

## Recollections

### How I Became a Biochemist

Athel Cornish-Bowden

CNRS-BIP, 31 Chemin Joseph-Aiguier, B.P. 71, 13402 Marseille Cedex 20, France



A question some of my colleagues might ask, especially some of those I knew at Birmingham early in my career, would be “Did you ever become a biochemist?” Nowadays even the experimentalists seem to spend most of their day sitting in front of a keyboard, but 40 years ago anyone who was mainly seen preparing punched cards and studying the computer output they generated was not to be taken seriously as a biochemist, or even as an enzymologist.

However, accepting that I have become a biochemist, how did it happen? I cannot claim that it was a lifelong ambition or

that I never wanted to be anything else; it was more the result of some very good advice, some excellent teachers, and some good choices made on the basis of their recommendations. I had no family background in science. My father had wanted to be an engineer, but his own father thought otherwise: unable to go into the Navy himself on account of poor health, he was determined that both of his sons should follow their grandfather and great grandfather into the Navy; and so they did. My uncle did not survive the War, and my father devoted most of his working life to a job that he had not chosen. Fortunately, he had no wish to repeat the same error with his own son, and accepted that what I wanted to be, from the age of about 10, was a chemist.

At my preparatory school there was no science teaching, but when I was able to take chemistry and physics at Shrewsbury School I did not hesitate. This was the same school that Charles Darwin had attended a century and a half before me, but whereas he thought had learned nothing there I had some gifted teachers and I learned a great deal, especially from Peter Hughes, who is still teaching chemistry half a century later at Westminster School. I learned while writing this article that my first day of learning chemistry was also his first day of teaching it. It was doubtless obvious that I had not done any chemistry before, but it was not at all obvious that he had not done any teaching before.

I did not start biology immediately, and as far as I recall it was not possible to start biology without 2 years of chemistry and physics. (As for biochemistry, I did not know that such a subject existed.) When I did start biology I enjoyed it, but I was not very impressed, as I had the physicist’s attitude that biology was not a real science. After my first term of biology, the teacher wrote in my report “he is not a great performer, but he plods along”—only to have the embarrassment of having to mark me among the first in the class on the basis of the exam that followed the writing of the report. Afterwards he took my participation in biology classes more seriously, and accepted that total incompetence for recognizing, let alone dissecting, the afferent branchial arteries of a dogfish did not necessarily exclude me from decent society.

I have no recollection of being taught anything about natural selection at Darwin’s school: he was respected as a distinguished alumnus, but not, I think, remembered for his life’s work. If my recollection is right (as it may not be) then it has

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Address correspondence to: Athel Cornish-Bowden, CNRS-BIP, 31 Chemin Joseph-Aiguier, B.P. 71, 13402 Marseille Cedex 20, France.  
E-mail: acornish@ifr88.cnrs-mrs.fr

some relevance to the current rise of hostility to evolution throughout the world. The conventional idea is that religious fanaticism eclipsed biology teaching for several decades of the 20th century, especially in the United States. However, I wonder how much teaching of natural selection there was in schools anywhere in the world at that time, and if my experience is anything to go by there was very little even in schools that were untouched by creationist propaganda. The centenary of publication of *The Origin of Species* occurred during my time at Shrewsbury, but it passed almost completely unnoticed. The Academy of Sciences of the Soviet Union sent a commemorative medal, but no one knew what to do with it, so it was passed on to the teacher of the Russian class I was taking (in those days Russian was the language that everyone was going to need in the future). At that stage I had no thoughts of becoming a biologist myself, let alone a biochemist.

So I went on to Oxford to study chemistry, and was fortunate to do so on the basis of excellent advice: Peter Hughes strongly advised against the College that I had thought of applying to, but instead recommended me to choose between Wadham and Merton. That year Wadham had its scholarship examinations in December, and Merton had its in March, so I ended up at Wadham. Once established at Oxford I found that this advice was the best I could have had. My tutor was Bob (R. J. P.) Williams, who gave me a solid grounding in physical and in inorganic chemistry, and who is still active half a century later. At that time Jeremy Knowles became a Fellow of Wadham and I started taking organic chemistry from him in my second year. The fourth year ("Part II") of chemistry at Oxford consists of a research project. Ideally the students choose projects in the area of chemistry that they want to study, but that was not what I did. I had very little idea of what sort of research Jeremy was doing, and was not particularly interested in aromatic nitration, which was what he had been doing just previously, but I did think I wanted to work with him.

So I found myself in a greatly enlarged Knowles group, with one student in the previous year increased to seven in ours. By that time I knew, of course, that what he was interested in was enzymology, and I started studying the pH-dependence of pepsin catalysis. I continued with Jeremy for my D.Phil., and with the same subject. In theory that was not allowed, but that is what I did. My Part II thesis was called *Studies in Pepsin Catalysis* and my D.Phil. thesis was called *Studies of Pepsin Catalysis*, with just a preposition to distinguish it. At that stage I still thought of myself as a chemist and had next to no knowledge of or interest in any physiological role that pepsin might have. I was more interested to know what pepsin could do well outside the physiological range of pH than in what it might do in the stomach: I like to think that I was the first person to check whether an enzyme can be active below pH 0.5, and found that it can: at pH 0.47 pepsin has the activity one would expect by extrapolating down from higher pH values; I tried to measure the activity at pH 0.14, but did not get any meaningful results. My D.Phil. examiners, Anthony Matthias and Stephen

Waley, attached much more importance to the physiological role than I did, and asked various questions about it that I was quite unable to answer. Fortunately, they also thought that post-doctoral research in the United States would do me more good than some additional months in Oxford learning some physiology. (A few years later I was the external examiner of one of Jeremy's D.Phil. students, and history repeated itself: by then I thought that physiological knowledge was desirable, but she did not have any.).

It would be nice to say that by then I had a clear idea of what I wanted to do with my life but it would not be true. Although I found the pepsin work interesting and rewarding, I thought I should broaden my horizons and had become interested in the regulatory properties of enzymes—this was in 1966, when everyone was talking about allosteric interactions, and I had been very impressed with Jacques Monod at a meeting of the British Biophysical Society and when he visited Oxford for a lecture. When I told Jeremy that that was the sort of thing I might like to do he said that it was a bit biochemical for him, so he would consult a biochemist (George Radda), who said that I should go for the best, which for him meant applying to Dan Koshland. So I did, and was accepted for post-doctoral research in his laboratory at Berkeley, where I spent 3 years working on subunit interactions and developing a passion for computer programming that has never left me. Luckily, I had found myself with almost the only senior biochemist in the United States who did not regard *theory* as a dirty word. Dan liked theory, and did not discourage his group from getting involved in it—warning them only that others were not so broad-minded, and that our possibilities for future employment might be jeopardized if we got too deeply involved.

Dan also had a capacity for enthusiasm and encouragement that is unmatched in my experience. After some years I returned to England (as a lecturer in biochemistry at Birmingham), and I went back for another summer in his lab. While he was away for a couple of weeks, I wrote up some ideas I had had about negative cooperativity. On his return I showed him what I had written and he expressed his usual enthusiasm. I also showed it to Jack Kirsch, who said it was all right but asked whether it was really the sort of thing I should be spending my time on. In my defense I said that Dan had liked it, so he asked how many years I had known Dan. About seven, I said; to which he asked whether in those 7 years I had ever shown Dan anything he did not like. The answer, of course, was no.

The story really ends here, because at some point during the 3 years at Berkeley I stopped thinking of myself as a chemist, and realized that I had become a biochemist, or more exactly an enzymologist, and I have remained one ever since. From isolated enzymes of interest mainly from the point of view of organic reaction mechanisms, I have become progressively more involved in their roles in metabolic pathways and in metabolic regulation. The study of liver hexokinase, which I started to develop early in my years at Birmingham, played an important part in this transition from organic chemist to biochemist.