Perspectives

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RNA Processing: A Postdoc in a Great Laboratory

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The author is Sterling Professor of Molecular, Cellular and Developmental Biology at Yale University and, in 1989, shared the Nobel Prize in Chemistry with Tom Cech for the discovery of catalytic RNA. This essay is based on a talk presented at the reunion of the Medical Research Council Laboratory of Molecular Biology (MRC-LMB) held at Cambridge, England, on April 26, 2003. Naturally, some of the local elements of that talk have been modified, and a discussion of topics and personalities has been added as extracts for the benefit of the readers of GENETICS.

—EDITORS

IN 1963, Sydney Brenner wrote a letter to Max Perutz about the future of research at the MRC-LMB. He said, ". . . The entry of large numbers of Americans and other biochemists into the field will ensure that all the chemical details of replication and transcription will be elucidated. . . ." (cited by BRENNER 1988). He then went on to describe the new plans for developmental biology he was exploring. I was one of the North Americans to come and work out the details Sydney had mentioned in his letter. I came with a rather modest reputation in biochemistry. Along my route as a postdoctoral fellow at the MRC-LMB, there were moments of great luck and disappointment. At every moment, however, I felt so extremely privileged to be an associate of the greatest laboratory of molecular biology at that time. That experience, in itself, made my stay worthwhile, even if nothing of significance in science emerged from my activities.

As a child, I became interested in the great age of physics in the twentieth century. I read a lot about Einstein and Bohr with his amazingly productive group. It was too much to ask for, but I hoped that one day I might be part of such a group, particularly one like Bohr's. Ultimately, I did join such an amazing collection of personalities, but they were in molecular biology and were located in Cambridge at the MRC-LMB.

> The atmosphere of the great physics groups and their intimate collaboration and communication can be briefly reviewed in A. Pais's books about Einstein and Bohr (PAIS 1982, 1991). Einstein had finished his major efforts and worked more or less by himself, even while in Berlin, although he was an astute and responsive listener. Bohr worked constantly with several young people around him, communicating and discussing new ideas throughout the days and weeks. Several of his associates went on to great fame.

My first contact with the group, if contact is the right word, came when browsing through an issue of *Nature* in 1961. I saw the Brenner and Francis Crick article about the nature of the genetic code (CRICK *et al.* 1961). I copied that article and read it. My fascination with that paper was in how anyone had been able to learn what the article said had been learned.

At that time, late in the spring of 1962, I was in Colorado, working and going to summer school as a physicist. Later that summer, I met George Gamow at a party for students. He was obviously the most colorful person there. Gamow was well known to anybody who studied physics, as I had up to that point. He made the first calculations on alpha particle decay and went on to a plethora of important contributions in physics, among them the theory of the Big Bang. He also played a critical role in the early days of the genetic code. After reading about the structure of DNA, Gamow recognized that there might be a relationship between the number of bases read in the linear sequence, three at a time in this case, and the order of amino acid residues in a protein (no discussion yet of mRNA) to make a protein. He made a simple calculation of the number of possibilities of amino acids you could code from a sequence of DNA (using the wrong number of amino acid residues)

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Figure 1.—Leonard S. Lerman.

and predicted what kind of sequence you would have in a protein (Gamow 1954). These calculations were incorrect partly because of the unknown nature of the code (overlapping, non-overlapping, etc.) and the incorrect number of amino acid residues used by nature. Nevertheless, the direction of the ideas was clear and accurate and spawned several years of intense speculation and experimentation about the nature of the code.

At Gamow's suggestion, because of my partial understanding and an interest in molecular biology, I contacted the Department of Biophysics at the Medical School in Denver. Ted Puck was the Chair of that small department. When I drove down from Boulder, I visited Leonard Lerman (Figure 1). That was the end of my career as a physicist. Leonard had just returned from a sabbatical year at the MRC-LMB. He and I hit it off, and I became his student. We agreed, shortly thereafter, on a topic for a thesis. In the meantime, Leonard did tell me about his work on acridine-DNA complexes, which he had discovered, and his life at the MRC-LMB. A few years later, in Nashville, Tennessee, where Leonard had moved and I finished my thesis, I met Sydney Brenner.

Sydney gave one of the greatest lectures I have heard in science. There were no slides. It was all about the genetic code and nonsense codons. Later, I told Sydney that I would like to work at MRC-LMB, but he said there was no space available at the moment. Disappointed, I went on, very fortunately, to Matt Meselson's lab, and there I saw Sydney again after another year or two. He was visiting the Boston area. He asked me if I was still interested in the MRC-LMB, and when I said, "Yes," he indicated that there was newly available space in the lab and suggested I might want to work on the three-dimensional configuration of tRNA, probably by NMR. Any physicist, or student of physics, could operate a big NMR machine.

I arrived in Cambridge in October 1969, just after the annual lab meeting, an important occasion that I happened to miss twice during my time in Cambridge. Very soon I had a meeting with Sydney and Francis. They told me that tRNA had been recently crystallized and that I should come by with a new, *i.e.,* my own, plan for study. Two weeks, they said, and we will meet again. They did suggest some possible fluorometric studies of tRNA in solution.

What an idea! Come up with my own research plan! I looked around, read some uninteresting papers, and then went back to Sydney and Francis. I suggested that I look for acridine-induced mutants of tRNAs. Since they had recently completed a classic study of substitution mutants of tRNAs, the idea I presented was met with what I perceived as an attitude of great boredom. Nevertheless, they said, if that is what you want to do—go ahead. I distinctly felt that if they spoke to me again, it would be an accident. The conclusion I drew was that studies of tRNA mutants were finished.

Brenner and Smith and their junior colleagues had recently published papers on substitution mutants of $tRNA^{Tyr}Su_{3+}$ that demonstrated the expected change in the anticodon of the tRNA as it became an amber suppressor and then how the properties of suppression changed as other nucleotides in the sequence were altered (Abelson *et al.* 1970; Smith *et al.* 1970).

I did have a few experiments left over from my previous work with Matt Meselson, which I decided to complete. Let us remember that they concerned a DNA endonuclease, so I had some experience dealing with an enzyme that cut nucleic acids. I also gave a seminar on that work, which did not excite me very much. To my surprise, Fred Sanger was the only senior member of the lab who attended, with only a few in the audience. It took me a while to figure out why Fred was there (to hear about new DNA endonucleases) and the reasons for the questions he asked. He was working on sequencing DNA and looking for new enzymes to recapitulate the work on sequencing of RNA. Jon King, another inventive T4 person with whom I did some very slow work on T4 encapsulization, was also there.

I did get started on making acridine-induced mutants of tRNA. John D. Smith (Figure 2), whom I had previously not met nor even heard much about, did help me set up the genetic system, and I worked on that for my first year. In fact, I started out with su^{+}_{am} mutants of $tRNA^{Tyr}$ and did succeed in making various non-suppressing mutants. These were made in *Escherichia coli* lysogenized for $\phi 80 su_3^{+}$: the cells were induced, and the tRNA genes transferred to the $\phi 80$ itself and then examined more closely. Indeed, I had several mutants that made no tRNA, but some did revert to the Sup^{+} phenotype at frequencies of about a few percent. By this time, May 1970, I was getting ready to leave the lab and look for jobs in other fields.

I should also say that I rented a sixteenth-century,

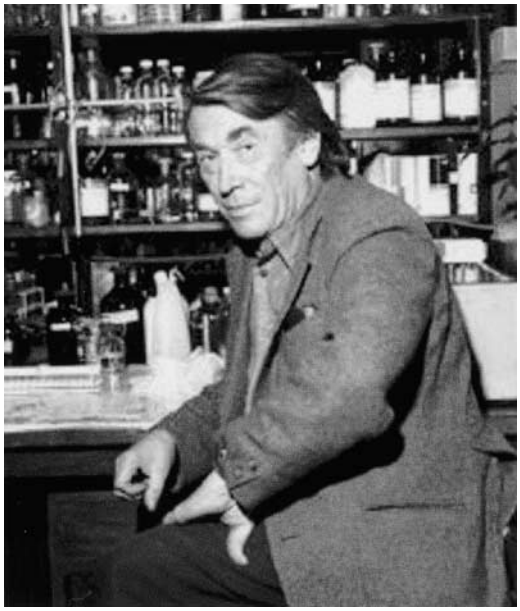

FIGURE 2.—John D. Smith (courtesy of the MRC-LMB).

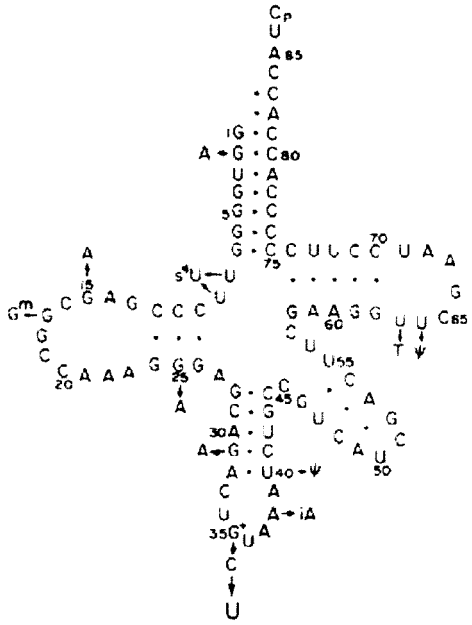

FIGURE 4.—A description of tyrosine tRNA with locations of mutations of the amber and ochre anticodons at position 35.

very small, thatched-roof cottage in Barley, a few miles from Royston (Figure 3). It had been the priest's cottage for many years and is on a map of the village dated 1545. My life there was very quiet and gave me a good chance to think about what was happening in the lab. It was made tolerable by my friendship with Jack Wilkerson and his family, Jack being one of the squires of the village and also a very good farmer, an amateur archeologist, and a historian.

I had a 1-year fellowship that was rapidly coming to a close. It was a bad time for jobs: the market in molecular biology had not yet expanded, and my search came up empty. That was a time of deep disappointment.

Sometime in May 1970, Sydney suggested to me that I had better get something published or my meager talents would be lost to science. He had one problem, not yet solved, concerning ochre-suppressing mutants of $tRNA^{Tyr}$. The idea was to make an ochre-suppressing tRNA mutant and sequence it to show that it had the expected anticodon. Amber-suppressing mutants had already been characterized in earlier publications by Brenner, Smith, and colleagues (Figure 4). I started the project Sydney suggested rather quickly in my spare time. Within a week or so, I had isolated the mutants, isolated the tRNAs, and started the sequencing to show that they were the correct tRNAs. This work went almost too smoothly; there were no problems. Others in the lab had previously tried this project without success. I did everything the same way they did, except that I used a new mutagen, hydroxylamine. It was the favorite mutagen of Bill McClain, another American. I had thought it was the perfect mutagen of choice from a chemical point of view, and he had a bottle full of it, ready to use. So now I had one publication.

FIGURE 3.—My cottage in Barley.

It is worth mentioning that I had read about Sanger's two-dimensional fingerprinting of RNA before I came to the lab. I watched people do it at MRC-LMB, but I still felt it was an impossible method; it seemed that too much voodoo was involved. So when I had to start sequencing, I asked for some help from another American, Hugh Robertson, and soon learned that there was no voodoo, although it had seemed that way to an observer. The method worked brilliantly over and over again. I tried to emulate Bart Barrell, who could do about seven or eight fingerprints simultaneously, but I never quite succeeded. The most I could do was six.

A few weeks before my fellowship terminated, I decided to do one more experiment on the tRNA acridine-induced mutants I was making. I thought that the mutants I had that reverted at high frequencies were probably partial duplication mutants and that their finished product was too "damaged" to survive for very long in

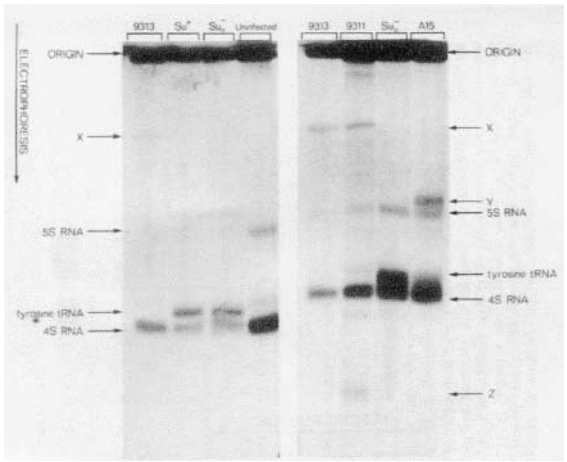

FIGURE 5.—Analysis of mature and precursor tRNAs in a polyacrylamide gel. Bands labeled X and Y are precursor tRNAs.

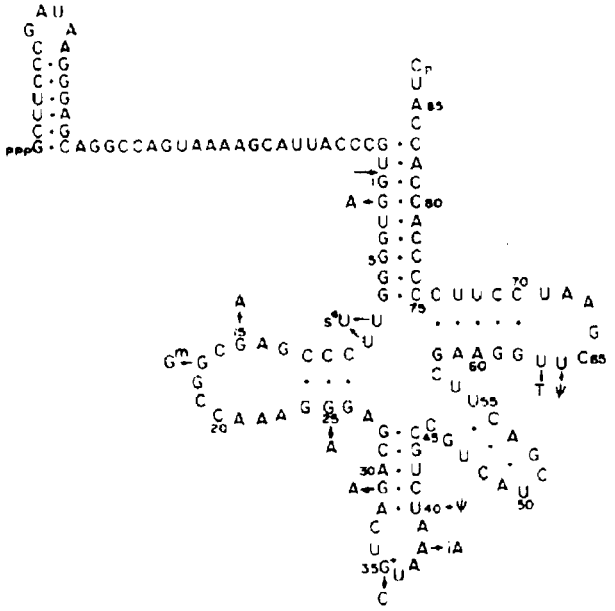

FIGURE 6.—The secondary structure of a precursor to tyrosine tRNA. The arrow between positions −1 and +1 is where RNase P cleaves this substrate. The amber anticodon is indicated at position 35, and other mutants and modified bases are also shown.

the cell. Consequently, I tried to see if I could isolate a precursor tRNA molecule in the fastest way possible. My decision was influenced by the fact that every time somebody reported such an experiment in the literature, there was always a centrifugation step to spin cells down. Even a 30-second centrifugation would be sufficient, in my mind, to allow the cells to destroy any unwanted transcript. I avoided such a step and added phenol directly to the cultures. The first experiment proved that I was on the right track, as I found some large molecular weight bands running above tRNA in the gel. Their size was appropriate for partial duplications (Figure 5). Soon I also included one of the older base substitution mutants and noticed that it, too, had a higher molecular weight band. My colleagues, namely, Bill McClain and Tony Cashmore, encouraged me to fingerprint these products (ALTMAN 1971). There was some skirmishing, because they wanted to see the fingerprint the moment it was developed. I think I managed to avoid that, but Tony, especially, was very excited when the fingerprint showed that I had precursor molecules.

My fellowship ended. What was I supposed to do? Francis, Sydney, and John Smith were away, but at least Sydney was accessible by mail. I wrote to Sydney explaining what I had done and asked for permission to stay, without salary, so I could work on this experiment and get the results I needed to allow me to apply for a job. Very fortunately, Sydney answered and indicated that there might be a standard, local MRC postdoc salary for 1 year. I am still grateful for this unexpected and generous hospitality.

The subsequent year found me identifying the processing enzyme that cleaved the 5′ sequence from precursor tRNAs (Figure 6). Hugh Robertson, who had extensive experience with RNases, guided me and supplied crude extracts ready to use. John Smith returned to the lab, and we worked together on mutants and other aspects of the problem.

John Smith was a venerable nucleic acids biochemist. He had worked on the nucleic acids of viruses long before coming to the MRC-LMB and was an expert on identification and characterization of nucleotides, much of it done on unlabeled material, detected by observing chromatographs under UV light. He was a quiet person but very lively in conversations about science.

We found that many previous substitution mutants of tRNAs had precursor molecules that were not cleaved properly by RNase P, our new enzyme. In addition, Bill McClain applied our knowledge to that of T4 tRNAs and, over the next few years, painted an extremely detailed picture of the genetics and biochemistry of tRNA synthesis by T4. When I went back to Yale, I followed Arthur Kornberg's dictum that every graduate student ought to purify an enzyme before he gets a Ph.D. and put a graduate student, Ben Stark, on purifying this enzyme. In the end, my MRC-LMB journey helped start the field of the enzymology of tRNA processing.

I did not realize what I had done with the precursor tRNAs. I knew it would get me a job, and it did. Sometime later that year, Gobind Khorana came through the MRC-LMB and was steered to me. It was hard for me to believe that this intellectual giant would want to hear about my work. But, of course, he was working on making a synthetic $tRNA^{Tyr}$ gene, and he wanted everything, including the gene sequence, characterized. He went away somewhat glum, but within a year or so he succeeded in doing what he wanted.

Paul Berg also visited the lab and wanted to find out more about my work because Dale Kaiser's student, Paul

Schedl, was working on a similar project. As I recall, nobody gave him much time, but one morning he came to me and I agreed to send him my phage strains. In fact, Schedl's work became quite interesting as he had unwittingly isolated a temperature-sensitive mutant in the protein subunit of RNase P.

[I should mention that no one had isolated a radioactive, pure precursor tRNA prior to this time. Burdon and Darnell separately had looked at putative collections of mixtures of tRNA precursors in mammalian cells and had shown that crude enzymology was involved in changing their size from somewhat larger than tRNAs to that of normal tRNAs (Bernhardt and Darnell 1969; Burdon 1971). That was the extent of similar work at the time. Our work started the processing and detailed enzymology of *E. coli* tRNA. Very soon, 30S ribosomal RNA precursors were isolated in *E. coli* by Apirion and Schlesinger, their colleagues, and others, and it was rapidly shown that RNase III was involved in their processing. tRNA processing was also pursued in human cells by my lab, and rRNA processing in eukaryotes had several converts. The processing of mRNA also followed in quick succession (Brookhaven Symposium 1974).]

In the summer of 1970, I learned that my father had leukemia. I went home to Montreal in the early fall for about two to three weeks to be with my parents. My father was originally a penniless immigrant to Canada. He died while I was in Montreal. When I arrived back in the lab, again having missed the annual meeting, Sydney saw me as I climbed the stairs to the second floor and, as might be expected, asked why I had taken so much vacation. I still do not know if he was joking.

Later that fall, Sydney came into the then large lab room on the second floor with a blue airmail letter in his hand. "Who wants a job at Yale?" was the greeting, shouted loudly enough so that everyone heard him. It is my recollection that my hand shot up: "I do." Ultimately, I did receive an offer from Clem Markert, the Chair of the Yale department. Of course, Markert offered me a salary that was much lower than that offered by other places, and when I timidly commented on this, his typical answer was, "You can be bought?" Nevertheless, he gave me a little more money, and I took the job. (That was my first experience with Markert, an outstanding developmental biologist and a superb, courageous person who fought with the Lincoln Brigade in Spain and was a determined and brave opponent of Senator Joseph McCarthy.)

The enzymology we did on RNase P at the MRC-LMB was a solid beginning to the next phase that was carried forward at Yale: the complete purification and characterization of the enzyme, which had, as it turned out, a large catalytic RNA subunit. It is worth remembering that in those days we were still in the millicurie era. Each experiment I did to label tRNA (or precursors) or to prepare substrates for RNase P involved putting about 3 mCi in a bubbler tube for several minutes and then extracting the labeled RNA. One day in the summer of 1971, shortly before I left, I was doing an experiment with 5 mCi in an attempt to label the wild-type $tRNA^{Tyr}$ precursor and to determine its fingerprint. In this case, without my knowledge the bubbler tube I was using developed a small hole in the water bath. A stream of highly radioactive ^{32}P was scattered all over my bench and the surrounding area when I removed the bubbler tube.

John Smith, our radioactive safety officer, was away, and Sydney muttered, "I'm too busy. Go and see Fred (Sanger)." Fred listened to me and came downstairs to the second floor. Without a word, he put on some rubber dishwashing gloves, grabbed a can of Ajax and some sponges, and knelt down to try to see how much radioactivity he could get off the floor. Not much. I objected to what he was doing because I thought I should be doing that job. Quite soon, he said that I had done enough and decided to clear the area. I stripped my clothing off, donned a lab coat, and drove home where I left the clothes in the coal shed to "cool" off. Hugh Robertson called the contaminated space Yucca Flats, and some time later that whole floor and bench area were removed.

I cannot imagine a person of Fred's reputation taking on such a modest and thankless task and refusing any help. The image of him, on his knees on the floor, trying to wash away the radioactivity I had spilled, is still fresh in my mind. There are many ways, I suppose, of exhibiting humility and greatness, and this was one of them.

I have described my history as a postdoctoral fellow at the MRC-LMB. The lab itself was such an amazing place in which to work and deserves significant comment. Mike Fuller ran the stockroom both efficiently and in a friendly fashion to ensure that we always had what we needed. The library, with a modest collection of journals, was always available and supplied with photocopies of articles on demand. There was, importantly, a collection of brilliant younger colleagues, each with his own bizarre identity. The air was bubbling with notions of both useful, practical ideas on how to go about things and theoretical notions that were interesting to discuss. The postdocs were international and vibrant. John Smith liberally dispensed his fund of knowledge, the more liberal the better you knew him. The generated ideas whizzed around the lab, many not useful, but when one was, it was recognized as such and shone brilliantly. There were also many extraordinary social and sporting functions with the postdocs and staff. I can instantly create a picture in my mind of playing football (soccer) for the MRC-LMB B team on a local village's meadow on a Sunday morning. Needless to say, while the events I have described are mostly joyful, there were moments of great disappointment during that first year, and episodes of quarrel and disagreement among the many prima donnas in the lab.

While I was at the MRC-LMB, Sydney was steadfastly

Figure 7.—Several of the senior leaders in the MRC lab around 1967. Seated from left to right: Hugh Huxley, Max Perutz, Fred Sanger, Sydney Brenner; standing left to right: John Kendrew, Francis Crick (courtesy of the MRC-LMB).

plugging away on the histology of the nematode and beginning to develop a system for mutant isolation. Occasionally, I would meet with him to discuss some science; those meetings were filled with dazzling fireworks. There were rockets and flares that fizzled and burned out, and others that cast their illuminated glow on the landscape and burned brilliantly forever. His fund of knowledge was enormous, and the ideas flowed freely. Many were not practical, but some always were.

Francis was preoccupied with chromosome structure. In fact, he surprised me on a solitary Saturday afternoon when he approached me in the hall, very excitedly, and wanted to tell me about a new theory. I was, of course, flattered but dumbfounded. I understood very little about the chromosome and the theory we were discussing, and this conversation did not further my knowledge much. Fred Sanger was working on the sequencing of DNA, I believe having already given up on using the various enzymes that he had employed with proteins and RNA (see Stretton 2002). Max Perutz was heavily involved in trying to understand the mechanism of hemoglobin action; Aaron Klug was finishing up further details of tRNA crystal structures and getting started on nucleosomes; and Cesar Milstein was busy with antibodies (Figure 7).

Sydney still had an abiding interest in tRNA suppressors, so in the summer of 1971, Larry Soll, who had recently received a Ph.D. from Stanford, came to give a talk on su_7^+. Sydney showed up after a while dressed in his usual James Dean outfit of chinos and a tee shirt with a cigarette pack stuffed inside one of the sleeves. He managed to ask some good questions and, afterwards in the hall, Larry asked, "Who was that far-out freak with the good head?" That created a round of hysterical laughter from the surrounding people. I am not sure we have heard a better definition of Sydney. In any case, John Sulston, in *The Common Thread*, writes about Sydney as a "complex and powerful personality" (Sulston and Ferry 2002). For those of us who know Sydney, that can be considered only the essence of a very vague description. More recently, Bargmann and Hodgkin described Sydney as "outrageously brilliant, charismatic and witty," a much more satisfying description when complementing Sulston's words (Bargmann and Hodgkin 2002).

One has to remember that Sydney and Francis shared an office, an assignment unheard of in the United States. That fact immediately marked the lab as unusual and interesting. Sydney and Francis needed to talk to each other. We can only imagine what wonderful conversations they had. And if one of them was not around, then whoever was in the coffee room became the focus of talks.

Conversation was always a pleasure. I enjoyed tea, mornings and afternoons, and lunch every day where everything, from local British politics to matters of serious scientific interest, was discussed.

Of course, the primary and most important feature for those of us who were new in the lab was that everybody was heard. Holding a position at the lab meant, as the senior people showed every day, that you had a respectable opinion on science and that your opinion was treated the same as everybody else's. The dedication to science was paramount. Everybody paid attention. However, if what you said was incorrect or foolish, you were promptly told so. You were also expected to work, more or less alone, with no immediate help from senior people. The assumption was that everybody could do experiments well. The senior people taught by example: everybody was in the lab, working. These permanent, abiding lessons of how to do science have remained with me and, I hope, have been passed on to my students over the years.

I spent the last several months in the MRC-LMB trying to finish up my experiments. Two years had seemed like a lifetime. I had some reasonable results to work on, and I seemed to be able to convince people that the results were important.

My time at the MRC-LMB frequently seems to me to be the beginning and the end of my supposedly fabulous career as a scientist. After I left, except for a brief visit to finish a manuscript that Hugh Robertson and I were working on, I stayed away for many years because I did not want the MRC-LMB to guide my life. My scientific work gradually drifted away from tRNA mutants and focused on RNase P, which I still work on. Later, when I did come back for a few days from time to time, it was always a great pleasure to see Sydney and the others. Gradually, as Sydney and Francis left the lab, my friendship with Aaron Klug grew, and we have worked on RNA proteins jointly.

Work on RNase P is usually a 3- to 4-year period of boredom and fright. Now we are in one of the fifth years. My lab is currently concerned with RNase P in both *E. coli* and human HeLa cells. In *E. coli*, we have

identified small, intergenic RNAs that are substrates for RNase P, an indication that this enzyme is involved in determining gene expression in operons. In HeLa cells, we have shown that there are at least ten protein subunits of the enzyme as well as an RNA subunit. We have also shown that in transient transfection experiments, the inhibition of the expression of the protein subunits does affect some but not all the subunits if one of them is specifically targeted.

There is no doubt that Sydney and the beautiful atmosphere of the lab for doing science were my greatest inspirations. Sydney, although from some viewpoints distant, arrogant, or hard to deal with, became for me a very familiar person. The community of immigrants in South Africa in which he grew up was not terribly different from the immigrant community where I grew up in Montreal. He is a tremendous comic when he wants to be, as well as arrogant and deprecatory, with humor, when he feels that it is appropriate. His knowledge of biology is encyclopedic. I learned, as a postdoc, not to speak to him unless I had something more or less correct to say. In more recent years, I have forgotten that discipline: questions can be asked that are not totally appropriate. In fact, about 2 years ago at Yale, Sydney suggested that what I was saying about a topic he was working on was "all tryptophan," a familiar phrase to those of us who know him and probably as close as he gets to profanity in public.

Memory can be elusive. Perhaps, we may consider this essay as "all tryptophan" or, if that is not adequate or fitting, please be kind in selecting your own appropriate word.

Recently, John Heuser wrote in *Science* of the words that Sir Bernard Katz used in describing his own career. Among these were, ". . . a good mentor and a great deal of luck" (Heuser 2003). My good fortune in the first category starts with Lee Grodzins in physics at MIT, went on to Leonard Lerman, a friend and thesis supervisor, Matt Meselson, and finally, as written here, Sydney Brenner and the amazing collection of senior personalities at the MRC-LMB. In fact, very shortly after I arrived at the MRC-LMB, I saw Sir Lawrence Bragg, who came to the lab to see a model of the new crystal structure of tRNA. The names that were to become famous were all about us every day.

All the postdocs worked very hard, knowing full well that when a word of advice was needed, it was always there, down the hall, at a door that was always open.

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