubtedly the best suggestion he ever gave me, even if it was not obvious at the time. "However," he said, "if you're interested in biophysics, why don't you take a course in biophysics?" Aha! Now I had him. I had practically memorized the catalogue. "Sir," I replied, with all the hypocritical tact I could muster, "the University does not offer a course in biophysics." "Well," he rejoined, "you're an enterprising fellow—get the faculty to offer you one!"

And thus began a trek around the Biochemistry Department, with truly amazing results. In brief, the next semester I was taking a biochemistry course that was simply called "Special Problems," but it had a faculty of three and a class size of one. Paul Kaesberg, with the help of his student, Dave Fulmer, taught me electron microscopy. Robert Bock, ably assisted by Harold Van Kley, taught me moving boundary electrophoresis and diffusion. And Robert ("Buzz") Baldwin taught me the theory and practice of analytical ultracentrifugation. It was clearly the high point of my graduate career and, I suppose, I owed it all to Dr. Baumann's bizarre reaction (later, in one of my more suspicious moments, I began to wonder if perhaps he had been appointed a committee of one to study the feasibility of a biophysics course within the Biochemistry Department). In a larger sense, however, I owed it all to John Ferry and his course in polymer chemistry—which I never was allowed to take.

Eventually, tact and diplomacy (plus a certain amount of luck) prevailed, and I received my degree. That might have been the end of it or (as we liked to quote in those days) the end of the beginning, except the spirit of John Ferry kept crossing my path. After a year in Sweden, I was working on the campus of the National Institutes of Health (NIH), which I never left. Before long, our Lab Chief decided to hire a deputy—someone with experience in the proteins of blood plasma. Who was the chosen candidate? It was John ("Newt") Ashworth, who had gotten his PhD under John Ferry, not on proteins (even though Newt had previously

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worked for E.J. Cohn and had co-authored some of the classic papers emanating from Cohn's laboratory) but on "elastomers with long relaxation times," in other words, Silly Putty.

Soon afterward, a very bright and indescribably enthusiastic physician named Mike Mosesson joined our lab. He set about trying to prepare human fibrinogen that was free of plasminogen and, in a remarkably short time, he succeeded. Then came the problem of characterizing the resulting product to see if it had been altered during the purification process. After going through the usual kinds of procedures—electrophoresis, ultracentrifugation, salt precipitation—none of which revealed any alterations, Mike asked me if there was a really stringent test of changes in protein structure.

It so happened that a couple of years earlier I had synthesized some of that brand new chromatographic medium, DEAE cellulose, and had found that ion exchange chromatography could reveal subtle changes in stored or heated albumin. Fortunately, we neglected to consult the NIH fibrinogen experts, who (we learned later) would have told us that it was impossible to chromatograph a molecule as large and relatively insoluble as fibrinogen. As a result, we forged ahead and, to make an excruciatingly long story short, discovered a major heterogeneity of human fibrinogen (many years later we found that the cause lay in the γ chain, and subsequently Mike and his colleagues showed that it was due to an alternate splice site). It was so striking that the demonstration that no structural change occurred as a result of plasminogen removal was almost incidental.

One day, after we had conducted numerous chromatographic experiments on human fibrinogen, Mike reached into the deep recesses of a refrigerator and pulled out a few bottles of crude animal fibrinogen that someone had bought from the Pentex company. Having learned by then that faint heart never won fair elution profile, Mike further purified these fibrinogens, and I chromatographed them with the same gradient as that used for the human protein. Again, a greater or lesser degree of heterogeneity was revealed. Eventually, we went on to chromatograph more than a dozen different animal fibrinogens, all purified in the same way, and all analyzed with the same gradient.

Along the way, however, someone questioned our approach. Shouldn't we optimize the chromatographic system for the fibrinogen of each animal species that we were studying? In fact, shouldn't we begin the optimization upstream, tailoring the purification procedure for each kind of fibrinogen?

The logic of that argument was unassailable. So was the fact that it posed an awful lot of work. As we were wondering, probably out loud, whether we should try this approach (at least with bovine fibrinogen, inasmuch as it was widely used in coagulation research), some other helpful person asked, "Have you read the papers of Ferry and Morrison?" There he was again! And still later, over the years, as Mike and I pursued our search for the structure of fibrinogen, his papers kept surfacing. Always it seemed, like Kilroy, he "was here" before we were.

Finally in 1982, well over a quarter of a century after that fateful non-encounter with his polymer course, I had the honor of meeting John Ferry himself, chatting with him, and hearing him speak at a meeting of the New York Academy of Sciences. It was the kind of moment that one savors at the time and treasures long afterward.

In one of those breathless novels about the marvels of science, the next step would be that John Ferry and I began a lifelong collaboration, culminating in some wondrous discovery. In reality, his laboratory career began long before mine and continued long after I began to spend most of my time behind a desk. Nonetheless, for someone whom I did not meet until very late in my career and barely knew even then, John Ferry had a huge influence, directly and indirectly, on my professional life. It is not too farfetched to say he was the most important man I never knew.