CHAPTER 5

From MRC-Cambridge to Madison, Wisconsin

William Dove and Alexandra Shedlovsky
McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, WI

Figure 5.1. Bill Dove.

Figure 5.2. Alexandra Shedlovsky.

PROLOGUE – A STYLE OF DOING SCIENCE

Our experience in the early 1960s as postdoctoral fellows in the MRC Unit for Molecular Biology led to our understanding the following principle: science is effectively driven by an idea when the seed is nourished by dialogue between contrasting outlooks. We shall share our experiences that illustrate this 'core principle'

by which the MRC unit thrived in that era. Since science does not function in a vacuum we include our perceptions of the cultural context that stimulated the growth of ideas through dialogue. This dialogue led to the remarkable edifice of molecular biology that emerged from the unit and its progeny around the world. Our comments are strictly matters of personal perception; however, Horace Judson's *Eighth Day of Creation* gives a more global view of this and surrounding eras,[1] while Sidney Altman wrote from a personal perspective of his experiences in the unit a decade later ['RNA processing: a postdoc in a great laboratory'[2]]. Finally, the core principle is revealed in the essay written by the physical chemist John Platt ['Strong Inference: Certain systematic methods of scientific thinking may produce much more rapid progress than others'[3]].

The messenger RNA experiments, the demonstration of the 'triplet code', and Marshall Nirenberg's polyU encoding polyPhe experiment were all published by the middle of 1961. Alexandra arrived at the MRC Unit while it was housed in the Cavendish Laboratory of Physics and Bill came in the autumn of 1962 after the move to Hills Road. A 'Crick Week' was established to present all of the emerging information and stimulate debate on the current status of the coding problem. Crick focused on the steps needed to establish the genetic code, while Brenner believed that the important issues involved regulation of genetic information, including the host-induced modification of genomes.

Bill's Caltech experience with Linus Pauling (on clathrates formed by general anaesthetics) fed into his frequent discussions in the canteen with the crystallographers. At the time, Bill sensed that any connection with Linus Pauling was cause for tension. Jim Watson's *mea culpa* ['The Double Helix'[4]] explains this fear of competition from Caltech's eminent structural chemist, a founder of 'molecular biology'. This nascent discipline, consolidated by the newly established *Journal of Molecular Biology* with John Kendrew as editor, radiated throughout academia. Departments of 'Molecular Biology' were set up across the United States, sometimes over the objections of the pre-existing biological departments. Francis Crick once quipped that soon there would be 'departments of molecular theology'.

In the early 1960s scientific discourse in the MRC unit involved daily debate, both between the structural and the functional analysis of biology and between the genetic code and the regulation of its usage. Ideas were tested in this crucible, but put into action in the hands of the group leaders and their members who carried out experiments. Tony Stretton (on the staff) and Anand Sarabhai (a graduate student) provided the hard work needed to establish the colinearity of the major coat protein of phage T4 and its genetic map. Roger Freedman, a doctoral student with Brenner, illustrated the synergy between creative thinking and active experimentation. At a conference that he attended with Bill, Roger recognised a way to test the Campbell model for insertion of a prophage into the bacterial chromosome. Roger's idea was proven at Stanford some years later ['The linear insertion of a prophage into the chromosome of *E. coli* shown by deletion mapping'[5]] . Similarly,

it was Roger, with Simon Pickvance, who recognised that the somatic division lineages of the nematode *C. elegans* could be followed in vivo by Nomarski interference optics; in this case the hard work was done by John Sulston, Bob Horvitz and others ['The Joy of the Worm'[6]]. Overall, in the MRC Unit for Molecular Biology, science was driven by ideas that were nourished or rejected by discussion and brought to fruition by rigorous experiments.

ECHOES ALONG THE CORRIDOR OF RESEARCH

Bill's secondary school, Phillips Andover, has the motto *Finis origine pendet* ('The end depends on the beginning'). As we reflect on the path of research that we have followed over the past decades, we can discern echoes from the MRC unit of 1962–3. A major theme is that of mutagenesis. With his doctorate in chemistry, Bill was initially attracted to the MRC by the frameshift experiment that established the triplet code ['General nature of the genetic code for proteins'[7]]. This experiment rested on the chemical evidence from Leonard Lerman that the mutagen proflavine differed in action from alkylating mutagens by intercalating into the double helix. The research in mouse and rat genetics and cancer biology that we have developed over time has rested on an understanding of the mutagenic mechanism of the directly acting alkylating agent ethylnitrosourea (ENU) ['Induction of recessive lethal mutations in the T/t-H-2 region of the mouse genome by a point mutagen'[8]]. This echo currently reverberates in interesting ways with sources from the '60s. We collaborate with investigators at the Sanger Institute to establish ENU-induced derivatives of a standard inbred mouse strain to permit genetic mapping under *isogenic* conditions. Curiously, this idea reflects the *isomorphous* replacement strategy of Max Perutz. And when Bill talks at the *Fred Sanger* Institute, it is in the *Francis Crick* Lecture Theatre!

Brenner's choice to concentrate on issues in genetic regulation at the time that the genetic code was being finalised led to his formulation with Francois Jacob of the Replicon Model ['On the regulation of DNA replication in bacteria'[9]]. Bill's research on replication control in phage lambda ['Positive and negative control of bacteriophage lambda DNA replication'[10]], the syncytial eukaryote *Physarum polycephalum* ['Cell cycle regulation of tubulin RNA level, tubulin protein synthesis, and assembly of microtubules in *Physarum*'[11]], and in intestinal tumours of the mouse ['A dominant mutation that predisposes to multiple intestinal neoplasia in the mouse'[12]] and rat ['A target-selected *Apc*-mutant rat kindred enhances the modeling of familial human colon cancer'[13]] has used mutagenesis to dissect replication control systems of increasing complexity.

Finally, the most distant source from MRC 1962 is echoed in a most recent investigation from our laboratory: the epigenetic modification of the genome. Alexandra worked with Sydney to demonstrate that the DNA of phage T4 is subject to a form of host-induced modification – the glycosylation of hydroxymethyl cytosine residues ['A chemical basis for the host-induced modification of

T-even bacteriophages'[14]]. Today we study the pathways by which the 'gatekeeper gene' (*Apc*) loses function in colonic neoplasms ('The many ways to open the gate to colon cancer'[15]]. We have found that one pathway involves epigenetic silencing ['Monoallelic silencing and haploinsufficiency in early murine intestinal neoplasms'[16]].

EPILOGUE – LEAVING TIME FOR TEA

It is striking that in the 1960s scientific progress at the MRC unit was fostered by a tradition unique to English life. The geneticist Frank Stahl commented that J.B.S. Haldane's method to find a mathematical function to generate a genetic map 'left time for tea'. So it was that the canteen provided a platform for discussion. Such opportunities for planned or spontaneous conversation come up in English life five times each weekday – breakfast, morning coffee, lunch, afternoon tea and supper. Even on Saturday mornings, lab denizens would congregate in the kitchen over coffee to hear Sydney Brenner free-associate about life and experiments. Americans who recognised the power of this cultural pattern tried more than once to transplant it across the Atlantic. But, to the best of our knowledge, it never took root overseas.

Scientists everywhere nourish their creative lives by fostering a passion outside the laboratory. The Cambridge scene gave each of us such an opportunity in the realm of music. Bill joined the Cambridge Morris Dancers, exploring on weekends the countryside of Cambridgeshire and beyond. Alexandra, while at the Cavendish, would plan her experiments to permit going to Evensong at the nearby King's College Chapel. The rich musical life in Cambridge continues and our visits over the years always include concerts – sometimes with local composers in the audience.

The parallel life outside the laboratory, dubbed 'episcience', involved more than these cultural aspects of Cambridge life to which we became attached. The scene included a rich array of parties. Bill's stay at 8 Scroope Terrace, in a house occupied by students from the continent and presided over by 'Pop Prior', featured many such gatherings. Famously, the Cricks hosted many a 'wild' party. After his Nobel Prize award, police were called to reduce the noise and Francis was required to explain the cause of the celebration. Hildegard Lamfrom (now remembered by a named professorship at Oregon State University) looked for any excuse to host a party: a visiting speaker, an exciting result, or … just for fun. The MRC unit of the early '60s showed the power of *camaraderie*.

Our own personal and professional trajectories were seeded within this dynamic scientific and cultural environment. They became entwined when we married in 1964 and soon after moved to the University of Wisconsin in Madison. Some aspects of the scientific life of the MRC unit have resisted transplantation. What persists for us is the excitement of joining together molecular and biological ideas, and the pleasure of living in a small but culturally rich city.

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