Perspectives

After DNA at the MRC

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1. Introduction

In 1959, when I went to Cambridge and first saw the MRC Laboratory of Molecular Biology, it was housed in a modest building buried inside the majesty of the famous Cavendish Laboratory. You could easily walk by without noticing it, thinking it was some kind of prefab workshop for physicists (figure 1). You would be partially right in that it was jam-packed with physicists; but what they were doing was not so much physics as laying the conceptual framework of life itself. The scientists you might run into were an extraordinary lot. There was Max Perutz, the founder-director of the laboratory, invariably in a neat tweed jacket; John Kendrew, the deputy director, with a shock of white hair; and of course Francis Crick, with his booming laugh, tall and patrician, sharing a small office with Sydney Brenner who was always bursting with ideas. The many post-docs, students and sundry visitors made up the rest.

February 28, 1953, when I was almost fifteen years old, was when the structure of DNA was discovered. 1953 was also the year in which Tenzing and Hillary climbed Mount Everest, Joseph Stalin died, Queen Elizabeth II was crowned the Queen of England and so on. Somehow I remember this year as one filled with both important and trivial events. Jim Watson's famous book "*The Double Helix*" describes the competition with Linus Pauling, the most famous of all chemists, for solving the DNA structure. It so happens that February 28 was also Pauling's birthday. The MRC Laboratory thus generated a birthday gift, welcome or otherwise. But more than that it helped set in place a conceptual framework to explore and explain the most fundamental aspects of life, the mechanisms of reproduction and inheritance.

When I was asked to write a short piece on the laboratory to mark the occasion of the 50th anniversary of the discovery of the structure of DNA, I hesitated. Accounts like this often are anecdotal and not interesting except for the person who is reciting the anecdote. On the other hand, there was something special about the MRC Lab in those days, not to mention the fact that it played an unrivalled role in ushering in the molecular biology revolution. I was privileged to be both an onlooker and a participant in some of the science that went on there in the early 1960s. What I can try to do is to give a flavour of what it was like to be in this incredible lab.

When asked whether there were simple guidelines to organize research so that it would be highly creative Max Perutz is said to have commented (according to Anthony Tucker): "No politics, no committees, no reports, no referees, no interviews – just gifted, highly motivated people picked by a few men of good judgement". Max ran the lab in this spirit and spent most of his time on haemoglobin crystallography. Likewise John Kendrew, on myoglobin. At the other end from crystallography was molecular genetics with Francis Crick and Sydney Brenner at the helm. In spite of the excitement and fast pace of science, a great deal of attention was paid to detail. Max as Director read all the papers which went for publication even if they were not in his field. In one instance he queried the common usage for sucrose density gradients and pointed out that the opposite of a steep gradient was not a shallow gradient. The opposite of shallow was deep and the opposite of steep was gentle. Francis Crick once commented that what I was saying was possible but not plausible. I remember going post-haste to the first dictionary I could lay my hands on to understand the difference between these two very similar words. As Francis Crick wrote in *The Scientist* "It was a blissful period, because the problems were important, only a few people (most of them friends) were working on them and thanks to the Medical Research Council's support, we didn't have to write grant requests and could study whatever we liked". Work and play co-existed. Francis and Odile Crick had a beautiful tall house on Portugal Place where the most lively parties were held. The artists, poets, philosophers,

historians and scientists who were invited made the parties memorable. Crick considered the chapels, a part of the history of the Cambridge colleges, as an unfortunate mistake of the past. Consequently, he refused to accept a fellowship in any college. Things changed when Churchill College was established with a promise not to build a chapel. Francis accepted a fellowship there. Such were the people and the philosophies which guided the MRC Laboratory and resulted in so many Nobel Prizes to Crick, Watson, Perutz, Kendrew, Klug, Milstein, Brenner, Sulston and others.

If you peered into the laboratory you could see a maze of equipment and glassware, all seemingly enjoying the chaos and crowding that was so obvious. Some of the visuals were quite comic, such as a rigged-up glass assemblage to grow large quantities of bacteriophage, called the Fraser Machine (figure 2).

One day I was struck by the sight of Francis Crick staring intently at some molecular structures and squinting in a special way. He told me that seeing a 3-D structure stereoscopically required practice and invited me to try it out. Try as I might, I just could not make my eyes squint in the required manner. The overriding impression for me was that the school of the time-tested British genius of "making do" was in action and that string and tape and chewing gum would be handy if required for an experiment.

If you ventured as I did in 1959, you felt a huge sense of energy and purpose with conversations and arguments

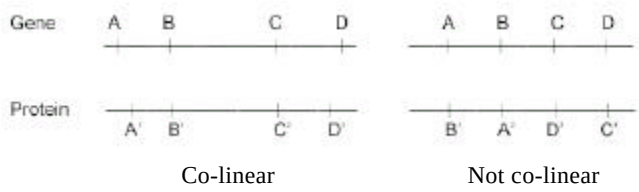
Figure 1. The old MRC prefab building (photograph taken in 2003).

Figure 2. Apparatus for growing phage on a large scale. F, Fraser apparatus; H, electric fire; A, air line connected to sinter of F; T, air trap filled with cottonwool.

galore. Francis and Sydney's office was just to the right as you entered the main door. It was tiny and the size of the book piles were huge, making one wonder whether they held up the roof. The blackboard was a visual treat and changed its appearance constantly (figure 3a), as many times during the day as new theories speculations and facts began to emerge. It conveyed a sense of energy reminiscent of a Cy Twombly painting (figure 3b).

The main experimental laboratory was largish, about 30 feet by 25 feet. I was given a bench top about 3 feet in length. I had walked over from the Biochemistry Department across the road to ask Francis and Sydney if they would accept me for a Ph. D Program. At Biochemistry the Professor and staff often wore a coat and tie. When I arrived at the MRC, Francis Crick was in blue jeans and a black sweater and Sydney was also in informal clothes. Without ado, I was told to address them by their first names, not Drs Crick and Brenner as would be the case at Biochemistry. The crystallographers at MRC, Perutz and Kendrew, were busy with deciphering the molecular structures of haemoglobin and myoglobin. Fred Sanger, who had just completed the chemical structure of insulin, was housed in Biochemistry and Sydney was collaborating with him on using the new protein fingerprinting technique to analyse bacteriophage head protein.

The original Watson-Crick DNA model stood in one of the small rooms in the prefab building. It was a reminder of how many new things needed to be explored. The little office of Francis and Sydney reverberated frequently with fascinating arguments and an ever changing blackboard. One of the key postulates of the "Sequence hypothesis" was that the linear sequence of bases in DNA of a Gene Coded for a linear sequence of amino acids for the protein product of that gene, i.e. that the gene and 'its' protein were topologically co-linear.



If A, B, C and D represent point mutations in a gene resulting in amino acid substitutions in the corresponding protein then there are, roughly speaking, two alternatives as shown above. The alternatives indicate what the main approaches to the problem were as pursued in a number of laboratories, the MRC at Cambridge, Charles Yanofsky at Stanford, George Streisinger at the University of Oregon and Cyrus Levinthal at Columbia University. The experiments consisted of creating point mutants and mapping

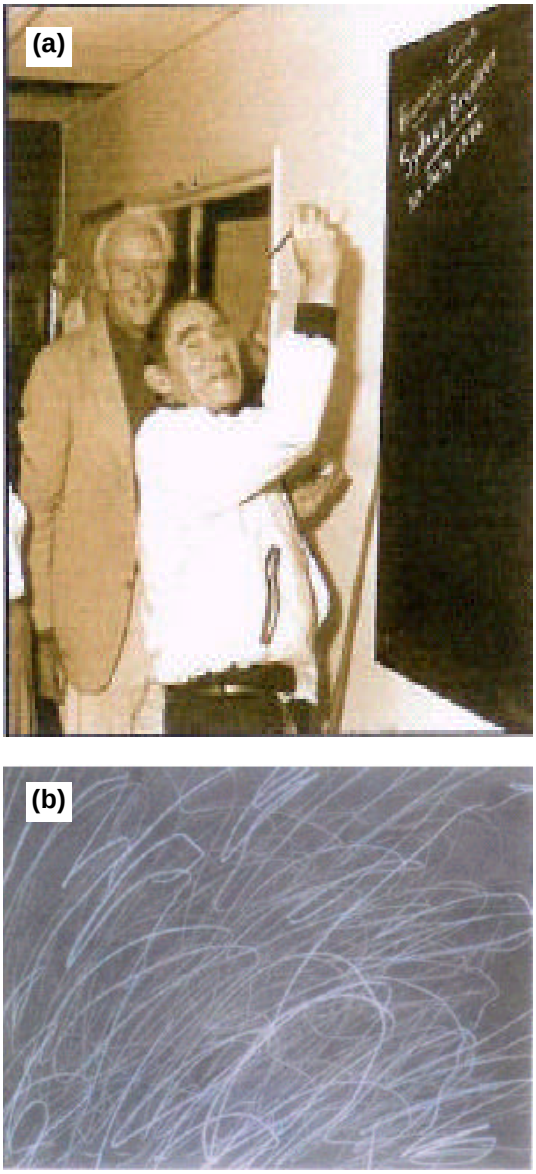
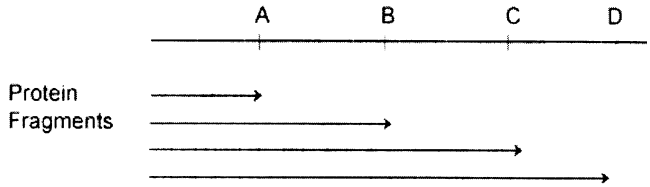


Figure 3. (**a**) Blackboard Reunion: Francis Crick and Sydney Brenner, 1986. Courtesy of MRC Laboratory of Molecular Biology. (**b**) Painting "Ohne Titel (Roma)" 1969.

them to create a genetic map. The protein product of the gene was fingerprinted to locate the amino acid substitution. Everyone believed that the gene and the protein would be co-linear but still this had to be proved. There was a sense of competition between the groups as to who would get the proof of co-linearity first. The books by Judson (1996) and Morange (1998) should be consulted in order to place this problem in context and for an appreciation of the discoveries that led to coding being, in a sense, the problem in molecular biology in the early 1960s. Whitehouse (1973) gives an excellent account of the experiments that led up to the deciphering of the genetic code. Both Crick (1988) and Brenner (2001) have provided first-person accounts.

My thesis problem was to show the co-linearity of the gene and its polypeptide chain using mutants of bacteriophage T4 that Sydney had isolated. He had selected mutants that were resistant to osmotic shock. It was conjectured that they would have an altered amino acid sequence of the head protein. In retrospect it was an ingenious but risky assumption; it did not work out. I had a lucky break when I met Dick Epstein, the discoverer of nonsense mutants (amber mutants) of T4 in Geneva. The mutants were so named by Dick after the mother of Bernstein, a Caltech graduate student; Bernstein is the German for amber. These mutants (it was believed) did not make a full polypeptide in a normal cell but did so in a suppressor-positive cell. What was not known was whether the amber mutations kept terminating and releasing the synthesized peptide or simply got jammed at the amber site.



I told Dick that I could test this in Cambridge quickly. What I found was that the amber mutants kept terminating and releasing the polypeptide, so that you got large amount of fragments of polypeptide of lengths dictated by the position of the amber mutations in the gene. This broke open the co-linearity problem (Sarabhai *et al* 1964).

The Yanofsky group succeeded at the same time by using point mutations and altered amino acid substitutions (Yanofsky *et al* 1964). We published our papers at the same time. For a graduate student, to take on a fundamental problem like this may have been foolhardy. But I enjoyed the race. Many visiting scientists from around the world would come by for a few days to give a talk or just to visit, some to get converted to doing biology. I remember the visit of Don Glaser while he was on his way back to Berkley after winning the Nobel Prize for Physics in 1960 for his invention of the bubble chamber. He came to find out what he could do in biology. After his return to California he got so deeply involved that he went on to establish the Cetus Corporation one of the first Biotechnology Companies. Meanwhile the MRC was in high gear on other projects: Sydney on messenger RNA, Francis and Sydney proving that the code was a triplet by using the most elegant genetics. I went on to define the properties of inter-cistronic space, the space between the stop signal of a previous gene and the start signal of the next gene in a constructed operon.

The blackboard kept on changing but now in a grand new multistory laboratory.

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