|  |  |
| --- | --- |
| **Medicine\_2009-** | |
| ID | 0535 |
| Biographical | **Childhood** I was born in the small city of Hobart in Tasmania, Australia, in 1948. My parents were family physicians. My grandfather and great grandfather on my mother’s side were geologists. My great-grandfather on my father’s side, before coming to Australia as a minister of the Church of England, had lived for some time in Hawaii, where he had collected Coleoptera (beetles). He continued his collecting in Australia, eventually selling his collection to the British Museum of Natural History. My uncle and aunt (my father’s sister and my mother’s brother) were also both family physicians, who moved to England, married there and permanently settled there to practice medicine and raise their families.  I was the second child of eventually seven siblings. I spent my first 4 years living in the tiny town of Snug, by the sea near Hobart. Curious about animals, I would pick up ants in our backyard and jellyfish on the beach. Then my family moved to Launceston, a town in northern Tasmania. Our first house, at 120 Abbott Street, was a one-storied, verandahed house of typical Australian suburban architecture. I started kindergarten at a girls’ school, Broadland House Girls Grammar School in Launceston (Figure 1).  I kept tadpoles in rapidly-smelly-becoming glass jars in a back living room at home. When I was a preteen we moved to a larger house called Elphin House, which had a good-sized garden (Figure 2). Over the years we had many pets: at one stage I enumerated the family menagerie of the moment as consisting of budgerigars and canaries in an aviary in one corner of the garden, goldfish in a garden pond, chickens and pullets (for eggs and the occasional roast fowl) in a hen coop and henhouse, rabbits and guinea pigs in cages, and cats and a dog, who lived all over the house and garden. I was fond of all these animals, and of animals and nature in general.  Perhaps arising from a fascination with animals, biology seemed the most interesting of sciences to me as a child. I was captivated by both the visual impact of science through science books written for young people, and an idea of the romance and nobility of the scientific quest. This latter was especially engendered by the biography of Marie Curie, written by her daughter, which I read and reread as a child. By the time I was in my late teens it was clear to me that I wanted to do science. I was educated at Broadland House Girls Grammar School, and received a generally excellent education. However, physics was not offered, so I took physics classes offered in the evenings at the local public high school. Latin and Greek were not taught at my girls’ school either, a gap in my education that I rather regret later in life. But my school did provide an excellent piano teacher, Helen Roxburgh, by whom I was taught all throughout my school years in Launceston. I loved playing the piano, and even at one time wistfully hoped that I might become a musician. Fortunately I was also quite realistic about this, because I recognized that I was competent rather than greatly talented at piano playing, so I went in the direction of science.  My family moved, after some family disruptions, to the city of Melbourne, Australia, in time for me to complete my last year of high school at University High School. There I gained the confidence that I needed to apply for the undergraduate science degree at the University of Melbourne. **University Education** I chose biochemistry as my major and graduated after 4 years with an Honours degree in Biochemistry. During that time, I had come to love biochemistry research, although I was just getting my feet wet in laboratory research.  The Chair of the Biochemistry Department, Frank Hird, then offered me a position as a Master’s student in his research laboratory, where they investigated the biochemistry of amino acid metabolism. My undergraduate Honours thesis research advisors, Theo Dopheide and the late Barrie Davidson, had advised and encouraged me to do my Ph.D. abroad. Barrie in particular had urged me to consider going to the MRC Laboratory of Molecular Biology (LMB) in Cambridge, England, where he had done postdoctoral research. But in order to be accepted as a Cambridge Ph.D. student in biology, those from outside Britain were required to have done a year of research. The Master’s degree with Frank Hird, studying the metabolism of glutamine in the rat liver, would constitute this required year. Frank Hird taught his laboratory group members the joy and aesthetics of research. He said he thought each experiment should have the beauty and simplicity of a Mozart sonata. His laboratory group, dominated by his strong personality, was cohesive and we would sometimes drive to the hilly areas outside Melbourne, all piled into his car, Mozart playing loudly on the car radio, to have an outdoor lunch picnic among trees and wildflowers. While I was still in Frank Hird’s lab, [Fred Sanger](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1958/) visited Melbourne. Frank Hird had done research in England on amino acids with Fred Sanger shortly after the Second World War, providing an introduction to Fred in which Frank encouraged me to tell Fred of my hope to study for my Ph.D. in Cambridge at the LMB. It was arranged that I would join Fred’s lab in the LMB and I was admitted as a Cambridge Ph.D. student.  The adventure of setting off to England, away from home and family, was a huge step, but I felt ready. My aunt and uncle and their family in Cambridge, who lived close to the LMB, became my anchor of a family away from home. I loved the LMB, the science being done there, the atmosphere of being at the epicenter of molecular biology, the intensity of the scientists and the constant discussions about science. It was a world of complete immersion. For my Ph.D. thesis research, I carried out sequencing of regions of bacteriophage phiX 174, a small single stranded DNA bacteriophage. I transcribed fragments of the phage DNA into RNA and then used the methods that Fred had pioneered for piecing together RNA sequences. We combined the sequences derived by this method with the DNA sequencing that had been done by John Sedat and Ed Ziff and Francis Galibert, members of Fred’s lab. All the sequences jibed. The first sequence of a 48 nucleotide fragment of this tiny bacteriophage DNA genome was a great excitement. I took it to show to my mathematically-talented Cambridge cousin, who was then about 12 years old, to see if any patterns emerged to his mathematically-inclined eye. He pointed out the repeats, but it was premature to think of analyzing DNA sequence patterns! **To the United States** The world of discovering DNA sequences was opening up and I was entranced by its possibilities. I had planned to do a postdoctoral fellowship, beginning in 1975, with Howard Goodman and his close associate Herb Boyer of UCSF, a mutual decision made after an interview–cum-conversation Herb and I had walking in the garden of a monastery in Belgium at which we were attending a scientific conference, I still as a graduate student. But then love intervened: John Sedat and I decided to marry, and as John was going to Yale, I decided to see if I could change my postdoctoral research plans (for which I had obtained an Anna Fuller Fellowship to work at UCSF) to a laboratory at Yale. Howard Goodman wrote me a kind and understanding letter upon my letting him know the reasons for my change of plan, and I began inquiries into possibilities of a laboratory for my postdoctoral training at Yale.  Thus it was that love brought me to a most fortunate and influential choice: Joe Gall’s lab at Yale. After a few hiccups engendered by misplaced international mail and other factors, at the beginning of 1975 Joe accepted me as a postdoctoral fellow in his lab, to which I was allowed to transfer my Anna Fuller Fellowship. I immediately began to work on finding ways to accomplish the sequencing of the DNA found at the terminal regions of the abundant, short, linear ribosomal gene-carrying “minichromosomes” that Joe and his colleagues, in parallel with Jan Engberg of Denmark, had discovered in the somatic nucleus of the ciliated protozoan *Tetrahymena* thermophila (which was at that time called *Tetrahymena pyriformis*, shortly thereafter to be renamed *Tetrahymena thermophila*). **To the University of California** After finishing my postdoctoral training in Joe Gall’s lab at the end of 1977, John Sedat and I, having married in 1975, moved to San Francisco, California. There John had accepted a position as Assistant Professor at the University of California San Francisco (UCSF). I had applied for several positions as an Assistant Professor in a variety of Universities and had been rejected from many of them, a discouraging experience. I had applied for such a position in the Department of Molecular Biology at the University of California Berkeley, but had not yet heard whether I was in the running for it. In the meantime, UCSF offered me a research track position and space in the Department of Biochemistry in the Genetics unit headed by Herb Boyer. My first NIH grant was the source of funding for my salary and research expenses. I had written this grant application with the encouragement of UCSF, in order to pursue my research on *Tetrahymena* telomeres and their associated proteins. This work grew out of that I had done in Joe Gall’s laboratory at Yale. My grant was funded by the NIH General Medicine Institute. Unsure of my chances at obtaining funding, I had sent the same grant application to the National Institutes of Health, the National Science Foundation and the American Cancer Society, hoping for funding from any one of these. Reflecting the more informal scientific habits of the basic sciences community in those days, some time later one of the grant reviewers told me that he had been so intrigued by my photograph of the autoradiogram, showing that telomeric DNA in *Tetrahymena* was mysteriously packaged as something other than nucleosomes, that he had kept the photograph.  Then UC Berkeley offered me an associate professor position in the Molecular Biology Department, which I immediately accepted. Once again, I transferred my funding from UCSF, this time to my own laboratory, at UC Berkeley.  Because research was, and still is, such a central part of my life, my autobiography would be incomplete without describing my research experiences. Thus, to convey a fuller flavor of them, here I describe some of the events of my early scientific research on the molecular nature of ends of chromosomes. **Early Work on the DNA at the Ends of Eukaryotic Chromosomes** Very soon after arriving in Joe Gall’s laboratory at Yale in early 1975, I started to apply methods for obtaining terminal DNA sequences to the *Tetrahymena* rDNA molecules. I had learned a collection of methods in Fred Sanger’s laboratory in Cambridge, England, where I had just completed my Ph. D. Eager to sequence the end regions of these minichromosomes, with Joe’s encouragement I set out right away early in 1975 to use end-labeling techniques on them. I incorporated 32P isotope-radiolabeled deoxynucleosides residues into the *Tetrahymena* rDNA molecules using commercially available DNA polymerases for *in vitro* DNA repair enzymatic reactions. The results were immediately promising. First, it became clear that the end regions of the rDNA were being selectively labeled by certain combinations of 32P isotope radiolabeled nucleoside triphosphate substrates. And by June 1975, I had become tremendously excited: I had obtained my first autoradiogram of the two-dimensional separation of the 32P labeled depurination products. A strong signal of a run of 4 cytosine (C) residues was apparent. Furthermore, each such C4 sequence was flanked by a purine residue (that is, an adenosine (A) or a guanosine (G) residue; this initial data did not show which). The way the depurination reaction worked was the following: Ken Burton, a New Zealander, had shown that a chemical reaction could be done that cleaves the DNA backbone on both sides of every purine nucleotide but leaves intact any runs of pyrimidine nucleotides (such as C residues) that are uninterrupted by purine nucleotides. This so-called depurination method, when applied to a complex sequence DNA like a whole bacteriophage genome, was further made useful by Vic Ling, when he was a postdoctoral fellow in Fred Sanger’s lab in Cambridge, England. Vic had shown that the resulting short pyrimidine tracts (mono-, di- tri-nucleotides, etc) would yield a pattern of products like a grid when a 2D fractionation method was used (see [2009 Nobel Lecture by Elizabeth Blackburn](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2009/blackburn-lecture.html), in this volume). The most frequent products, on a random basis, of course are mono and dinucleotides, with the longer tri- and tetranucleotide tracts being less and less abundant on a random basis. Thus this strong C4 spot was interesting and informative.  It was also clear to me that the rDNA molecules were not simply lambda phage-like DNA. First, the terminal fragments were heterogeneous. In contrast, for any one type of lambdoid phage, in every viral particle the DNA molecule is just the same − a perfect carbon copy − as in every other viral particle. Second, on a per DNA molecule basis, much more incorporation of radiolabeled nucleotide precursor substrates occurred than expected if rDNA molecule ends were like those of the sticky DNA ends of lambda phages. It was also fortunate that the C4 repeat had such a regular nature and that it happened to have four Cs in a row. Even three C’s would have been striking, but harder to unravel. As it was, the C4 spot consistently stood out like a beacon through my repeated productions of 2D fractionations (“homochromograms” as we called them in Fred Sanger’s lab).  Next, I needed to validate independently that what I was radiolabeling *in vitro* validly reflected the rDNA sequence, and also try to get a closer estimate of the number of C4 runs per rDNA molecule. I therefore decided I needed to 32P isotope-label the rDNA *in vivo*. The vast majority of the 32P isotope (chemically in the form of inorganic phosphate ions) taken into the cells would be incorporated into other molecules, including the much more abundant cellular RNA, with very little ending up in DNA, and even less in the rDNA (in *Tetrahymena*, only a percent or so at most of the DNA is rDNA). Therefore, with some trepidation I asked Joe Gall for permission to order sufficient 32P phosphate to be added to the cell growth medium for labeling the rDNA. This meant handling 2 milliCuries at once, which Joe’s lab had not done before. But I knew that this was the only way currently available to get a sufficient amount of 32P into rDNA to detect the C4 spot in an autoradiogram, above background. Possibly with some trepidation on his side too, Joe agreed. I worked in the “hot room”, a room set aside for doing work with radioactive isotopes. On October 9, 1975 the 32P was shipped to Yale. My laboratory notebook from that time reads: “32P stored in refrig. until use – assayed for 10/14 . 3 pm 10/14. Zeroed [the cell culture] on 1% PPS medium blank … Added 2 mCi 32P as h3 PO4 in water in 1 ml from syringe.” For the next preparation I raised it to 5 milliCuries. Curious about this very radioactive departure from the more usual activities of the lab, my Gall labmates periodically looked in through the window set in the door of the hot room as I worked.  By October 22, 1975, I had the 32P rDNA purified. I triumphantly wrote down in my notebook that day my plans for this precious sample:  “1) Depurination 2) denaturing gel after EcoRi treatment 3) 1.4% agarose gel”  One by one, I inflicted various nucleases on the terminal region of the rDNA. I found it could be selectively radiolabeled using one triphosphate 32P labeled at a time. Then I carried out the battery of analyses possible at the time that would allow me to piece together the nucleotide sequence: I digested the radiolabeled end regions with Endonuclease IV nuclease or micrococcal nuclease, and performed depyrimidations and nucleotide nearestneighbor analyses, and spleen phosphodiesteriase digestions (Figure 3).  Piecing together the rDNA end sequence was a matter of careful puzzle-solving. At an intermediate point, my notebooks of the time show that I had to consider two possibilities – CCCCAG and CCCCAA repeats (Figure 4). But it was apparent that there were a large number of repeated copies.  But by April 8, 1976, I was confident that the correct sequence was deduced, because the entry in my laboratory note-book page headed with that date reads:  Another laboratory note-book page, dated August 17, 1976, shows I was already referring, in a routine way, to (CCCCAA)n sequence – by then in the course of experiments designed to see whether this same repeated sequence was also present in the other (much longer) chromosomal DNAs of *Tetrahymena.*  I put together a picture which tried to take into account all of my many observations. The deduced sequence consisted of a tandem array of CCCCAA repeats. One experiment done in 1979, radiolabeling the rDNA using just 32P-labeled dCTP, and unlabeled dAT P, and separating the products on a denaturing gel electrophoresis, showed this visually as a beautiful ladder of tiger stripes extending up the gel. The size of every band in this regular ladder was 6 bases more than the band below it! This strikingly characteristic visible pattern of bands presaged the pattern that would later become important for our discovery of telomerase enzyme activity, as described in this volume in the [2009 Nobel Lecture by my co-awardee, Carol Greider](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2009/greider-lecture.html).  In the months following April 1976, much of my effort was also devoted to trying to understand the arrangement of the strand discontinuities along the tract of CCCAA repeat DNA. For this, I performed a great many experiments following the kinetics and specificity of radiolabeling the RNA end regions, using multiple different enzymes and protocols and analyses. This also was a matter of piecing things together – there was no template for me to work from as this was all uncharted territory.  In the late 1970s and early 1980s, I did a variety of radiolabeling experiments trying to divine the structure right at the termini of telomeres of both ciliated protozoans and yeast linear plasmids. I could put together a composite but still incomplete picture. Some of the features, I realize in retrospect, might be attributed to the terminal G strand sequence at the very ends of the telomeres assuming G-G paired or G-quartet structures. But other features are not so readily explainable. Why I was able to label the strands with DNA polymerase or a kinase to get the patterns of labeled strands and nucleotides I did has still not been completely fitted into a coherent view of the molecular structure of DNA ends. Various kinds of *in vitro* radio-labeling experiments had suggested that, in both *Tetrahymena* rDNA and the macronuclear DNAs of hypotrichous ciliates, there is a short overhang of the G-rich strand consisting of a few telomeric repeat sequences. Currently the view is that in mammalian telomeres there is a long protruding G-rich strand. Yet this does not take into account the clear evidence for the short C strand repeat oligonucleotides that I discovered can be readily melted off the telomeric DNA. This I found for both the *Tetrahymena* rDNA minichromosome molecules and linear plasmids purified from yeast. These tiny telomeric sequence oligonucleotides could be radiolabeled and clearly identified by two dimensional fractionations. However their significance is still unknown. To this day, aspects of the structure at the very terminal region of the telomeric DNA are enigmatic; the very ends of chromosomes remain as challenges. **Telomere Proteins: Earliest Attempts and Failures** In my early work, my molecular views of telomeres were first focused on the DNA ; not only because DNA was uppermost in my mind, but for several years DNA was also the only component of the telomeres that was identified. This was not for want of trying. I thought that DNA would not be the entire story of chromosome ends and, by extension from work emerging about chromatin in general in the 1970s, that it was likely that the telomeric DNA repeats tract would be packaged with proteins. The 1970s had seen great interest in chromatin, and the discovery of nucleosomes as the basic packaging unit of eukaryotic DNA. Telomeric sequences in *Tetrahymena* looked very intriguing to me in that regard, and as soon as I had identified the telomeric DNA I wanted to get my hands on whatever packaged it. Therefore, while still a postdoctoral fellow in Joe Gall’s laboratory, I performed micrococcal nuclease treatment on isolated *Tetrahymena* nuclei. I found that the CCCCAAn tracts of the telomeres were protected in chromatin as a heterogeneous class of DNA fragments very different from that expected for nucleosomal packaging.  Soon after moving from Joe Gall’s lab at Yale, while still temporarily at the University of California San Francisco (UCSF) in an independent research position (before I moved to the University of California Berkeley as an Assistant Professor), on March 1, 1978, I wrote to Joe Gall: “I am getting quite excited about getting a CCCCAAn-binding protein complex from the *Tetrahymena* macronuclei, so I’ve been busily making rDNA, the CCCCAAn probe, and macronuclear micrococcal nuclease digests. Results so far are that I’ve found a simple salt fractionation that enriches for CCCCAAn sequence plus putative protein(s). The plan at the moment is to purify this some more so I can get some structural characteristics of any such complex, i.e. S value, and some identification of protein(s) in terms of 1-D and 2-D gel eletrophoretic properties … The other aspect of course is to fish for something that will stick to a CCCCAAn column.”  By 1980 I had done experiments to show that telomeric tracts of DNA in *Tetrahymena* were encapsulated in a protective sheath of protein that did not include nucleosomes. The vast majority of chromosomal DNA is packaged as nucleosomes: DNA-protein complexes. Each nucleosome is a flattened ball made up of histone proteins, around which the DNA is wrapped twice. The very basic (positively charged) histone proteins neutralize the negative charges of the phosphate chemical groups arrayed along the phosphodiester backbone of DNA and allow chromosomal DNA to become very closely packed and compactly folded in the nucleus. Nucleosomes in artificially stretched-out chromosomes are like beads on a string, although mostly in the nucleus they are closely packed into shorter thicker fibers. If one clips up chromatin using an enzyme, micrococcal nuclease, that cuts across the two strands of the linker DNA between neighboring nucleosomes, after getting rid of the histones, one can see that there are nucleosome-sized fragments of DNA left – a fragment of about 142 base-pairs is protected by the histone core of the nucleosome, once the DNA linkers have been trimmed away. This kind of nuclease clipping behavior is a hallmark of a nucleosome. In contrast to nucleosomal regions of chromosomes, special regions of DNA, for example promoters that must bind transcription initiation factors that control transcription, have proteins other than the histones on them. The telomeric repeat tract turned out to be such a non-nucleosomal region. We found that if we clipped up chromatin using an enzyme that cuts the linker between neighboring nucleosomes, it cut up the bulk of the DNA into nucleosome-sized pieces but left the telomeric DNA tract as a single protected chunk. The resulting complex of the telomeric DNA tract plus its bound cargo of protective proteins behaved very differently, by various tests, from standard nucleosomal chromatin, and therefore we concluded that it had no histones or nucleosomes.  By 1977, it was known from work of Rekosh *et al*. that adenovirus DNA has a covalently bonded terminal protein, presumably for viral genome replication. Thus, in 1979, Marsha Budarf, a postdoctoral fellow in my laboratory at UC Berkeley, began using used radioactive iodine procedures (the Bolton-Hunter reagent) to see if we could find any comparable protein at the ends of rDNA. Although Marsha found a covalently attached protein (that in hindsight may have been topoisomerase I) enriched toward the end of the rRNA transcribed region, it was not enriched in the terminal parts of the rDNA molecules. She was unable to detect any other covalently attached protein elsewhere on the rDNA. Any evidence for a protein on the bulk of the rDNA molecule ends, such as their behavior in gel electrophoresis and the appearance of the rDNA molecules under the electron microscope, was conspicuously lacking. This made me feel all the more confident that there was no covalently attached protein at the very ends of this minichoromosome. But what other proteins were at telomeres?  My lab was the first to try to identify these protective proteins. We used biochemical fractionations of *Tetrahymena* nuclear extracts. My 1979 notebooks record that, together with my technician San-San Chiou in the Department of Molecular Biology at UC Berkeley, over and over I made attempts to purify the telomeric proteins from nucleoli. Nucleoli are the tiny bodies within the *Tetrahymena* nucleus that harbor the actively transcribed rDNA minichromosomes. Fractionations after fractionations, mostly using sucrose gradients, were patiently performed by San-San. Then we scaled up the preparations – I purchased a huge industrial-sized Waring blendor that loomed like a leviathan on the laboratory bench. *Tetrahymena* cells were blended in order to disrupt them just enough to shake their nucleoli free from the rest of the nuclear contents. At one time my note-book laconically reported: “Respun only one-third of total … Waring blender broke.”  All these early efforts were to no avail. In retrospect, the experimental approach had been reasonable − to purify nucleoli, as being the most enriched form of telomeric chromatin known, then to digest them with micrococcal nuclease into fragments, the end ones containing the telomeric DNA terminal tracts and their bound proteins. Then, I would further fractionate these away from the rest of the chromatin by selective precipitation in potassium chloride solutions, or fractionate them by size on sucrose gradients. The goal was to see what protein(s) would co-purify, through these multiple fractionation steps, with the telomeric repeat tract DNA, which I followed through the multiple steps by its hybridization signal. But we were only able to obtain limited amounts of chromatin and binding factors, and we tried without success to get enough to identify any factors that might be specific to the rDNA ends. Looking back, I see that we were fighting against the numbers game – our detection methods were too frail, our preparation scale-ups too modest. Therefore, it was yeast genetics and approaches done by others that turned out to provide the next great leaps forward in understanding telomeric proteins. That I failed in this by my early attempts using *Tetrahymena* made me all the more determined, if anything, to use other approaches to try to understand the nature and biological significance of those strange-seeming repeated sequences at the ends of chromosomes.  I also recall that our failure to find telomeric proteins taught a lesson that became useful when it came to our work on *Tetrahymena* telomerase. As Carol Greider’s Nobel lecture describes, at one point the value of scaling up the telomerase activity preparations became evident to her. Thus, when Carol proposed the purchase of a very large glass column for preparative gel filtration chromatography, I was very willing to make this expensive-seeming purchase, ruefully recalling the past history of my too-pusillanimous scale-ups of *Tetrahymena* chromatin preparations. **To the University of California San Francisco** I became a Full Professor at UC Berkeley in 1986 (after 8 years on the faculty of UC Berkeley), and in the same year a mother (our son Benjamin David was born in December 1986). By around 1989, I decided that as the long drive to Berkeley each day from our home in San Francisco made it difficult to pursue both science and our family life optimally, it was time to begin investigating alternatives. I settled upon a professorship at UCSF, and the move of my laboratory to UCSF’s Department of Microbiology and Immunology was accomplished in mid-1990. I have remained on the faculty of UCSF ever since. There, I have had the great good fortune to be able to keep delving into the nature and mechanisms of telomeres and telomerase. Together with colleagues in and out of UCSF and with my many talented students and postdoctoral fellows and technicians in my laboratory (Figure 6), I have been able to address the wondrous biological systems comprised of telomeres and telomerase. A fanciful depiction evoking both telomere dynamics and telomere researchers is shown in Figure 7. This painting, done by the artist Julie Newdoll in 2008, elicits the idea of a telomere as an ancient Sumarian temple-like hive, tended by a swarm of ancient Sumarian Bee-goddesses against a background of clay tablets inscribed with DNA sequencing gel-like bands. **Out of the Laboratory** In the 1990s my research’s implications for humans began to intrigue me, but with scientific research, faculty and Department Chair duties, family and many associated commitments, I had little time to indulge in delving into the philosophical and policy questions that can arise as science opens new possibilities. I served as President of the American Society for Cell Biology in 1998 and become more cognizant of the world of national science policy. Thus it was that in late 2001, the request to consider becoming a member of a newly created U.S. Federal Commission, the President’s Council on Bioethics, had a certain appeal. I felt that my knowledge of the relevant fields of science, and long experience in the world of research, would be useful contributions to the Council, a body that, as a Federal Commission, would be advisory on some matters of national science policy. A further appeal was the coincidence with my growing thinking about these issues. I reasoned that if I joined this Council, it would be an opportunity to contemplate some of these dimensions of research’s ramifications, and the possible reverberations of my own area of research.  Time for quiet contemplation of these and related questions in the abstract was not forthcoming. I understood from the beginning that the Bioethics Council would be occupied with publicly debated topics including human somatic cell nuclear transfer and embryonic stem cell research, as well as other topics less clearly defined at the outset of the council’s deliberations. I thought I should agree to serve on this Council because, as a seasoned scientist (particularly in cell and molecular biology), I might be able to offer perspectives that would be helpful in advising national scientific policy. I knew the topics upon which this Council, appointed by the George W. Bush administration, would advise would be politically charged ones. For this reason especially, I felt that a strong base of scientific fact and evidence would be particularly important, and useful advice in this vein was something that I could in fact offer to this advisory body.  I publicly made clear my views on some of the council’s recommendations, views that did not generally accord with those of the White House or with those of the Council’s Chair. After two years, I was informed by the Personnel Office of the George W. Bush White House that I would no longer be on this Council. This dismissal from the Council received quite a lot of public attention at the time. In the course of it, I was overwhelmed by the great many letters and communications I received. Almost without exception positive and supportive, they came from all over the United States and even from as far afield as a musician in London. His somewhat (to me) unexpected concern for science policy brought home to me how widespread is the wish among the public that science policy be informed by good scientific evidence. This entire episode was a broadening education. It reinforced my love of the searches for truth to which so many in research and academia aspire. **People Who Have Had Important Influences on My Life as a Scientist** I am indebted to so many individuals that I can only describe a few of them here. Growing up, three of my schoolteachers in particular encouraged my interests in biology and chemistry and mathematics, not least by letting me know that they believed in my abilities to succeed in these areas – Nan Hughes, Jenny Phipps and Len Stuttard.  As I embarked on research in biological science, my teachers, advisors and mentors − notably Frank Hird in Australia, Fred Sanger in Cambridge, England, and Joe Gall in the U.S.A. − not only imparted their scientific knowledge, visions and wisdom, but also their examples of how to be a scientist. In particular, a photograph of Joe Gall from 1999, although taken several years after I had been in his lab, captures in a succinct visual way some of Joe’s characteristics that influenced me when I was a member of his lab group (Figure 8). I took the photograph during a conference he was attending in Prague in the summer of 1999. During the conference a partial eclipse of the sun took place, and all the conference participants rushed out of the lecture hall to witness its progress. Joe is seen in the photograph demonstrating that it could be seen very simply and safely: All one had to do was hold a flat sheet of paper under a leafy bush so that the light, diffracted through the leaves onto the paper, caused to appear on the sheet of paper images of the “bite” being taken out of the disc of the sun by the moon passing in front of it. I recall that most of the conference participants had never seen this applied optics demonstration before. This photo evokes at once Joe Gall’s desire and ability to teach − by his use of a very striking demonstration to teach something new to the conference participants − and, not least, one glimpse of his wide knowledge encompassing optics and natural science in general.  Like so many who are fascinated by chromosome behavior, I owe much to Barbara McClintock for her scientific findings. But in addition, [Barbara McClintock](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1983/) also gave me a memorable lesson: in a conversation I had with her in 1977, during which I had told her about my unexpected findings with the rDNA end sequences, she urged me to trust my intuition about my scientific research results. This advice was surprising to me then, because intuitive thinking was not something that at the time I allowed myself to admit might be a valid aspect of being a biology researcher. I think her advice recognizes an important and sometimes overlooked aspect of the intellectual processes that underlie scientific research, and for me it had a liberating aspect to it. For this, also, I am very grateful to Barbara McClintock.  My husband, John Sedat, himself an accomplished scientist, has always urged me to dig deeper into myself and find the reserves of strength I might not have tapped – his encouragement in this way has helped me through years of doing science. Our son Ben (Figure 9) inspired me to try to find ways of combining family and science, something that I have tried to convey to young scientists making their careers. Finally, my parents were both family physicians. From them I imbibed a sense of the importance of serving people kindly and as well as one can. I continue to believe that bioethics, done well and underpinned by the best available scientific evidence, can be an important part of our consideration, as a society, of the impact on people of scientific research in the biological sciences and medicine. |
| Autobiographical |  |
| Podcast | **“The way you do science should have an intrinsic beauty to it”** In this conversation, conducted in October 2021, Elizabeth Blackburn speaks openly about the value of science and how better to engage others in its importance – and beauty. Also up for discussion is our current climate crisis, as Blackburn has just been to Antartica and witnessed the severe consequences of the world’s climate change. Last but not least, she speaks about the future of science and the future of her own research.  The host of this podcast is nobelprize.org’s Adam Smith. |
| Telephone  interview | 0535=EB  [Elizabeth Blackburn] Hello.  [Adam Smith] Good morning, may I speak to Elizabeth Blackburn please?  [EB] This is she speaking.  [AS] Hello, it’s Adam Smith, calling from the Nobel Foundation web site.  [EB] Oh, yes. I was told to expect your call.  [AS] How nice. Thank you and congratulations.  [EB] Thank you.  [AS] It’s terrifically early in the morning where you are, I guess?  [EB] Don’t even tell me how early it is!  [AS] Had you managed to go to bed before they woke you up with the call?  [EB] Well, I had, yes. But, the night was definitely truncated – in a good way.  [AS] Indeed. I’ve just spoken to Carol Greider and Jack Szostak and to them I asked the same thing: you presumably had a suspicion that this was on the way, given the number of prizes that have been coming your way recently?  [EB] Well, there had been some press speculation which I had tried to ignore. But, believe me, it still was a very great surprise.  [AS] Now, the Prize has been awarded for research work you did mainly during the early 80s …  [EB] Right, right.  [AS] But, you’ve devoted your whole life to telomeres and I wanted to ask what was their particular fascination for you?  [EB] Well, so many aspects. First of all, just how does it work? Why are telomeres working the way they do? And, every time we looked with an experiment, we would find something ever more complicated and clever that the cell did. And, we realized the old truism from the original cytogenetics which was that the telomere is really important for protecting ends and, as you might expect, the cell actually devotes all sorts of machinery to make sure that never goes wrong, or goes wrong as little as possible. And so that intricacy, the machinery is really just a marvellous thing. And then in recent years it has become very interesting to look at what happens to telomeres in humans because they really do seem to reflect our status of health and our risk of disease in quite a striking way that suggests that what one sees at telomeres gets integrated from a lot of different inputs but it really serves as a kind of indicator of how well cells are doing. So it’s just been endlessly fascinating because the science of it is endlessly fascinating.  [AS] I want to turn to humans in a second. But, the original observations you just mentioned about the protective role of telomeres were made in the 30s by [Muller](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1946/index.html) and [McClintock](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1983/index.html), for instance.  [EB] That’s right, absolutely. And, we always have to remember that they worked from the deduction of genetics and cytogenetics with no knowledge that even the genetic material was DNA. And so, what my work had been doing was to first of all show the molecular nature of the telomeric DNA itself and then with Jack Szostak we were able to extend that and show that something strange was going on. And, then with Carol, that was when we worked together to hunt for this enzyme, or activity that we suspected existed, which was telomerase. So that put these cytogenetic observations onto a molecular footing. You know, before the telomere had sort of been the ‘blob’ at the end of the chromosome.  [AS] Exactly. It had sort of lain there for decades, if you like. Known about, thought about, but nobody was particularly able to tease apart its function.  [EB] Right. Like so many things in science, it depended on first of all understanding what was the nature of the chromosome, which was DNA as well as proteins. And, then, thinking about, as Kornberg did, thinking about how DNA is replicated – not only thinking, he showed – and then that showed that there were problems with replication at the ends of chromosomes. And so that was one of the big impetuses for looking for telomerase, which was to try to see how the cells answer the question of how their incomplete replication problem gets solved.  [AS] In your sort of journey through telomeres, how much has been dependent on finding the right companions to work with? Because, for instance, you met Jack Szostak at a Gordon conference in 1980. Or, at least, you decided to collaborate then.  [EB] Right, right. I think that’s the way all science happens, right. And, I suppose there’s an element of chance favors the prepared mind. But, that’s the way science happens. It’s a lot of meetings of minds and the concepts of telomeric DNA and the sequencing, well that was very dependent on the sequencing methodologies that were being worked out even before the now conventional methods of DNA sequencing happened. We didn’t use those. I was using very unconventional methods to sequence the telemetric DNA originally. Methods devised by, for example, my husband John Sedat and Ed Ziff while we were in Cambridge in England.  [AS] That’s right. Because you were post docs together with [Fred Sanger](https://www.nobelprize.org/prizes/chemistry/1980/sanger/facts/), is that …  [EB] I was a graduate student with Fred Sanger and John Sedat, who is now my husband, now, he was a post doc. So, everything builds on other technologies so I was building on … I was curious about the ends of chromosomes and building on technologies, completely, which were methods of sequencing DNA and people like Ray Wu and Murrays in Edinburgh, all these people had been figuring out ways to sequence the very ends of chromosomes. So, it’s a tremendous sort of interactive process, as I’m sure you have heard a thousand times!  [AS] But, it’s nice to hear it described. Your current work is, as you said, fixed on humans and in particular on the relationship between chronic stress and telomerase …  [EB] Yes, we’re very interested in that. That’s a corner of my lab. You know, we have part of our lab where we interact with clinical colleagues and one in particular at my institution, Elissa Epel, who was the person who first started to ask with us this question of chronic stress and how was it related to telomere maintenance? Actually, we still do a lot of basic research. We’re still fascinated by those same questions you addressed earlier. You know, what is it that keeps you so interested in the telomere? It’s so intricate and complicated and you want to know how it works. Actually, most of my lab does the very basic research. The chronic stress part, is to me, just fascinating though. Because it is really related to what a lot of humanity undergoes.  [AS] And, is it the case that telomere length and maintenance is affected directly by stress and is that, perhaps, causative of problems that then arise from stress? Or is it some kind of epiphenomenon?  [EB] There’s two parts to the question. So, one is, the association of telomere shortness, and actually even poorly regulated telomerase we’re finding, that association and chronic stress is very real. And, there are certain situations where our studies – and Elissa Epel has looked at cohorts of women who are caregivers of a chronically ill child, and more recently even dementia caregivers, where the dementia patient is their husband or partner – what we find is that it really does look causative. Particularly, in one study, the number of years that a mother had been in her situation was related to the extra telomere shortness and the dampening of telomerase. And, that made us really think that this is likely to be causative. Because, number of years relating to those parameters, it’s very – number of years the person was in that stressful situation relating to those parameters being worse – it’s very hard to imagine a scenario where it could work the other way round. That the shortness of the telomeres and the dampened telomerase was causing that mother to have been in that situation, one year, five years, twelve years, it doesn’t logically follow. So that kind of evidence makes us think that there is a causality. Now, the question is, does that cause the bad, clinical effects of stress, which have been well-documented in the literature for years and years. Does the telomere shortening cause it? It’s a plausible model actually. And, I’m inclined to think it does. But, you have to be very careful about what exactly is the complete mechanism by which these adverse effects of stress are mediated. But certainly we see the effects on telomere maintenance in the immune system which is, it turns out, a very good window into what’s happening in terms of disease risks in the body. So we do think that there’s a lot of good reason to think that it might actually be a causative chain.  [AS] Your window into the immune system in that case is studying white blood cells. Is that correct?  [EB] That’s the one that participants in studies give you and we now look at many, many different cohorts of various kinds. And, generally, we try to have a situation where the person is healthy so you’re not confounded by disease. So, that means that healthy individuals are donating their blood samples for the studies. So, blood is one of the cell types one can look at.  [AS] I just wanted to ask you one last thing which was that it’s been commented previously that telomerase and telomere research is a field which has, happily, a large number of women working in it. Do you agree with that and is that something that …  [EB] Yes, and, I’ll turn your comment around and say it’s fairly close to the biological ratio of men and women. It’s all the other fields that are aberrant.  [AS] Absolutely, yes.  [EB] This is the normal field, right? Because it is a much more even distribution between men and women, absolutely. No, I can’t compare with other fields. You know, this is the one I know. But, it is true.  [AS] Yes, but is it something you think you have actively worked on promoting, to make it like that?  [EB] You know, I’ve only actively promoted what we always hope is good science. And, then it’s not as if one would favor a woman researcher in the area over a man researcher in the area. But, women have come into this field perhaps because in the molecular days of the field, that is the kind of things that I’ve been doing and that Carol … we were women, we tended to have women students and post docs, which was not 100%. They tended to be 50-50, men and women, which is already a little higher than the usual ratios. And so there’s a sort of self-perpetuating aspect to that. Because there’s nothing particularly about the science per se which has any, sort of gender-like quality to it. You know what I’m saying? I think we’re looking very much at sort of sociological phenomena here.  [AS] Yes, but one might hope that since it’s seen to be possible in this field it could be possible in all fields.  [EB] You really do hope that when people see something like this working, that this could be seen as, that this would be, the norm. And, the different ratios of men and women researchers in other fields would be the aberrancy. That’s what I’d like to see, because you want women to have access to science because it’s such a wonderful thing to do. Anything that makes it more feasible for women to be in science and do the science they like, that’s good.  [AS] Thank you, that’s a good note to stop on for now. Thank you very much for giving us your time. When you come to Stockholm in December, then happily we have the chance to interview you at greater length.  [EB] Great, and hopefully, I’ll be a little less sleepy!  [AS] Do you plan on trying to return to sleep tonight or is the day beginning?  [EB] Hmm. Well, I’ve made a couple of calls to the family and I might try and get a little sleep right now. That might be a good idea. It is after all three in the morning.  [AS] Good luck with it.  [EB] Nice to talk to you.  [AS] Thank you very much indeed, bye, bye.  [EB] Thank you, bye. |
| Interview |  |
| Q13 | Your Nobel Prize is of course associated with a couple of interesting numbers. This is the hundredth time, I am sure you’ve heard, that the Nobel Prize in Physiology or Medicine has been awarded and also this is the first time ever that two women have been co-recipients of the same Nobel Prize in the sciences, and telomere research in general is one where the proportion of women is more normal, if you like, its more representable of the maked up society. Is there a reason for that, do you think? |
|  | Elizabeth Blackburn: I think we should turn it around and ask why everybody else is so aberrant, seriously, because I think that actually might frame the question a little bit more instructively as to why things are not, as you said, the biological or societal representation of women. We can point to various sorts of things such as the fact that some of who have been in the field are females, but actually there are plenty of men in the field as well and I think what stands out is that the numbers are a little different, but certainly, having examples of women who have done well in science – we all know that kind of example does make it more encouraging for others, younger people, to visualize themselves being successful in science – and so I think there has been a kind of perpetuating effect there, but I do like to think that this is the normal way it can be and perhaps we should think about, well, how do we make this more normal in other fields of science. |
| Q13 | We will pick up your question, why is it aberrant in other fields do you think? |
|  | Elizabeth Blackburn: Somebody else can take that one.  Jack Szostak: There is obviously a lot of historical reasons, bias, familiar /- – -/ that takes a long time to get rid of and a lot of good role models to get rid of. |
| Q21 | Have you found it difficult being a woman in science? |
|  | Carol Greider: No, I have not found it difficult, but I think that one of the things that I have always done is sort of put blinders on and done what I wanted to do, but it was when I then started to get to the higher levels in ranks that I could then look back and see what the data was. At graduate school there were 50% women, at graduate school there was postdoc fellows usually 50% and then as you get higher and higher up the representation is lower. I didn’t feel like I personally had experienced any big obstacles, I am a scientist, I can look at the data and see that there is something that is not quite representative, as one moves up the higher ranks. I think that role models are one good thing, that the more people there are in the higher ranks the more the younger people can look up and say Yes, there is something that I can do, and it doesn’t seem like an impossible task. |
| Q4 | Is there more that needs to be done than role models? I mean, would it naturally change, or does it have to be aggressively tackled do you think? |
|  | Elizabeth Blackburn: I think aggressive tackling is good. Look at something like smoking, it took very aggressive actions to make smoking less of a wide-spread practice and certain amount of imposition of things. I don’t think it will happen organically completely from within. When you talk to colleagues, individually they are very well disposed to the idea that they see the value of having more women and more diverse groups of people’s insights, because like any enterprise the more diverse sorts of backgrounds come into it, the better way the problems can be solved. I think there is not a lack of good will among a lot of people to do this. It is a question of how do you do it, and then I am sure a mixture of various sorts of strategies will be hopeful, not least education and not least just seeing a woman there sort of makes it more possible. I think we are very visual species, and you look at something and that’s evidence in front of you, that you seem to think Oh, that’s me. If you were a young woman, I could do this.  I think further that we have to make the career structure a little bit more flexible because there has been a one size fits all model for careers in science which have been very much that based on a man having a supportive wife or partner or something to take care of life and family and that’s been something that has been daunting, we find, to young women. I personally found it very daunting as a young woman into the career structure, not the science, but the career structure, and so I think we can be much more imaginative about how we make sure women don’t leave sciences during the time when they have preoccupations with family or with elderly parents who need long term care, the sort of things that women often do. |
| Q4 | Yes, that requires one to have really quite a strong support structure within science. |
|  | Jack Szostak: A lot more broadly than that, there are a lot of things done here in Sweden that would be kind of chocking in the United States.  Elizabeth Blackburn: Yes, absolutely!  Carol Greider: A support in terms of general /- – -/ support.  Elizabeth Blackburn: Yes, because I think the seeking point for many women, at least in my personal experience from what I see is, they say “I just can’t see being a scientist and I also do want to have a life” and I think that that is something that we shouldn’t say to young people. “Oh no, you can’t have a life and be a scientist” and yet that is the perception that they have. I think as senior scientists we could do a lot more to try to think of active ways in which this one kind of career structure model that we have could be thought of more imaginatively. And I just know examples of women who have gone part-time as their families and other needs have happened, and then they go back in full time and they just come roaring back and have done really well, and they are not all in the United States unfortunately, which again tells us something about the United States situation and support. |
| Q23 | I think it’s your own phrase … I have heard you say it. They were known in the 1930s, it was known that they had an important protective role of the chromosomes, but people didn’t know what they were. It was you in the late 1970s that sorted out the molecular nature. |
|  | Elizabeth Blackburn: Began to, its still an on-going saga, none of us are out of jobs yet. That’s right. I think it was so wonderful the science that was done /- – -/ genetically in which such deductions were made about what’s going on with chromosomes and their inheritance. Now we look back at it and we say they didn’t know it was DNA and yet the thinking about what was observed, and I particularly enjoyed [McClintock](https://www.nobelprize.org/prizes/medicine/1983/mcclintock/facts/)’s work because that’s what I got more familiar with. It was so elegant and there are so many treasures in there, of insights into what turns out to be going on in meiosis and as it turned out with what’s going on with telomeres, although her fame more broadly was, I think, perhaps more for jumping genes for many years. What she said, something written in 1931, about a telomere being distinctive, and she didn’t call it a telomere, was so clear and I think very important and it was just lack of the research tools of the time.  Jack Szostak: Molecular understanding was there …  Elizabeth Blackburn: Right they had microscopes, they had genes, phenotypes, they had really wonderful other kinds of thinking, but they were not playing with the same sort of toys in the lab that we have played with. |
| Q11 | Ahead of time … Then you two met at this Gordon conference in 1980 and it’s sort of the way science is supposed to happen, two people meet each other, have an idea, do an experiment and prove something wonderful. |
|  | Elizabeth Blackburn: And then … nobody pays for it, but they do pay for it, no they pay for a broad sort of setting in which you can go and do experiments and explore and ask questions without somebody saying, Oh, is this going to be useful for this year’s economy or for somebody’s /- – -/ medicine. I think that is really important, I mean we thought that was something … we didn’t really think about it at the time, it was such a given that you can do an experiment with broad funding that is never going to be wasted. Scientists don’t throw away money, they work very hard and giving scientists money to ask questions that hadn’t been planned, it’s really important.  Jack Szostak: That meeting, or that kind of meeting, it’s great for bringing people together, who are working on different things.  Elizabeth Blackburn: These meetings are famous for …  Carol Greider: You had met each other before?  Jack Szostak: No, that’s how we met. After your talk I came up …  Elizabeth Blackburn: We walked across this lawn and just talked and talked.  Jack Szostak: Because I was working on broken DNA molecules’ ends and then Liz had these ends that behaved completely differently, and it was just a contrast that was kind of chocking so we had to talk about it and see what we could do to figure out what was going on.  Carol Greider: So Liz, you gave your talk first?  Elizabeth Blackburn: Yes. |
| Q11 | It was after the talk the two of you teamed up? |
|  | Elizabeth Blackburn: Yes, I talked about what we knew about the molecular nature of these DNA molecules. You know the ends, you could get your hands physically on. |
| Q11 | We will turn to the experiment in a minute, but I just want to ask you in general about choosing companions in science, because it is so important to get the right people to work with. Is there some, and of course one works with lots of different people throughout one’s career, but are there some criteria that you applied choosing companions to work out with? |
|  | Jack Szostak: I think it’s mostly a matter of, you know, is there an interesting experiment that actually can get done?  Elizabeth Blackburn: And then if you have the luxury of choice, yes, you do want to work with people who really do rigorous science, I think, and that can be very different kinds of science, can be done with rigour, but I think that’s important as one collaborates with people outside new areas. Jack and I, we were really much in the same sort of area, it was a molecular genetic tradition, but when you collaborate even further out, now you don’t have the deep expertise, then I think you have to have a real respect for that person’s quality of their research.  Jack Szostak: And you also need to have someone who is fun to talk to and you can exchange ideas with, each way. Some people are better at that than others. More fun to work with.  Elizabeth Blackburn: But you are right, if the scientist is really exciting you will make it happen.  Jack Szostak: You will find a way. |
| Q26 | And when you are picking companions who don’t have a track record, students that come in into the lab, what do you look for in them? |
|  | Carol Greider: Really, it’s just the excitement of what they are doing and they simply need to communicate that excitement back and forth and I think if people really are interested and care, just interacting with them over a period of a few weeks, one can tell whether or not there is a compatible set of interest that are there. So usually there is an opportunity to do that when students may be coming into the lab, you have a chance to get to know them a little bit and see where the capabilities are on both sides. It’s not just a mentor choosing a student for a very … there is opportunities for students to go around and choose mentors and make sure that they are compatible with them as well, and I think both of those things are important. |
| Q12 | I was going to go on to ask what do you think are the important characteristics of being a mentor, what do you try and provide for the student? |
|  | Carol Greider: Again, it’s all about the science and it’s about being a /- – -/, sit down and have a conversation and really understand that person’s interest. Some problems are very interesting, but somebody may approach it from a particular angle and somebody else approach it from a different angle and then when those two people talk it may not be as easy to understand, but a third angle, there may be a shared understanding like, you know, languages, if somebody speaks a language that is close to a language, if somebody speaks Italian and Spanish, maybe they will understand each other better than somebody speaking some other languages. So I think that that is true in terms of people in their interpersonal interactions as well, so finding those compatibilities is just a matter of spending some time together and talking about their science. |
| Q12 | I don’t know if you want to add anything? |
|  | Elizabeth Blackburn: And finding their strengths too, which is something I learned not by being clever, but somebody once said to me that Shirley Tilghman, who is now the President of Princeton, but she is a very accomplished molecular geneticist, and somebody who knew her very well in her science days said she always is very good finding what people are good at and then making sure that gets used very well. It’s not an altruistic thing necessarily, she is making sure they thrive and do the best in science and I thought that was a really good hint and I try and look for that as well because some people have real strengths in some areas, some will ask all these questions all the time and they will never do this experiment, but its also important that they are doing that. Others will say, Yes, I will do the experiment but also be critical. Carol was actually somebody in the latter, she said, “I will do the experiment” and be very smart and critical at the same time. But other people will question, question, question, and if you can make use of that and say, this is really good that someone’s bringing into their really critical thinking and not say, Well, I really want you to do it this way and stopping it, and think, Ah this person actually is smart and they probably got some good reasons for what they are thinking about and so try and use what strengths you feel you discern in people is important.  Jack Szostak: I like to find people who are pretty independent and have some initiative and the best students are the ones where I can tell them that’s never going to work and then they go and do it and show that it does work.  Elizabeth Blackburn: My problem is that I always think that it is going to work, and they are the ones who say, Well actually …. It goes both ways and you have to have both going on and you have to have the sort of Let’s try it, and things that you really have reasoned through very well, that sometimes is the route to doing something new as you reason something very well and you do that and then something new comes of that too, so both ways in biology really can work and you can’t always predict which is going to be the formula. |
| Q12 | Presumably it often takes quite a long time to find out what people are good at, because there must be a lot of graduate students who start and then find they don’t hit the ground running, it takes time to get going. That can be quite a dissolution at time, so it’s important for people to understand it can take time for one to work out what one should be doing. |
|  | Elizabeth Blackburn: I think people’s quality of thinking that emerges relatively easily I think, now as you say what unfolds in the experiment can of course be very slow because you know by definition you are doing things that are difficult. If they are easy someone would have done them, and so that’s I think the hard, unpredictable road for graduate students. Back to your questions of mentoring, that’s were you have to realize that that’s going on and that people will go through periods in science as we all have done, when you’re just seeming to fail all the time and the experiments don’t work, sometimes for reasons that are boring, but sometimes for reasons that are significant. You have to be able to fail a lot of the time, scientists just have to be terrific at getting slapped back on the face by nature all the time.  Carol Greider: I have told my students and I am famous in the lab for saying “That’s why they call it research” because somebody would come into my office and we will be talking about an experiment with a great result and I say “Great, go and do it again!” Somebody would come into my office and say “Nothing worked at all, nothing worked at all”. “Great, go and try it again!” And I say that’s why it is called re-search, you always have to do it again.  Elizabeth Blackburn: I realized the opposite because somebody said it isn’t research because somebody already searched for the /- – -/ rediscovering it or something. I like yours better.  Carol Greider: You have to repeat that good experiment just like you have to try again at the failed experiment. |
| Q23 | Yes, Carol’s is less depressing, yes. So back to the experiment, together you demonstrated that telomeres from one species could protect DNA from an entirely unrelated species and thus the mechanism of the telomere protection was more fundamental than perhaps one might have though initially. And that result was very clear, you understood that immediately so where you aware of what an important piece of information you had just discovered at the time? |
|  | Jack Szostak: I think we knew that it was going to open up a lot of new experiments, because we could use all the tools available in yeast as well as you could do in *Tetrahymena* and then in other organisms. So we knew that it was going to allow more progress.  Elizabeth Blackburn: And I think it also felt somewhat fundamental in the sense … you know molecular biology was very dominated by there will be universal solutions for things because we were so influenced by the genetic code, DNA, everything was very universal and so when you saw something crossing lines of phylogenetic divisions … Don’t you think there was a bit of a sense when we found the sequences looked similar and they looked like there is something fairly deeply universal in the eucariotic world.  Jack Szostak: That is an important point, because it was already clear that in bacteria and many viruses there were lots of different solutions, so it didn’t have to turn out to be universal.  Elizabeth Blackburn: Yes, it was completely nonintuitive what would go on in terms of actually more the replication problem in terms of … and protection too. |
| Q23 | And you also observed that the telomeres in yeast were lengthening and that something had to be causing that lengthening and that’s when you come into the story, because you set out to find the activity that was causing the lengthening. |
|  | Elizabeth Blackburn: By chemically speaking yes, because I thought that was … I am sort of a biochemist, somewhat by training I suppose and I had gone through biochemistry and then molecular biology and so it felt natural to try and say this is very direct, you know, reactions take place in real time sort of more or less in front of your eyes in sort of, you know, biochemical way.  Jack Szostak: You had the right organism for doing the right chemistry.  Elizabeth Blackburn: And the organism was right and it turned out … There was a biology of the organism that set this burst of telomere synthesis that takes place and there was an abundance, relatively speaking, of telomeres and so that all pointed to, well, this is a good system to try and answer questions and I had been trained in the lab of Joe Gall, which is where I actually did the sequencing of the telomeric ends, as we now call them, the DNA ends of the mini-chromosomes in the ciliated protozoans. Joe had very much always said that you should find this system in which you would answer the question best, what I think is a fundamental idea. Things will be pretty conserved throughout much of life and so this idea that find the good system was very much in my mind so I started out doing a little out of foray into things, got ten years, felt brave and Carol joined the lab and felt really brave. |
| Q40 | She was one of your unusual students who took one of your ideas and said, Yes I can do that and off she went. |
|  | Elizabeth Blackburn: I had actually offered it to a postdoc who turned it down: Very nice Liz, but I think I will do something different. It was very politely, but. |
| Q23 | And you got this now famous Christmas present in 1984, the first indication that you got your hands on the activity that was causing the lengthening of the telomeres. |
|  | Carol Greider: Yes, I was doing experiments, it was about nine months of trying various things. Liz and Jack had proposed that there may be something that would lengthen the telomeres and so, not knowing exactly what that is or what the properties were. We would just try different things and Liz and I would talk to each other every day or so and say, Okay let’s try this, like cooking, you add some ingredients and you taste it and that doesn’t taste so good so you add a little bit more salt. After trying various things there was one particular change that I made in the experiment. I was just interested in … It was an exciting time to do an experiment and then a few days later, it would take several days for the experiment to sit on an autoradiograph and so I went back in on Christmas day to develop the results of the experiment that I had done several days before and that’s when I saw this very clear repeating pattern on the autoradiograph that just looked like a six-base repeating pattern that you would expect of a telomere repeat.  That first instinct is like, Wow, this might really be what we think, of course, then after the excitement there is the, Well, are we being fooled? And so then has to follow all of the ways where we would then be our own worst critics in a sense. It’s like how could we be being fooled by this? Maybe it’s really some normal polymerase that is copying something that is a repetitive sequence in the extract. So that is were the real work of the self criticism is very important and so that is why the discovery was Christmas 1984, but the paper was published in December -85.  Elizabeth Blackburn: It just shows how fast these things go actually. |
| Q7 | It is an obvious point, but obviously you were enjoying yourself tremendously and going in on Christmas morning was just something that was natural and the enjoyment of what you do is key, is absolutely the essence of it. Its not work, its enjoyable, I presume. |
|  | Elizabeth Blackburn: That’s right, it’s the best kept secret in science. We never tell people what fun we are having and maybe we are a little afraid because somehow society will frown upon the idea that you actually really … And yet at serious play, but it’s completely the element and the resources, I wonder what, because often the trajectory of the experiments, you find out something the next day because something has rather been incubating or autoradiograms exposing, things like this. There is often this thing where you would leave something and the next day come in and I have just been driving to Berkeley and I am driving up university avenue, really impatient because the traffic would get very slow off the free way, and you knew there would be something at the end of that university avenue when you got out of the car and went into the lab.  Carol Greider: That’s why I lived up on the hill and I came down on my bike.  Elizabeth Blackburn: Yes, you came down on your bike fast, that’s right. And you had a Volkswagen once. At least you were on the bike, that’s good. But I think that’s really an important point because many young people are saying, Oh you know science is so hard, its so true, and we all complain bitterly because we just take completely for granted the fact that we are having such a good time so we sort of have the luxury to complain about the other stuff. But it’s a really good career and very autonomous, nobody tells us what to do in terms of our choice of research and when you think about how many jobs that’s true for it’s a mince and its not as if scientists waste money. We really are so driven, we want to find things.  Carol Greider: I remember when I was a graduate student and it was the first time that I was sort of on my own and supporting myself, and I was like, Wow, they are going to pay me to come in and play everyday ,and I was being paid now what would now be you know, but it was great and I thought Wow, this is just amazing. Maybe if I just keep it up, and it’s worked so far.  Elizabeth Blackburn: No, it’s true, as an Assistant Professor you’re suddenly given this playground. They really trust me to do this – that was my feeling. And Berkeley was very /- – -/ actually and they sort of really trust you to go out and … I think now mentorship in young peoples careers is much more thoughtfully done and maybe that’s not always good because we had huge freedom just as Assistant Professors, right?  Jack Szostak: We just had the resources to go.  Elizabeth Blackburn: Yes, you have to gather the resources, but then you work really hard because you are just driven. |
| Q7 | Perhaps it’s too big a question to ask whether its changing for the good or for the bad. Its presumably going in both directions in the same time. |
|  | Elizabeth Blackburn: I think those who love science are still driven in the same way.  Jack Szostak: I don’t know, it might be, it probably takes more time and effort to raise the money to support lab. There are more frustrations there, maybe its more bureaucratic than it use to be, but if you really want to do it, you can still do it and then you have the luxury of doing whatever experiments you think are the most interesting. |
| Q23 | Okay, so back to the enzyme, the enzyme you discovered was unusual, it was a reverse transcriptase with extra protein and RNA and it took some time to sort all that out. When you did sort it out, it turned out that it solved the end replication problem because this problem had been laying around for a while unsolved of how DNA polymerase, well the fact that DNA polymerase could not, on its own, synthesize both chains of DNA to the end. And it seems strange that that problem had been there without anybody being able to solve it for quite a long time. DNA polymerase was revealed in 1958 by [Kornberg](https://www.nobelprize.org/prizes/chemistry/2006/kornberg/facts/) and it was pointed out in what 1970 or so, 1972 by [Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/) and others, there was this problem. And it was the late 80s or mid 80s the solution came. |
|  | Carol Greider: There were solutions in other organisms as Jack had alluded to, that various viruses … what wasn’t known was how the eucariotic chromosomes solved the problem and that did wait for the sequences, until Liz found the sequences you couldn’t really ask the question until you had the actual molecular details.  Elizabeth Blackburn: And there was some peculiarities about the sequences, there were different numbers of repeats of the ends of different molecules in a population of molecules. This wasn’t like viruses although there are some viruses in which they do have recombination at the ends and they have some end repeats as well, so there were solutions that looked very plausible, that the viruses of bacteria had already evolved to have. It was really various lines of evidence that sort of said, Aha, this does not seem to be the kind of solution that new eucariots have.  Jack Szostak: But if you go back and read all our early papers we were through a lot of models, they were mostly based on recombination-like mechanisms and we held on to those to the bitter end until the sequences said that can’t possibility be.  Elizabeth Blackburn: Because people could draw beautiful diagrams, right, and the literature was, you did …, I don’t know how to draw beautiful ones. No but there was definitely some ideas out there and some of them have turned out to be quite applicable actually to some viruses and stuff like that, so the ideas were not completely useless.  Carol Greider: … applicable to telomerase in theory, as well.  Elizabeth Blackburn: Yes!  Jack Szostak: Yes, that’s right.  Carol Greider: There really were two answers, it’s just that one turned out to be a little bit more dominant then the other.  Elizabeth Blackburn: A lot more dominant.  Carol Greider: A lot more dominant, yes!  Elizabeth Blackburn: As almost universal eucariots, with exceptions, and exceptions are always instructive, that is sort of the richness of the question because there is such a lot that goes on in what seems very simple, but technically a different chromosome, it sounds like you just stick a fortress around and that’s okay, but its much more interesting and dynamic than one had thought, which again makes it fascinating. |
| Q38 | It is fascinating, is it interesting because one tends to tell the story of science in retrospect as being a problem followed by a solution and its not quite that, is it? Its much more complicated. |
|  | Elizabeth Blackburn: And often observations come and then they are what you expect and then you start thinking about them and what they might mean and then realize, Yes, that might be providing a solution to something. You know it doesn’t happen in …  Carol Greider: But there are also possible solutions that aren’t correct, or pursue things, that’s not how they found out, that’s not how it works and you go back and pursue a different angle and what you end up hearing about historically is those things that were correct, so it seems like a linear path when actually it was a branch in a tree of which were interesting ideas. They just didn’t turn out to be how it actually worked.  Elizabeth Blackburn: Yes! Or at least not in that situation.  Carol Greider: Yes, that particular situation.  Jack Szostak: And also you get a solution to say the problem that you were thinking very originally, but once you have that solution you realize, Oh, now there is three other problems you hadn’t even thought of before and so it goes. And that is really true in the case of like human telomeres where the biochemistry is unbelievably complicated.  Elizabeth Blackburn: And yet there is an inevitability to the complexity because people say, Well, if you want a very robust sort of system it has to be inherently complex and so suddenly it makes sense in a way that we didn’t think of. We really simplified the question where we just said, we are just going to think about the DNA and the enzyme that does it and just so, you have to do that, I think, up to a point, you have to take away the irrelevancy, but always knowing that it is taking place in a cell, an incredibly complex entity which is a cell inside an incredibly complex identity which is, in our case a human, and yet you can take these things and sort of push them up to a point and then you have to realize when you have to take the blinders off, that’s the key. But again, the inherent complexity of it, its not like a curse, its sort of like, This is the way it is, because the really interesting reasons why systems have to be that way and yet we have to, on the other hand, sort of reject the complexity at certain stages in the research. |
| Q37 | 20 years on you are still working on telomeres and telomerase and sorting out the system and one thing that … Oh yes, I am coming to Jack, I’m coming back to that. One aspect that is growing up is the therapeutic implications of the fact that telomere shortening was seen to be associated with the disease states and indeed the maintenance of telomere length in both directions seems to be important, maintained equilibrium is important. What do you feel are the potential therapeutic benefits of studying telomerase and telomeres? |
|  | Elizabeth Blackburn: It is usually divided into two general categories, one is the rather hyperactive telomerase that characterizes the great majority of human cancers, on the other hand the telomerase that is presents in much more regulated form in the natural cells of the body. The normal cells, the telomerase is present in much more regulated form in normal cells of the body and various indications, such as the associations you mentioned of short telomeres with many disease states or risks of it that’s intriguing this genetic data in cases of insufficient telomerase action which says that clearly is not good for humans to not have enough telomerase in their normal cells that have to replenish to decades of adult life if we are fortune enough to move past our re-productive years and we are looking at old age, we are interested in what our health is like for that. So understanding what’s going on in cells at this fundamental level, I think you really do understand this, just to understand what’s going on in the trajectory of humans as we age, because all of the social and other settings are now letting us age, we have this sort of unexpected biological reality to live with, so we are understanding that first of all.  Now, are there quick-fixers magic pills? Not tomorrow, but maybe there is interesting things that could keep telomerase a little more active, but you have to be careful and I like to think it’s like aspirin, you take two aspirins – good – take a bottle, that’s bad. Clearly any measure would have to be carefully thought through how you would, if you want to keep telomere maintenance better, not to push it too far, because too much telomerase can help cancer cells, but I mean, really a lot to much. Then the question of course is can you exploit the high telomerase in cancer cells to selectively target cancer cells and there is beginning efforts in industry to do very early stages, to look at these kinds of things. But I think just understanding what’s going on is actually really important in understanding human ageing.  Carol Greider: And it’s not just telomerase, because one of the things that we have learned in the research over the years is really that’s the short telomeres that cause the end effect and as Jack has mentioned, any time you ask a question and you find out the answer there is many more other questions to ask. There are various regulatory mechanisms that allow the telomere length to be maintained at a certain equilibrium and telomeres is essential to provide the raw material to do that, but both the telomere is regulated as well as the proteins that are on the telomeres, that the telomeres has to interact with. I think that really understanding those details of all of the components and the complexity that goes in to the regulation will tell us a lot about these diseases, these age related degenerated diseases that may not be just telomerase related but they may be a number of other genes that one can look at that may be associated with these degenerated diseases that aren’t directly the telomerase, so there is a lot of interesting avenues to pursue still, to really understand the different directions these diseases may come from. |
| Q41 | Because there was a great deal of therapeutic excitement about telomerase and telomeres early on and there still is. Was there an initial kind of pressure on you suddenly, that everybody was getting excited about the potential? Does it make life difficult if people’s expectations are a little bit too elevated early on? |
|  | Elizabeth Blackburn: I work in the basic science area, so I felt immune from that.  Carol Greider: It’s all the companies that have to worry about that kind of expectations because we never really said as scientists that there was going to be that kind of therapy to come in tomorrow because we didn’t have the vested interest to be doing that.  Elizabeth Blackburn: I think it is good to have these avenues explored for sure and I think that the fact that it hasn’t gone all that fast is actually not to do with the science or other sorts of things. In the meantime it’s really important to try and understand what is going on because any therapeutic is going to be all the better for having a better sense of what underlies the usefulness and where its danger points might be. It’s not clear how we think about these issues of long term diseases that affect huge numbers of people, you don’t necessarily put everybody on statins, that’s a common thing, but perhaps that equivalent isn’t necessarily the best way to go either, although we tend to be a very ‘take a pill’ oriented society and nothing wrong with that, I mean. I am all for western medicine, believe me, but I am just saying that we don’t want to limit our thinking I think to that …  Jack Szostak: And jump into something too quick and not recognize a problem.  Elizabeth Blackburn: Exactly, that’s right. |
| Q43 | I wanted to end just by dealing with these questions of staying with your subject or not. You two have stayed with the subject … |
|  | Carol Greider: That’s debatable, the subject really has changed continuously |
| Q43 | I am sorry, the subject expands… |
|  | Carol Greider: Yes, I was a biochemist you know and now I am working on recombination and human disease and various other things.  Elizabeth Blackburn: I work with clinicians on chronic psychological stress, but the point is I am not the expert. I bring my expertise and they bring theirs, so it stays very fresh by keeping one’s expertise that you really have. Now interfacing with other expertise’s so it’s actually a very broad topic. Anything that says our cells are going to be able to keep replenishing got a lot of broad implications even though we are focused on one part of it. |
| Q45 | Maybe I will discover my questions completely redundant, but let’s say you two are at least following the questioning in the same general vein and yes, it’s taking you to new places. You, on the other hand, have seemed to jump from one question to another, but there is almost a clear break between one question and the next and they seem from the outside the two different ways to do science. One is to say, There is a problem, I will work on it for a while and then I will look for another problem, actively go and find a different problem. Would that be fair to say? |
|  | Jack Szostak: I think you could find lots of examples of people who you know have one system and they use it to address lots of different questions and that can be extremely productive and then there are other people who just like to find interesting questions in different areas and go for it. |
| Q45 | But what I was going to ask was what for you is the attraction of jumping from question to question. |
|  | Jack Szostak: Well its fun to think about new things, get into an area where you don’t really know very much so you don’t have to be fooled by the preconceptions that might dominate the field so you might have a chance of making a contribution in a different way. So that is part of the attraction. |
| Q45 | Is there also an attraction in going to less populated places? |
|  | Jack Szostak: For me, I don’t like to be working in an area where there are a lot of other people who are going to do the same experiment at the same time or a few months later. I find it more fun to be doing something that is probably unique.  Elizabeth Blackburn: And that’s what telomeres were initially to. Nobody was asking these questions and it is a the most fun way to do science actually. I agree with you.  Jack Szostak: In the mid or late 1980s I think the implications of all the telomere work were becoming clear and it was I think clear that a lot of people would be going into that field and so I think that helped to make me look around for other areas and all the stuff about ribozymes was very new and exciting and I was very surprised that there were very few people going into that area so I thought that we might …  Carol Greider: You had already got the Nobel Prize by that time?  Jack Szostak: That was 1989 and we started working on it in actually -85.  Elizabeth Blackburn: And how life begins, I mean that’s a pretty important question.  Jack Szostak: It’s a lot of questions when you start to break it into pieces, it’s a lot of interesting questions, so that has come to dominate what we do today. |
| ID | 0536 |
| Biographical | was born in San Diego, California in 1961. My brother Mark was born in January of the previous year. My father Kenneth Greider was a physicist who had recently graduated with a Ph.D. from University of California at Berkeley. My mother Jean Foley Greider also had received her Ph.D. from UC Berkeley in Botany. My father worked in high-energy nuclear physics and my mother was a mycologist and a geneticist. After both parents completed postdoctoral fellowships in San Diego in 1962, my father took a faculty position in the Physics Department at Yale and so the family moved to New Haven, Connecticut. My mother took a postdoctoral position at Yale in the laboratory of Norman Giles, where she worked on Aspergillus as well as other fungal species. A few years later in 1965, my father took a faculty position in the Physics Department at UC Davis and so the family moved back to California. My mother first took a teaching position at a Sacramento community college and then later at American River College in nearby Sacramento.  **Davis** Mark and I grew up in Davis, where we could walk to school. My parents built a house in a development in West Davis shortly after we moved to Davis. The street was conveniently located about a four block walk from the West Davis Elementary School (Grades K-4) and half a block from the new West Davis Intermediate School (Grades 5 and 6). Mark and I would walk to school together as kids, and later bike to high school, year-round. It gave us a sense of independence to come and go. The idea of parents driving their kids to school was one I had never heard of until moving to the east coast and becoming a parent myself. This early responsibility was something that shaped my sense of independence. For me school was something that was a kid’s responsibility. Parents were not really involved.  In December of 1967 my mother died when I was in first grade and Mark was in second. In retrospect, this event played a major role in my learning to do things on my own. Mark and I continued to get ourselves to school and to go on with our lives as best we could. School was not easy for me. I was put in remedial spelling classes because I could not sound words out. I remember a special teacher coming into the classroom every week to take me out for special spelling lessons. I was very embarrassed to be singled out and removed from class. As a kid, I thought of myself as “stupid” because I needed remedial help. It was not until much later that I figured out that I was dyslexic and that my trouble with spelling and sounding out words did not mean I was stupid, but early impressions stuck with me and colored my world for a time.  **Heidelberg** In 1971 my father was invited take his sabbatical at the Max Planck Institute for Nuclear Physics in Heidelberg, Germany. We moved to Germany for the year and Mark and I went to the Englisches Institut,a private school. Despite its name, it was a typical German Gymnasium and all of the instruction was in German. So for the first six months or so, we learned German by immersion. Mark and I took the city bus to school each day so we quickly learned to navigate the public transportation system, as well as navigate our way around a new school and new language and new culture. In Davis we had been used to getting to school on our own, so we welcomed this independence and developed an appreciation for how things were done in a very different culture.  I remember my grades were particularly poor in this school and especially so in the English class. The English teacher would give a dictation and we were supposed to write down what she said in English. It seemed too simple and pointless to me, but when I got my graded notebooks back, the scores were usually D’s or F’s because every other word was misspelled. Looking back over those notebooks later, I saw the pattern of backwards words and letters and gross misspellings that led me to suspect I was dyslexic. The other confusing thing about school for me was the “religion” class. You had to declare if you were Catholic or Protestant (as if those were the only choices) and then each group had their own class. Back home, my father was music director for the Unitarian Church, but as kids, we rarely went to church. It was too hard to translate what Unitarian meant to the Germans, so my father asked the school to excuse me from this religion class, and instead have a free period to do homework. This is how I met my friend Jiska, who was one of the few Jewish kids in the school and who was also excused from religion class. In my friendship with Jiska, both of us different from the rest, I began to develop an appreciation for people who were not like the others and who stood a bit outside the mainstream. This understanding of and affinity for people outside the mainstream served me well later in life. In high school and college I never felt the need to be part of a popular group, but rather sought out friends for their personal qualities. This appreciation may have also shaped many choices later in life; for example, working on the unusual organism Tetrahymena.  I spent a lot of time on my own in Heidelberg, playing down by the stream near our house or hiking the hill to the top of Boxberg. I took the bus into town on my own and learned to dress and speak like a German. There was a large American army base in town and I did not want to be mistaken as an army kid. I liked being more unusual: an American kid who understands German culture. By the middle of the year, I had learned German and became fluent in speaking and reading, but like all other written tasks, the writing and grammar eluded me. Mark and I had some German-American friends a few stories up in our apartment complex and we made up games like tapping out a code on the radiators and sending notes on string outside the kitchen windows to communicate. These games irritated the other apartment residents and resulted in the building manager coming to talk to my father. We were typical kids in that fashion, breaking some rules, where we could, but not going too far.  **Davis – part II** When we returned from Germany I went into 6th grade, which was a transition year, the last in intermediate school before junior high school. I spent much of it readjusting to being back and making new friends. Unlike many scientists I know, I was not a kid who knew from early on that I wanted to be a scientist. I think one important thing I learned in my early years was to focus intently on the task at hand, such as learning German when we were in Heidelberg, to the exclusion of other things going on around me. This survival skill served me very well in later years. Focusing on certain goals and ignoring obstacles came naturally to me.  In junior high school I learned that I could be good at school. I remember liking the freedom to choose classes and the pleasure of learning and doing well. My perseverance and love of reading had somehow allowed me to overcome many disadvantages of dyslexia, and I read a lot of books for pleasure. I found I had to memorize words to spell them, as sounding them out did not work for me. This coping mechanism proved also to have an upside; memorization in biology and history was easy for me. My father encouraged us to do well in school and to do it for ourselves. He said that we should want to do well because it would “open doors” for us. He emphasized that being able to choose what you want to do in life is so important, and doing well early on will allow more possibilities in the future. I also discovered the pleasure of the outside reward of getting all A’s in classes, it made me feel good and I got positive feedback from people outside the family.  In high school I focused on doing well in my classes and finding a supportive group of friends. In junior high I had been attracted to outsiders, perhaps from my experience in Germany. But the outsider group I found myself with in junior high was not as interested in school as I was. I took the opportunity of the change in schools from Emerson Junior High to Davis Senior High as an opportunity to find a new group of friends. I met Lori Lopez and Resi Zapfel at an American Field Service (AFS) Club meeting in the first weeks of high school, and they quickly became friends. Resi was an exchange student from Austria and Lori was the AFS club president. Lori’s family and Resi’s host family the Robertsons became like a second family to me. I liked the foreign students in the ASF group, and the American kids who were a part of this group were not interested in mainstream popularity. I affiliated myself with the AFS student group throughout high school and was even president of the club my senior year. I did not focus particularly on science in high school, or join any science-related groups, although I continued to do well in all of my classes; I considered it a challenge to get all A’s. I never considered myself one of the smart kids, they seemed confident and driven. I just enjoyed learning and especially spending time with friends.  After my junior year at Davis High School, I knew I needed to think about where to go to college. I had done well in biology in school and was particularly captivated by my 12th grade biology class, where we learned a lot of physiology from a very motivated science teacher who had a Ph.D. I loved learning new material and being challenged, so I decided to major in biology in college. Many of my fellow high school graduates intended to go to nearby schools, either UC Davis or UC Berkeley. I did not want to go to either. I wanted to do something different from the norm, get out and have new experiences. My friend Alyssa Ingalls, whom I had known since 6th grade, was taking a trip to visit several University of California schools with her family Liz and Bob Young. I was happy to be invited along on this school tour. We visited UC Santa Cruz, UC Los Angeles and UC Santa Barbara.  I had a contact at UCSB, Beatrice Sweeney, who was a professor there and who had known and worked with my mother at Yale. My father put me in touch with Beazy, as she was known, and Alyssa and her family and I got a tour of the campus from her. Beazy was a cell biologist by profession but a naturalist at heart. She took us for a walk on the beach near her house and told us fascinating stories about the biology of all the marine animals and plants that we walked by. I was captivated by her and by the beautiful UCSB campus. I decided I wanted to study Marine Ecology at UCSB.  **Santa Barbara** Beazy was on the faculty of the College of Creative Studies, a small college that is part of UCSB. The College of Creative Studies was founded by Marvin Mudrick, a professor in the English Department, to foster independent learning and interaction between disciplines. The requirements to get into CCS were significantly higher than to get into UCSB. My grades were very good, but my Scholestic Aptitude Test (SAT) scores were not. I never spent time practicing to take standardized tests and the dyslexia made them hard for me. I was very happy when CCS accepted me. So off I went in the fall to Santa Barbara.  The most important thing about UCSB and CCS was that Beazy [Professor Sweeney] encouraged me to begin working in a lab my freshman year. I was scared that I needed more time to adjust to college, but she said to start as soon as possible. I did a project first with Adrian Wenner studying sand crab populations in Santa Barbara. Though I thought I wanted to be a Marine Ecologist, this experience did not captivate my attention. The science was mostly statistics, which I did not understand or relate to. Beazy kept in close contact with me and saw I needed a different experience. So I then worked with a postdoc in Beazy’s lab studying the movements of chloroplasts during dark/light circadian cycles in Pyrocystis,a dinoflagellate. I enjoyed the work in the lab. I liked coming in to do my own experiments and was challenged when Beazy said I had to come up with a way to plot and describe my experiment on my own, with no set form. The simultaneous pain and joy of trying to create something that made sense to describe my observations was exhilarating.  I enjoyed watching cells and describing the circadian rhythms, but after a while I felt the work was too descriptive. So next Beezy took me to work in Les Wilson’s lab on microtubule dynamics. I am not sure if it was the topic or the personalities in the lab, though it was likely both, that captivated me. I worked first with Kevin Sullivan and later with David Asai studying microtubule associated proteins. The work in the lab was focused on understanding molecules and how they interact and behave. We would do experiments to examine how fast microtubules would assemble from the tubulin building blocks, then make a change to the tubulin preparation and see how that affected the results. Being able to manipulate molecules and understand the mechanics of how things worked fit my way of thinking. In addition, talking with both Kevin and David and the others in the lab was fun. People knew each other well, were playful, and would tease each other a lot. There were inside jokes and an easy way of laughing about experiments as well as everyday life that was infectious. I worked with Kevin for my sophomore year studying the assembly kinetics of chick brain microtubules under different conditions. The experience that Beezy and the CCS program provided me, to try out several different laboratory experiences, was instrumental in my finding how much I loved mechanistic thinking and biochemical experiments. By comparing several different labs, it became clear to me when I was having fun and when I was not. I saw that laboratory work was about people and interactions as well as about science. It could be playful and was appealing as a potential path I could enjoy.  **Göttingen** My junior year in college I spent as a student at the University of Göttingen in Germany. Ever since my early experience in Heidelberg and visits to see Resi Zapfel (now Schmall) in Austria, I wanted to experience what it was like to live as a student in a foreign country. I took the opportunity to go to Germany for a year on the University of California’s Education Abroad Program (EAP). Before I left, Kevin Sullivan and Les Wilson encouraged me to continue lab work in Germany. They contacted Klaus Weber who had a lab at the Max Planck Institute for Biophysical Chemistry, and he agreed I could work there. I would split my time between classes at the University, such as Biochemistry and Genetics, and time at the Max Planck working on intermediate filaments in the Weber lab. In addition to lab work, I also became close friends with a number of Americans in Göttingen who were also on exchange programs.  At the beginning of the second semester I was looking for biology courses in the course catalogue and found one on chromosomes that looked interesting. When I showed up in the assigned room at the right time it turned out it was the regular lab meeting for Professor Ulrich Grossbach. Professor Grossbach had listed his lab meetings as a course so the graduate students could get credit. I was very embarrassed to walk into a private lab meeting, but the researchers in the group were all very nice and they asked me to stay. Michel Robert-Nicoud, a research associate in the group, took me under his wing and asked if I wanted to help in a study of polytene chromosomes of Chironomus, a diptera distantly related to Drosophila. I enjoyed learning how to do the preparations. It was satisfying to prepare the salivary glands just right and see the giant polytene chromosome under the microscope. I finished the work I had begun in the Weber lab and moved to work with Michel in the Grossbach lab.  Michel collaborated with Tom and Donna Jovin, who were also at the Max Planck Institute for Biophysical Chemistry, on an unusual left handed helical form of DNA called Z-DNA. Tom and Donna had studied the biophysics of sequences that could form this unusual DNA structure. To understand if Z-DNA is found in natural chromosomes and where it might be located, they developed antibodies to Z-DNA. They were collaborating with Michel Robert-Nicoud to locate the Z-DNA by staining the giant Chironomus polytene with their Z-DNA antibody. There were controversies about whether Z-DNA might be located in bands or interband regions of the chromosome. There was also discussion about whether the regions that stained with the antibody normally had Z-DNA or if the binding of the antibody itself induced Z-DNA where it might not normally be. There was a lot of excitement in the lab about this project and Donna Jovin was preparing to submit a paper on these findings. It was thrilling to know that my work staining chromosomes was of use for realexperiments and not just as make-work, and might be part of a publication. This experience with Chironomuspolytene chromosomes gave me an appreciation for the beauty of chromosomes. It may be that I gained an affection for chromosomes that I brought with me several years later when I first met Liz Blackburn.  **Santa Barbara – part II** When I returned to Santa Barbara for my senior year I wanted to go back to work in the Wilson lab. Kevin Sullivan was writing his thesis and planning to move to a postdoctoral position. Kevin suggested I work with David Asai who was a research associate in the Wilson lab. Kevin was very excited about his future studying the genes for tubulin, because he said genes and DNA were the most exciting work going on. Talking to Kevin and David helped me decide that I wanted to go to graduate school. I enjoyed the camaraderie in the lab and liked the challenge to think creatively. I worked hard my senior year, and CCS made it possible for me graduate in 4 years by their flexibility about transferring credit from my course work in Germany.  For graduate school entrance I took the Graduate Recorded Exam (GRE) exams and, as with the SATs, did not do well. I applied for admission to eight different graduate programs, but did not make it through the numerical cut off for grades + GRE’s. I got many rejection letters. However, two schools did decide to interview me. I may have seemed like an interesting case to those people who actually read the applications, rather than pre-screening with a numerical cut-off. I had a 3.9 GPA and A+’s in O-Chem, P- Chem and pharmacology, a lot of lab experience, but poor GRE scores. California Institute of Technology interviewed me and each of the 10 professors with whom I talked asked me why my GREs were low. I talked science with all of them and also explained the dyslexia and poor scores on standardized tests. After the interview I was accepted to Cal Tech. UC Berkeley also accepted me and asked me to come for an interview. It was during that interview that I met Elizabeth (Liz) Blackburn. I felt her enthusiasm for chromosomes and telomeres was infectious. I wanted to talk to her more after the allotted interview time so I made plans to come back again the next week to talk in more depth about her telomere work. After that interview, I decided I wanted to go to Berkeley and work with Liz.  Both of my advisors at UCSB, Bea Sweeney and David Asai encouraged me to go to Cal Tech instead. David had done his Ph.D. there and felt it was a special place to he wanted me go there too; Beazy did not want me to go to Berkeley “just because my parents had gone there.” Somehow my interest in potentially working with Liz was great enough to for me to go against the recommendations of two mentors. So I signed up as a Ph.D. student in the Department of Molecular Biology at Berkeley.  **UC Berkeley** When I got to Berkeley I had missed the week of orientation for new students, because I decided to attend the wedding of my friends Monica and Chris Morakis whom I had met in Göttingen. My first few weeks at Berkeley felt overwhelming. Although I had done biochemistry, I had not taken any molecular biology courses and had never worked with DNA. My classmates were an impressive bunch with a strong background in molecular biology and it seemed they were all clearly smarter and better prepared than I was. It was thrilling to be part of such an impressive group of interesting people, and soon we all became very close friends.  Although I had come to Berkeley to work with Liz Blackburn, all first year students had to do three laboratory “rotation projects” for 2–3 months each before decisions were made about which lab to join. My first rotation was with Richard Calendar studying phage P2 and P4 interactions. I was very fortunate that that year, two of us first year students were both assigned to Rich’s lab at the same time. My fellow ‘roton’, Jeff Reynolds, was very smart, very friendly and it seemed he knew everything about DNA. So I could lean on Jeff and his knowledge to get me started at Berkeley. From those first days, Jeff became, and still is, one of my best friends.  My second rotation project was in Liz Blackburn’s lab. There was a certain amount of anxiety among the first year students as we could not choose our rotation labs; assignments were made by the Department chair, Nickolas Cozarelli. I was very happy to get assigned to Liz’s lab because of my strong interest in working with her. For the rotation I worked on a project to clone telomeres from trypanosomes and the related species Leishmania. By the time I arrived in the lab, Liz and Jack Szostak had already shown that telomeres from Tetrahymenawould function as telomeres in yeast. This was incredible because Tetrahymenaand yeast are in different kingdoms phylogenetically. They had shown that when Tetrahymenatelomeres were ligated to both ends of a plasmid, they allowed that plasmid to be grown as a linear chromosome in yeast. By removing one Tetrahymenatelomere they were able to clone a functional yeast telomere. I was using this same technique to try to capture telomere fragments from Leishmania. I enjoyed the laboratory environment and by talking to people I got a sense of what projects I found most interesting; I was intrigued by the question of how telomeres get elongated.  In the second quarter, I also took a graduate course on chromosomes taught by Liz in which students were assigned papers that they then presented to the entire class. I was assigned the Szostak and Blackburn 1982 Cellpaper that identified yeast telomeres. I was petrified, having never presented a paper in front of a large group before. I studied the paper inside and out. I was scared, but I was energized and got a thrill out of presenting that paper. I found it satisfying to convey the excitement I had about telomeres to my fellow students.  Janice Shampay, a student in Liz’s lab had recently published an important follow-up paper to the Cellpaper. They showed that Tetrahymenatelomeres had yeast sequences added to them as the linear plasmid was maintained in yeast. The excitement grew with the idea that these telomere sequences must be somehow added to chromosome ends. A previous rotation student and friend of mine, Jim Bliska, had done his first rotation in Liz’s lab. He had been testing ways to find an activity that might elongate telomeres. From what I knew about telomeres, I thought this project was exciting because it directly approached the heart of the biggest question: How are telomeres elongated?  I had to wait until after my third rotation before I could ask Liz about working with her, according to the graduate program rules. Toward the end of the 3rd rotation, I made an appointment to talk to Liz. As I went into her office I was both scared and excited. I asked her first if I could work in her lab, and second, whether I could work on the telomere elongation project. I was thrilled when she said “yes” to both. I think the conversation lasted all of a minute, but it was a very momentous minute for both of us.  **The Blackburn Lab** I joined Liz’s lab in May of 1984 and I set out to see if I could find biochemical evidence for telomere elongation in Tetrahymena. Liz had first sequenced telomeres in Tetrahymenaand she reasoned that this single celled ciliate would be a good source for a telomere elongation activity. Each cell has over 40,000 telomeres and perhaps more importantly, there is a stage of its life cycle where new telomeres are added onto fragmented chromosomes. I made extracts from Tetrahymenacells and examined whether artificial telomeres could be elongated by enzymes present in the extracts. These experiments are described in detail in the accompanying published lecture.  After about nine months of trying variations on experiments, we found our first strong evidence for telomere elongation. An 18 nucleotide telomere “seed” was elongated with a repeated sequence that was six bases long – precisely the length of the TTGGGG telomere repeat in Tetrahymena. Now we had a biochemical assay that we could use to determine if this was a new telomere elongation mechanism. We set out to critically examine whether the 6 base pattern we were seeing was indeed due to a new activity or perhaps instead was a well known polymerase fooling us. Liz and I worked very well together. We would talk most every day and each of us would assert what we thought should be done next. Often we agreed but sometimes we did not, and we would try to convince the other of our reasoning. I remember for one experiment we talked for a long time and neither of us would give up our stance. It was an impasse. The next day when I came in to the lab and we talked, we had both shifted sides. I decided to do her proposed experiment first. We both laughed that we had each convinced each other.  I learned many important lessons that first year after the initial telomerase discovery. Mostly, I learned the importance of questioning your own assumptions. We did not set out to prove we had a new enzyme, rather we imagined all the ways our own thinking could be deceiving us and allowing us to interpret our results in a way that favored our bias. I learned that getting the correct answer is more important than getting an answer you might hope for. I learned to step aside from myself and view my data through the eyes of a skeptic. We worked for a year before we convinced ourselves that the telomere terminal transferase was indeed a unique activity. The initial discovery was in December of 1984 and the paper was published in Cellin December 1985.  **Stanley Hall Cold Room – UC Berkeley** We first called the activity we identified “telomere terminal transferase” because it transferred telomere sequences onto termini, but later shortened it to “Telomerase”. My friend and fellow student Claire Wyman and I would joke around in the lab a lot. Claire pointed out telomere terminal transferase was too long and suggested various humorous names as alternatives. Names were further discussed later that night over a few beers and telomerase was one Claire had proposed initially as a joke. She thought it was funny, but Liz and I both liked it.  The next most exciting question was – where does the information for the TTGGGG repeat addition come from? I wondered if there might be an RNA component that specifies the TTGGGG sequences added. I set out to do an experiment to pre-treat the Tetrahymenaextract with either DNase or RNase or nothing and see if that affected the activity. I remember that day [Tom Cech](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1989/) was visiting Berkeley for a seminar. Tom had a long-standing interest in both telomeres and in RNA biology. Liz and I met with Tom in the morning and I told him about my idea of testing to see if the activity was RNase-sensitive. He agreed that was an interesting experiment. Throughout the day, as he was being walked around the department from appointment to appointment, Tom would stop by the lab and see how the experiment was going. I was flattered that he was so interested.  The RNase experiments indicated that activity was eliminated when RNA was degraded, implying there was an RNA component. Liz and I felt that the best way to really show that an RNA was involved was to find the actual RNA. So I went into the cold room to try to purify the enzyme. I read as many books on biochemical purifications as I could, and set out to purify telomerase. As a complete amateur, I spent an inordinate amount of time in the cold room setting up and running columns to purify telomerase. My friends would come to find me to go get coffee at Café Roma, and I would have on my puffy down jacket covered over with an extra-large white lab coat. They joked that I looked like the Pillsbury Doughboy.  The friends in Stanley Hall were a very close group. We would walk to get a latte at least once every day. We would talk science, tell jokes, tease each other and complain to each other about experiments that did not work. There were a lot of practical jokes that we played on each other. I was having trouble with experiments one afternoon and complained to Jeff that I was “bored”. So late that night Jeff filled my umbrella with home made confetti with the word boredon each piece. The next day I was leaving genetics class, it was raining so I opened my umbrella and thousands of pieces of paper fell out. I knew I had to retaliate. The next day I got into the lab very early. I went to Jeff’s lab bench; he had 40 bottles of different chemical reagents for his experiments lined up on the shelf above his bench. They were all glass bottles filled with clear liquid, I removed the labels that were taped on for every one of them (I marked each with a number underneath and kept a paper key). When Jeff came in to work in the morning, he started his experiment for the day, reached up for his TE buffer and found 40 identical unlabeled bottles. He was shocked at first, then, being clever, he saw the small numbers on the bottom and realized what I had done. He came into our lab and said “OK so where is the key?” I pretended to not know what he was talking about, but was glad when he admitted I had gotten him back. These kinds of jokes were common in Stanley Hall. Often they involved dry ice inside plastic tubes, which would burst and sounds like a bomb when placed in a metal garbage can.  We found every excuse imaginable to have parties at one of our graduate student houses. One party invitation flyer copied a Departmental memo that said “Emergency water outage-Party time” we decided this was a good reason for a time for a party at Jeff’s house. Some of our parties involved making up skits for the “follies” where we would roast our professors and fellow students. We all worked very hard and we played hard too. The creativity was not just at the lab bench, but spilled over to our daily life together at work; being creative in all aspects of our lives in the lab and out was wonderful. Spending time with people who understood me and what I was doing and who loved to laugh and play was extremely rewarding.  After four years in graduate school, my thesis committee members encouraged me to finish up and look for a post-doctoral position. I remember Jasper Rine specifically telling me it would be good to finish the thesis in four years, because I had enough material and it looked good to finish quickly, so why not try? Mike Botchan, who was on my committee, strongly encouraged me to apply for postdoctoral fellowship positions at Cold Spring Harbor Laboratory, where he had been for a number of years before coming to Berkeley. So I sent letters inquiring about positions to four people at CSH, Bruce Stillman, Yasha Gluzman, Doug Hanahan and Mike Wigler, and was asked to go there for an interview.  **Cold Spring Harbor Laboratory** I think there may have been only eight or ten people in the audience for my interview talk at CSH. I gave a talk on telomerase activity in the James library. All four lab heads with whom I had applied to work were there, as well as Jim Watson whom I had never met before. It was a cold and rainy day, and afterwards Jim Watson wanted to take me to lunch. I was both excited and terrified at lunch and did not know what to say, but he was clearly interested in telomerase. Several days after the interview when I was back in Berkeley, I got a call from Bruce Stillman, he said that he would be happy to have me as a postdoc in the lab if I wanted to come, but that there was also an opportunity to have an independent position as a Cold Spring Harbor Fellow and work on whatever I wanted. I had not heard of or applied to an independent fellowship position so I was a bit surprised. I later found that Mike Botchan from Berkeley had quietly nominated me for this without my knowing. When Bruce called, I first said that I would just work with him as a postdoc; but then I thought it over for a week and realized there were so many interesting questions I still wanted to ask about telomerase that I would love to keep working on it. So I called Bruce back and told him that I would like to accept the independent Fellow position. So I filed my thesis in November of 1987 and continued to work on trying to identify and sequence the RNA that co-purified with telomerase for a few months. January 1, 1988 I started as a Cold Spring Harbor Fellow.  My main goal in my new lab at CSHL was to clone the gene for the telomerase RNA. I had already obtained several partial sequences through direct RNA sequencing using specific RNases. I made short oligonucleotides to the regions of RNA sequence and used them to probe genomic libraries from Tetrahymena. After searching through many libraries, I found one clone where the sequence matched the partial RNA sequence AND also contained CAACCCCAA, the complement to the TTGGGG telomere sequence. I was excited and told my friends in the building about the sequence. I was very surprised to hear later at lunch in Blackford Hall that many other people knew of the result. A few hours later Bruce Stillman stopped me on the street to say he heard I got a great result. News traveled fast at CSH and people really cared about what other people were doing. It was fun to again be with people who cared about each other and who kept up with what science people around them were doing; it was a very exciting time.  Having a clone with a telomere repeat was tantalizing, but how could I show that it was required for telomerase activity? I devised a series of experiments using antisense oligonucleotides and RNase H to show that this RNA was indeed required for telomerase activity. I wrote a draft of a paper and sent it to Liz since I had initiated the sequencing efforts while working in her lab. I presented my work in Bruce Stillman’s lab meeting and he encouraged me to propose a model for how I thought the enzyme might work in the paper. This model, drawn crudely on a Macintosh SE, has stood the test of time. It turned out what I conceived of as a possible mechanism is indeed the way telomere repeats are made by copying the RNA template. I sent Liz the clone encoding the RNA component before our paper was published, and she and her student Gou-Liang Yu were able to express a telomerase RNA with a change in the template sequence in Tetrahymenaand show that change was incorporated into the telomere repeats. This was definitive evidence for the templating model proposed.  Having success in cloning telomerase soon after arriving at CSH was a great start. I soon had my first graduate student, Lea Harrington, and was rapidly promoted through the different scientific staff positions to the position of “Rolling 5”. We continued to pursue our curiosity about the function of telomerase and role of telomerase in cells that are discussed in more detail in the Nobel lecture. In 1993 I married Nathaniel Comfort, whom I met when he was the science writer in the Public Affairs office at CSHL. In 1996 our son Charles Comfort was born in Huntington, New York. Nathan completed his Ph.D. in history of science at the University at Stony Brook in 1997 and was offered a position on the faculty at George Washington University. I was concurrently offered a position in Tom Kelly’s department of Molecular Biology and Genetics at Johns Hopkins University. So when Charles was one year old, we moved to Baltimore to start new lives.  **Johns Hopkins University School of Medicine** I was very fortunate to come to Johns Hopkins to a very interactive and cohesive department. Although the institution as a whole is much bigger than CSH, the department of Molecular Biology and Genetics felt as small and homey as CSH. I was fortunate to have outstanding graduate students and postdocs come to work with me. I was able to branch out into both yeast genetics and mouse genetics and follow my interests in what happens to cells when they don’t have telomerase. I enjoy having smart people around to talk to who are excited by the work on telomeres. The different directions the lab has gone have been driven not just by my own interests but by the interests of the students in the lab. Finding something new that nobody knew before is exhilarating, and discussing ideas with students and postdocs and helping them to pursue their most interesting questions leads to new insights.  Two years after I moved to Johns Hopkins, my daughter Gwendolyn was born. Having two kids and a full time job in the lab is a challenge, but having Charles and Gwendolyn is the best thing that has ever happened to me. My lab knows that I am a mom first, and the flexibility that academic science provides makes having a career and a family possible. I can go home when needed, or to a school play in the middle of the day, then come back and finish my work-day; or work from home on the computer. The main thing is to find the time to get things done, it is not the hours at work but the overall productivity that counts. Having flexibility takes a huge amount of pressure off.  In 2002 Tom Kelly, the Department Director (the Hopkins name for Chairman) told me he was leaving Hopkins to take a position at Memorial Sloan-Kettering Cancer Center in New York. I kept the note that my assistant left on my desk that day that said “Tom Kelly wanted to talk to me” – and marked it as a Black Day; I actually cried when he told me he was leaving. Tom was an ideal director for the department. He cared about everybody and worked hard to help create the collegial environment that attracted so many top scientists. After a two-year search process, I was appointed as the Daniel Nathans Professor and Department Director for Molecular Biology and Genetics. I am extremely honored to hold the Daniel Nathans Chair, as it was Dan who created the department and established the interactive environment that Tom Kelly helped build. Dan Nathans, who died in 1999, personified thoughtfulness, caring and above all integrity, traits that we all strive to show the way that Dan did.  I know that I cannot fill the shoes of either Tom Kelly or Dan Nathans, but I try to bring my own style of leadership to the department. Being director is made easy by the terrific faculty in the department; the science is outstanding and everybody talks and cares about the other faculty. The flat structure of the department that was established early on makes it clear that everyone has a voice. Decisions are made by discussion and consensus and not in a top-down fashion. I have been able to learn about leadership in a hands-on fashion and the faculty have all helped me tremendously in that.  **Mentors, friends and lessons** One of the lessons I have learned in the different stages of my career is that science is not done alone. It is through talking with others and sharing that progress is made. Work done today, of course, builds on the past work of many others, but in addition, experiments are often suggested by friends and colleagues either directly or indirectly. The ideas generated are not always the result of one person’s thoughts but of the interaction between people; new ideas quickly become part of collective consciousness. This is how science moves forward and we generate new knowledge.  I am grateful to the many scientists who have influenced and helped me in my journey from Davis to Baltimore: Bea Sweeney, Michel Robert, Kevin Sullivan, David Asai, Les Wilson, Elizabeth Blackburn, Jasper Rine, Mike Botchan, Bruce Stillman, Rich Roberts, Dan Nathans, Tom Kelly. These colleagues and many others have helped me move from one stage to the next and taught me many essential lessons along the way. I would not have been able to do the science that I have done without the students, postdocs and wonderful technicians who brought their energy and great ideas to the lab. Finally, the close friends I have made in Davis, Berkeley, CSHL and Baltimore are my constant support group. I value them above all else. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0536=EB  [Carol Greider] Hello  [Adam Smith] Oh good morning. May I speak to Carol Greider please?  [CG] Yes, speaking.  [AS] Oh, hello, this is Adam Smith, calling from the Nobel Foundation website.  [CG] Yes, they said that you would be calling me.  [AS] Yes, well, many, many congratulations of course.  [CG] Well, thank you very much.  [AS] I imagine you might have been asleep when the call came from Stockholm?  [CG] Well, actually I usually wake up a little bit early, so I was actually doing the laundry when the call came.  [AS] Did you carry on doing the laundry after the call came?  [CG] Ah, no! I decided we could do that later.  [AS] You’ve been the recipient of quite a few prizes in recent years, so I imagine there was always the suspicion that this might be coming  [CG] I mean you can’t really ever expect something. I mean I had no expectation but, you know, people had certainly had, you know said that there was information out in the press about predications and things like that. But, I don’t really follow those sorts of things very much.  [AS] No, of course, one can’t. You were awarded the Nobel Prize for your discovery of telomerase together with Elizabeth Blackburn when you were a graduate student in her lab. And, it seems, I suppose, to those who might be choosing their graduate projects that you made an absolutely dream choice. It was the perfect one. What attracted you to it?  [CG] Oh, it was just the most interesting question at the time. You know, I had been working in the lab before I chose a project and, it just seemed like the unanswered question, and so why not, you know, go for the most interesting thing that there is to work on. It really was, you know, curiosity that just drove me there.  [AS] Was it a difficult question to answer?  [CG] It was really unknown. It wasn’t clear whether it was going to be difficult or not. We basically had to make things up as we went along because there had been no previous, you know, examples of such an unknown kind of polymerase. So, we took examples from people that had worked on other kinds of polymerases and made our best creative guesses about what kind of experiments to do. But it wasn’t clear whether it would be hard or not. It was just, you know, diving into the unknown.  [AS] And, I gather that the first evidence for the activity that was later shown to be telomerase came Christmas day, 1984. Was it normal that you would work every day of the year?  [CG]  Most of the time. I was just very excited about what I was doing at the time. We had kind of been chasing potential activities and … so I had actually done the experiment several days before but then it takes a few days for the autoradiograph to develop. So I went in on Christmas day just to see what was there.  [AS] Perhaps there’s a lesson there for others wanting to emulate you that.  [CG] I wouldn’t necessarily say that it’s a requirement to be out on Christmas day. I was just curious about that particular experiment at that time. I wouldn’t necessarily say that it’s a, you know … that one shouldn’t take breaks and take Christmas off. But, if you’re excited about something and you want to go see, then go ahead and do it.  [AS] As you mentioned, telomerase, was a novel sort of DNA-synthesizing enzyme; it’s a reverse transcriptase, containing both protein and RNA. So, presumably, it took a long time and is taking a long time to untangle it. Do we yet understand it?  [CG] I think we understand a lot about telomerase. There are, still large unanswered questions. Some of the detailed biochemistry isn’t yet entirely worked out, about how the enzyme actually uses a small template reiteratively and, probably more importantly, exactly how it’s regulated in elongating the telomere. Very clearly the establishment of length equilibrium in cells so that telomeres can maintain their length is really critical. And, both the level of telomerase as well as its, regulation by other proteins and modifications clearly plays a role in establishing that equilibrium. And, given the recent, exciting work showing telomerase levels involved in human genetic disease, I think understanding that length equilibrium is going to be really paramount.  [AS] That’s interesting because, yes, I suppose one’s always focused when talking in the sort of popular way about telomeres on maintaining them at a sufficient length to protect the chromosome, but I suppose there’s a balance. You can’t get too long otherwise it becomes damaging also.  [CG] Precisely. So the cell goes to a lot of trouble to establish an equilibrium and regulate that very tightly, so that telomeres are neither too long nor too short. And, how, that regulation comes about really is going to be questioned for the next several years. We know that telomerase is the enzyme that is needed to put the repeats on. But, there are many other factors that go into the establishment of the equilibrium length.  [AS] Right, right. And, one of the things that’s come out of your laboratory with these telomerase null mice. Mice that are born without any telomerase.  [CG] Yes.  [AS] And, yet they are born and they live. Is that saying that telomerase’s role is, again, more complicated than …  [CG]  It’s really what we’ve been able to show is that what really matters is the telomere length. So, when a telomere gets short, that’s when either senescence or apoptosis is triggered. So, short telomeres are the things that are really critical and will cause disease as well as problems with tissue turnover. The telomerase just needs to maintain the telomere length equilibrium, as I said, to be able to keep the telomeres from getting short. So, in the telomerase null mice, in the first few generations, the telomeres are still long. So, it takes several generations of cell division before the telomeres get short. So, it’s not the telomerase enzyme per se that causes these phenotypes that we see in the mice but rather it’s the short telomeres.  [AS] Right, right. I wanted to ask about women in telomere research because it’s been commented before that it’s a field where, happily a large number of women have contributed. Is there something particular about the subject, do you think, that has made that happen?  [CG] I don’t think it’s necessarily about the subject. I think it’s one of those examples of a jackpot effect, where you have somebody that trains a lot of women, and then there’s a slight gravitation of women to work in the labs of other women. I don’t think it’s a large effect but a small effect. And so, because the founding group was women, it tends to then, you know, sort of grow out as a jackpot effect. So then, Joe Gall, with whom Liz Blackburn worked was extremely supportive of the women that worked in his lab and he trained a number of telomere biologists – Liz and Ginger Zakian and others. And so, I really think that the fact that he sort of founded a group of strong women that then went on and had other women in their labs was most likely the reason that there was so many in the telomere field.  [AS] Right, right, so …  [CG] It’s a founder effect, sort of.  [AS] Exactly, from small seeds, yes. And is it something that you continue to propagate? You said that there is a sort of slight gravitation. Is it something that one has to actively promote, do you think?  [CG] I think actively promoting women in science is very important because the data has certainly shown that there has been an under-representation and I think that the things that contribute to that are very many social … subtle, social kinds of things. So, yes, I think that one should definitely be cognizant of that and be aware of it.  [AS] Ok, well, thank you very much indeed. I was just going to finish by asking whether you have any idea how today’s going to pan out now?  [CG] I don’t! I heard that you were going to call and then I’m supposed to call the Johns Hopkins Press Office. They said if I got a call, I should call them. But, I was waiting to talk to you first before everything starts happening.  [AS] Well, thank you very much. And, best of luck with it all and, when you come to Stockholm, we’ll have a chance to speak at greater length so I very much look forward to that.  [CG] Thank you very much.  [AS] Thank you, bye, bye.  [AS] Bye. |
| Interview |  |
| Q13 | Your Nobel Prize is of course associated with a couple of interesting numbers. This is the hundredth time, I am sure you’ve heard, that the Nobel Prize in Physiology or Medicine has been awarded and also this is the first time ever that two women have been co-recipients of the same Nobel Prize in the sciences, and telomere research in general is one where the proportion of women is more normal, if you like, its more representable of the maked up society. Is there a reason for that, do you think? |
|  | Elizabeth Blackburn: I think we should turn it around and ask why everybody else is so aberrant, seriously, because I think that actually might frame the question a little bit more instructively as to why things are not, as you said, the biological or societal representation of women. We can point to various sorts of things such as the fact that some of who have been in the field are females, but actually there are plenty of men in the field as well and I think what stands out is that the numbers are a little different, but certainly, having examples of women who have done well in science – we all know that kind of example does make it more encouraging for others, younger people, to visualize themselves being successful in science – and so I think there has been a kind of perpetuating effect there, but I do like to think that this is the normal way it can be and perhaps we should think about, well, how do we make this more normal in other fields of science. |
| Q13 | We will pick up your question, why is it aberrant in other fields do you think? |
|  | Elizabeth Blackburn: Somebody else can take that one.Jack Szostak: There is obviously a lot of historical reasons, bias, familiar /- – -/ that takes a long time to get rid of and a lot of good role models to get rid of. |
| Q21 | Have you found it difficult being a woman in science? |
|  | Carol Greider: No, I have not found it difficult, but I think that one of the things that I have always done is sort of put blinders on and done what I wanted to do, but it was when I then started to get to the higher levels in ranks that I could then look back and see what the data was. At graduate school there were 50% women, at graduate school there was postdoc fellows usually 50% and then as you get higher and higher up the representation is lower. I didn’t feel like I personally had experienced any big obstacles, I am a scientist, I can look at the data and see that there is something that is not quite representative, as one moves up the higher ranks. I think that role models are one good thing, that the more people there are in the higher ranks the more the younger people can look up and say Yes, there is something that I can do, and it doesn’t seem like an impossible task. |
| Q4 | Is there more that needs to be done than role models? I mean, would it naturally change, or does it have to be aggressively tackled do you think? |
|  | Elizabeth Blackburn: I think aggressive tackling is good. Look at something like smoking, it took very aggressive actions to make smoking less of a wide-spread practice and certain amount of imposition of things. I don’t think it will happen organically completely from within. When you talk to colleagues, individually they are very well disposed to the idea that they see the value of having more women and more diverse groups of people’s insights, because like any enterprise the more diverse sorts of backgrounds come into it, the better way the problems can be solved. I think there is not a lack of good will among a lot of people to do this. It is a question of how do you do it, and then I am sure a mixture of various sorts of strategies will be hopeful, not least education and not least just seeing a woman there sort of makes it more possible. I think we are very visual species, and you look at something and that’s evidence in front of you, that you seem to think Oh, that’s me. If you were a young woman, I could do this.I think further that we have to make the career structure a little bit more flexible because there has been a one size fits all model for careers in science which have been very much that based on a man having a supportive wife or partner or something to take care of life and family and that’s been something that has been daunting, we find, to young women. I personally found it very daunting as a young woman into the career structure, not the science, but the career structure, and so I think we can be much more imaginative about how we make sure women don’t leave sciences during the time when they have preoccupations with family or with elderly parents who need long term care, the sort of things that women often do. |
| Q4 | Yes, that requires one to have really quite a strong support structure within science. |
|  | Jack Szostak: A lot more broadly than that, there are a lot of things done here in Sweden that would be kind of chocking in the United States.Elizabeth Blackburn: Yes, absolutely!Carol Greider: A support in terms of general /- – -/ support.Elizabeth Blackburn: Yes, because I think the seeking point for many women, at least in my personal experience from what I see is, they say “I just can’t see being a scientist and I also do want to have a life” and I think that that is something that we shouldn’t say to young people. “Oh no, you can’t have a life and be a scientist” and yet that is the perception that they have. I think as senior scientists we could do a lot more to try to think of active ways in which this one kind of career structure model that we have could be thought of more imaginatively. And I just know examples of women who have gone part-time as their families and other needs have happened, and then they go back in full time and they just come roaring back and have done really well, and they are not all in the United States unfortunately, which again tells us something about the United States situation and support. |
| Q23 | I think it’s your own phrase … I have heard you say it. They were known in the 1930s, it was known that they had an important protective role of the chromosomes, but people didn’t know what they were. It was you in the late 1970s that sorted out the molecular nature. |
|  | Elizabeth Blackburn: Began to, its still an on-going saga, none of us are out of jobs yet. That’s right. I think it was so wonderful the science that was done /- – -/ genetically in which such deductions were made about what’s going on with chromosomes and their inheritance. Now we look back at it and we say they didn’t know it was DNA and yet the thinking about what was observed, and I particularly enjoyed [McClintock](https://www.nobelprize.org/prizes/medicine/1983/mcclintock/facts/)’s work because that’s what I got more familiar with. It was so elegant and there are so many treasures in there, of insights into what turns out to be going on in meiosis and as it turned out with what’s going on with telomeres, although her fame more broadly was, I think, perhaps more for jumping genes for many years. What she said, something written in 1931, about a telomere being distinctive, and she didn’t call it a telomere, was so clear and I think very important and it was just lack of the research tools of the time.Jack Szostak: Molecular understanding was there …Elizabeth Blackburn: Right they had microscopes, they had genes, phenotypes, they had really wonderful other kinds of thinking, but they were not playing with the same sort of toys in the lab that we have played with. |
| Q11 | Ahead of time … Then you two met at this Gordon conference in 1980 and it’s sort of the way science is supposed to happen, two people meet each other, have an idea, do an experiment and prove something wonderful. |
|  | Elizabeth Blackburn: And then … nobody pays for it, but they do pay for it, no they pay for a broad sort of setting in which you can go and do experiments and explore and ask questions without somebody saying, Oh, is this going to be useful for this year’s economy or for somebody’s /- – -/ medicine. I think that is really important, I mean we thought that was something … we didn’t really think about it at the time, it was such a given that you can do an experiment with broad funding that is never going to be wasted. Scientists don’t throw away money, they work very hard and giving scientists money to ask questions that hadn’t been planned, it’s really important.Jack Szostak: That meeting, or that kind of meeting, it’s great for bringing people together, who are working on different things.Elizabeth Blackburn: These meetings are famous for …Carol Greider: You had met each other before?Jack Szostak: No, that’s how we met. After your talk I came up …Elizabeth Blackburn: We walked across this lawn and just talked and talked.Jack Szostak: Because I was working on broken DNA molecules’ ends and then Liz had these ends that behaved completely differently, and it was just a contrast that was kind of chocking so we had to talk about it and see what we could do to figure out what was going on.Carol Greider: So Liz, you gave your talk first?Elizabeth Blackburn: Yes. |
| Q11 | It was after the talk the two of you teamed up? |
|  | Elizabeth Blackburn: Yes, I talked about what we knew about the molecular nature of these DNA molecules. You know the ends, you could get your hands physically on. |
| Q11 | We will turn to the experiment in a minute, but I just want to ask you in general about choosing companions in science, because it is so important to get the right people to work with. Is there some, and of course one works with lots of different people throughout one’s career, but are there some criteria that you applied choosing companions to work out with? |
|  | Jack Szostak: I think it’s mostly a matter of, you know, is there an interesting experiment that actually can get done?Elizabeth Blackburn: And then if you have the luxury of choice, yes, you do want to work with people who really do rigorous science, I think, and that can be very different kinds of science, can be done with rigour, but I think that’s important as one collaborates with people outside new areas. Jack and I, we were really much in the same sort of area, it was a molecular genetic tradition, but when you collaborate even further out, now you don’t have the deep expertise, then I think you have to have a real respect for that person’s quality of their research.Jack Szostak: And you also need to have someone who is fun to talk to and you can exchange ideas with, each way. Some people are better at that than others. More fun to work with.Elizabeth Blackburn: But you are right, if the scientist is really exciting you will make it happen.Jack Szostak: You will find a way. |
| Q26 | And when you are picking companions who don’t have a track record, students that come in into the lab, what do you look for in them? |
|  | Carol Greider: Really, it’s just the excitement of what they are doing and they simply need to communicate that excitement back and forth and I think if people really are interested and care, just interacting with them over a period of a few weeks, one can tell whether or not there is a compatible set of interest that are there. So usually there is an opportunity to do that when students may be coming into the lab, you have a chance to get to know them a little bit and see where the capabilities are on both sides. It’s not just a mentor choosing a student for a very … there is opportunities for students to go around and choose mentors and make sure that they are compatible with them as well, and I think both of those things are important. |
| Q12 | I was going to go on to ask what do you think are the important characteristics of being a mentor, what do you try and provide for the student? |
|  | Carol Greider: Again, it’s all about the science and it’s about being a /- – -/, sit down and have a conversation and really understand that person’s interest. Some problems are very interesting, but somebody may approach it from a particular angle and somebody else approach it from a different angle and then when those two people talk it may not be as easy to understand, but a third angle, there may be a shared understanding like, you know, languages, if somebody speaks a language that is close to a language, if somebody speaks Italian and Spanish, maybe they will understand each other better than somebody speaking some other languages. So I think that that is true in terms of people in their interpersonal interactions as well, so finding those compatibilities is just a matter of spending some time together and talking about their science. |
| Q12 | I don’t know if you want to add anything? |
|  | Elizabeth Blackburn: And finding their strengths too, which is something I learned not by being clever, but somebody once said to me that Shirley Tilghman, who is now the President of Princeton, but she is a very accomplished molecular geneticist, and somebody who knew her very well in her science days said she always is very good finding what people are good at and then making sure that gets used very well. It’s not an altruistic thing necessarily, she is making sure they thrive and do the best in science and I thought that was a really good hint and I try and look for that as well because some people have real strengths in some areas, some will ask all these questions all the time and they will never do this experiment, but its also important that they are doing that. Others will say, Yes, I will do the experiment but also be critical. Carol was actually somebody in the latter, she said, “I will do the experiment” and be very smart and critical at the same time. But other people will question, question, question, and if you can make use of that and say, this is really good that someone’s bringing into their really critical thinking and not say, Well, I really want you to do it this way and stopping it, and think, Ah this person actually is smart and they probably got some good reasons for what they are thinking about and so try and use what strengths you feel you discern in people is important.Jack Szostak: I like to find people who are pretty independent and have some initiative and the best students are the ones where I can tell them that’s never going to work and then they go and do it and show that it does work.Elizabeth Blackburn: My problem is that I always think that it is going to work, and they are the ones who say, Well actually …. It goes both ways and you have to have both going on and you have to have the sort of Let’s try it, and things that you really have reasoned through very well, that sometimes is the route to doing something new as you reason something very well and you do that and then something new comes of that too, so both ways in biology really can work and you can’t always predict which is going to be the formula. |
| Q12 | Presumably it often takes quite a long time to find out what people are good at, because there must be a lot of graduate students who start and then find they don’t hit the ground running, it takes time to get going. That can be quite a dissolution at time, so it’s important for people to understand it can take time for one to work out what one should be doing. |
|  | Elizabeth Blackburn: I think people’s quality of thinking that emerges relatively easily I think, now as you say what unfolds in the experiment can of course be very slow because you know by definition you are doing things that are difficult. If they are easy someone would have done them, and so that’s I think the hard, unpredictable road for graduate students. Back to your questions of mentoring, that’s were you have to realize that that’s going on and that people will go through periods in science as we all have done, when you’re just seeming to fail all the time and the experiments don’t work, sometimes for reasons that are boring, but sometimes for reasons that are significant. You have to be able to fail a lot of the time, scientists just have to be terrific at getting slapped back on the face by nature all the time.Carol Greider: I have told my students and I am famous in the lab for saying “That’s why they call it research” because somebody would come into my office and we will be talking about an experiment with a great result and I say “Great, go and do it again!” Somebody would come into my office and say “Nothing worked at all, nothing worked at all”. “Great, go and try it again!” And I say that’s why it is called re-search, you always have to do it again.Elizabeth Blackburn: I realized the opposite because somebody said it isn’t research because somebody already searched for the /- – -/ rediscovering it or something. I like yours better.Carol Greider: You have to repeat that good experiment just like you have to try again at the failed experiment. |
| Q23 | Yes, Carol’s is less depressing, yes. So back to the experiment, together you demonstrated that telomeres from one species could protect DNA from an entirely unrelated species and thus the mechanism of the telomere protection was more fundamental than perhaps one might have though initially. And that result was very clear, you understood that immediately so where you aware of what an important piece of information you had just discovered at the time? |
|  | Jack Szostak: I think we knew that it was going to open up a lot of new experiments, because we could use all the tools available in yeast as well as you could do in *Tetrahymena* and then in other organisms. So we knew that it was going to allow more progress.Elizabeth Blackburn: And I think it also felt somewhat fundamental in the sense … you know molecular biology was very dominated by there will be universal solutions for things because we were so influenced by the genetic code, DNA, everything was very universal and so when you saw something crossing lines of phylogenetic divisions … Don’t you think there was a bit of a sense when we found the sequences looked similar and they looked like there is something fairly deeply universal in the eucariotic world.Jack Szostak: That is an important point, because it was already clear that in bacteria and many viruses there were lots of different solutions, so it didn’t have to turn out to be universal.Elizabeth Blackburn: Yes, it was completely nonintuitive what would go on in terms of actually more the replication problem in terms of … and protection too. |
| Q23 | And you also observed that the telomeres in yeast were lengthening and that something had to be causing that lengthening and that’s when you come into the story, because you set out to find the activity that was causing the lengthening. |
|  | Elizabeth Blackburn: By chemically speaking yes, because I thought that was … I am sort of a biochemist, somewhat by training I suppose and I had gone through biochemistry and then molecular biology and so it felt natural to try and say this is very direct, you know, reactions take place in real time sort of more or less in front of your eyes in sort of, you know, biochemical way.Jack Szostak: You had the right organism for doing the right chemistry.Elizabeth Blackburn: And the organism was right and it turned out … There was a biology of the organism that set this burst of telomere synthesis that takes place and there was an abundance, relatively speaking, of telomeres and so that all pointed to, well, this is a good system to try and answer questions and I had been trained in the lab of Joe Gall, which is where I actually did the sequencing of the telomeric ends, as we now call them, the DNA ends of the mini-chromosomes in the ciliated protozoans. Joe had very much always said that you should find this system in which you would answer the question best, what I think is a fundamental idea. Things will be pretty conserved throughout much of life and so this idea that find the good system was very much in my mind so I started out doing a little out of foray into things, got ten years, felt brave and Carol joined the lab and felt really brave. |
| Q40 | She was one of your unusual students who took one of your ideas and said, Yes I can do that and off she went. |
|  | Elizabeth Blackburn: I had actually offered it to a postdoc who turned it down: Very nice Liz, but I think I will do something different. It was very politely, but. |
| Q23 | And you got this now famous Christmas present in 1984, the first indication that you got your hands on the activity that was causing the lengthening of the telomeres. |
|  | Carol Greider: Yes, I was doing experiments, it was about nine months of trying various things. Liz and Jack had proposed that there may be something that would lengthen the telomeres and so, not knowing exactly what that is or what the properties were. We would just try different things and Liz and I would talk to each other every day or so and say, Okay let’s try this, like cooking, you add some ingredients and you taste it and that doesn’t taste so good so you add a little bit more salt. After trying various things there was one particular change that I made in the experiment. I was just interested in … It was an exciting time to do an experiment and then a few days later, it would take several days for the experiment to sit on an autoradiograph and so I went back in on Christmas day to develop the results of the experiment that I had done several days before and that’s when I saw this very clear repeating pattern on the autoradiograph that just looked like a six-base repeating pattern that you would expect of a telomere repeat.That first instinct is like, Wow, this might really be what we think, of course, then after the excitement there is the, Well, are we being fooled? And so then has to follow all of the ways where we would then be our own worst critics in a sense. It’s like how could we be being fooled by this? Maybe it’s really some normal polymerase that is copying something that is a repetitive sequence in the extract. So that is were the real work of the self criticism is very important and so that is why the discovery was Christmas 1984, but the paper was published in December -85.Elizabeth Blackburn: It just shows how fast these things go actually. |
| Q7 | It is an obvious point, but obviously you were enjoying yourself tremendously and going in on Christmas morning was just something that was natural and the enjoyment of what you do is key, is absolutely the essence of it. Its not work, its enjoyable, I presume. |
|  | Elizabeth Blackburn: That’s right, it’s the best kept secret in science. We never tell people what fun we are having and maybe we are a little afraid because somehow society will frown upon the idea that you actually really … And yet at serious play, but it’s completely the element and the resources, I wonder what, because often the trajectory of the experiments, you find out something the next day because something has rather been incubating or autoradiograms exposing, things like this. There is often this thing where you would leave something and the next day come in and I have just been driving to Berkeley and I am driving up university avenue, really impatient because the traffic would get very slow off the free way, and you knew there would be something at the end of that university avenue when you got out of the car and went into the lab.Carol Greider: That’s why I lived up on the hill and I came down on my bike.Elizabeth Blackburn: Yes, you came down on your bike fast, that’s right. And you had a Volkswagen once. At least you were on the bike, that’s good. But I think that’s really an important point because many young people are saying, Oh you know science is so hard, its so true, and we all complain bitterly because we just take completely for granted the fact that we are having such a good time so we sort of have the luxury to complain about the other stuff. But it’s a really good career and very autonomous, nobody tells us what to do in terms of our choice of research and when you think about how many jobs that’s true for it’s a mince and its not as if scientists waste money. We really are so driven, we want to find things.Carol Greider: I remember when I was a graduate student and it was the first time that I was sort of on my own and supporting myself, and I was like, Wow, they are going to pay me to come in and play everyday ,and I was being paid now what would now be you know, but it was great and I thought Wow, this is just amazing. Maybe if I just keep it up, and it’s worked so far.Elizabeth Blackburn: No, it’s true, as an Assistant Professor you’re suddenly given this playground. They really trust me to do this – that was my feeling. And Berkeley was very /- – -/ actually and they sort of really trust you to go out and … I think now mentorship in young peoples careers is much more thoughtfully done and maybe that’s not always good because we had huge freedom just as Assistant Professors, right?Jack Szostak: We just had the resources to go.Elizabeth Blackburn: Yes, you have to gather the resources, but then you work really hard because you are just driven. |
| Q7 | Perhaps it’s too big a question to ask whether its changing for the good or for the bad. Its presumably going in both directions in the same time. |
|  | Elizabeth Blackburn: I think those who love science are still driven in the same way.Jack Szostak: I don’t know, it might be, it probably takes more time and effort to raise the money to support lab. There are more frustrations there, maybe its more bureaucratic than it use to be, but if you really want to do it, you can still do it and then you have the luxury of doing whatever experiments you think are the most interesting. |
| Q23 | Okay, so back to the enzyme, the enzyme you discovered was unusual, it was a reverse transcriptase with extra protein and RNA and it took some time to sort all that out. When you did sort it out, it turned out that it solved the end replication problem because this problem had been laying around for a while unsolved of how DNA polymerase, well the fact that DNA polymerase could not, on its own, synthesize both chains of DNA to the end. And it seems strange that that problem had been there without anybody being able to solve it for quite a long time. DNA polymerase was revealed in 1958 by [Kornberg](https://www.nobelprize.org/prizes/chemistry/2006/kornberg/facts/) and it was pointed out in what 1970 or so, 1972 by [Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/) and others, there was this problem. And it was the late 80s or mid 80s the solution came. |
|  | Carol Greider: There were solutions in other organisms as Jack had alluded to, that various viruses … what wasn’t known was how the eucariotic chromosomes solved the problem and that did wait for the sequences, until Liz found the sequences you couldn’t really ask the question until you had the actual molecular details.Elizabeth Blackburn: And there was some peculiarities about the sequences, there were different numbers of repeats of the ends of different molecules in a population of molecules. This wasn’t like viruses although there are some viruses in which they do have recombination at the ends and they have some end repeats as well, so there were solutions that looked very plausible, that the viruses of bacteria had already evolved to have. It was really various lines of evidence that sort of said, Aha, this does not seem to be the kind of solution that new eucariots have.Jack Szostak: But if you go back and read all our early papers we were through a lot of models, they were mostly based on recombination-like mechanisms and we held on to those to the bitter end until the sequences said that can’t possibility be.Elizabeth Blackburn: Because people could draw beautiful diagrams, right, and the literature was, you did …, I don’t know how to draw beautiful ones. No but there was definitely some ideas out there and some of them have turned out to be quite applicable actually to some viruses and stuff like that, so the ideas were not completely useless.Carol Greider: … applicable to telomerase in theory, as well.Elizabeth Blackburn: Yes!Jack Szostak: Yes, that’s right.Carol Greider: There really were two answers, it’s just that one turned out to be a little bit more dominant then the other.Elizabeth Blackburn: A lot more dominant.Carol Greider: A lot more dominant, yes!Elizabeth Blackburn: As almost universal eucariots, with exceptions, and exceptions are always instructive, that is sort of the richness of the question because there is such a lot that goes on in what seems very simple, but technically a different chromosome, it sounds like you just stick a fortress around and that’s okay, but its much more interesting and dynamic than one had thought, which again makes it fascinating. |
| Q38 | It is fascinating, is it interesting because one tends to tell the story of science in retrospect as being a problem followed by a solution and its not quite that, is it? Its much more complicated. |
|  | Elizabeth Blackburn: And often observations come and then they are what you expect and then you start thinking about them and what they might mean and then realize, Yes, that might be providing a solution to something. You know it doesn’t happen in …Carol Greider: But there are also possible solutions that aren’t correct, or pursue things, that’s not how they found out, that’s not how it works and you go back and pursue a different angle and what you end up hearing about historically is those things that were correct, so it seems like a linear path when actually it was a branch in a tree of which were interesting ideas. They just didn’t turn out to be how it actually worked.Elizabeth Blackburn: Yes! Or at least not in that situation.Carol Greider: Yes, that particular situation.Jack Szostak: And also you get a solution to say the problem that you were thinking very originally, but once you have that solution you realize, Oh, now there is three other problems you hadn’t even thought of before and so it goes. And that is really true in the case of like human telomeres where the biochemistry is unbelievably complicated.Elizabeth Blackburn: And yet there is an inevitability to the complexity because people say, Well, if you want a very robust sort of system it has to be inherently complex and so suddenly it makes sense in a way that we didn’t think of. We really simplified the question where we just said, we are just going to think about the DNA and the enzyme that does it and just so, you have to do that, I think, up to a point, you have to take away the irrelevancy, but always knowing that it is taking place in a cell, an incredibly complex entity which is a cell inside an incredibly complex identity which is, in our case a human, and yet you can take these things and sort of push them up to a point and then you have to realize when you have to take the blinders off, that’s the key. But again, the inherent complexity of it, its not like a curse, its sort of like, This is the way it is, because the really interesting reasons why systems have to be that way and yet we have to, on the other hand, sort of reject the complexity at certain stages in the research. |
| Q37 | 20 years on you are still working on telomeres and telomerase and sorting out the system and one thing that … Oh yes, I am coming to Jack, I’m coming back to that. One aspect that is growing up is the therapeutic implications of the fact that telomere shortening was seen to be associated with the disease states and indeed the maintenance of telomere length in both directions seems to be important, maintained equilibrium is important. What do you feel are the potential therapeutic benefits of studying telomerase and telomeres? |
|  | Elizabeth Blackburn: It is usually divided into two general categories, one is the rather hyperactive telomerase that characterizes the great majority of human cancers, on the other hand the telomerase that is presents in much more regulated form in the natural cells of the body. The normal cells, the telomerase is present in much more regulated form in normal cells of the body and various indications, such as the associations you mentioned of short telomeres with many disease states or risks of it that’s intriguing this genetic data in cases of insufficient telomerase action which says that clearly is not good for humans to not have enough telomerase in their normal cells that have to replenish to decades of adult life if we are fortune enough to move past our re-productive years and we are looking at old age, we are interested in what our health is like for that. So understanding what’s going on in cells at this fundamental level, I think you really do understand this, just to understand what’s going on in the trajectory of humans as we age, because all of the social and other settings are now letting us age, we have this sort of unexpected biological reality to live with, so we are understanding that first of all.Now, are there quick-fixers magic pills? Not tomorrow, but maybe there is interesting things that could keep telomerase a little more active, but you have to be careful and I like to think it’s like aspirin, you take two aspirins – good – take a bottle, that’s bad. Clearly any measure would have to be carefully thought through how you would, if you want to keep telomere maintenance better, not to push it too far, because too much telomerase can help cancer cells, but I mean, really a lot to much. Then the question of course is can you exploit the high telomerase in cancer cells to selectively target cancer cells and there is beginning efforts in industry to do very early stages, to look at these kinds of things. But I think just understanding what’s going on is actually really important in understanding human ageing.Carol Greider: And it’s not just telomerase, because one of the things that we have learned in the research over the years is really that’s the short telomeres that cause the end effect and as Jack has mentioned, any time you ask a question and you find out the answer there is many more other questions to ask. There are various regulatory mechanisms that allow the telomere length to be maintained at a certain equilibrium and telomeres is essential to provide the raw material to do that, but both the telomere is regulated as well as the proteins that are on the telomeres, that the telomeres has to interact with. I think that really understanding those details of all of the components and the complexity that goes in to the regulation will tell us a lot about these diseases, these age related degenerated diseases that may not be just telomerase related but they may be a number of other genes that one can look at that may be associated with these degenerated diseases that aren’t directly the telomerase, so there is a lot of interesting avenues to pursue still, to really understand the different directions these diseases may come from. |
| Q41 | Because there was a great deal of therapeutic excitement about telomerase and telomeres early on and there still is. Was there an initial kind of pressure on you suddenly, that everybody was getting excited about the potential? Does it make life difficult if people’s expectations are a little bit too elevated early on? |
|  | Elizabeth Blackburn: I work in the basic science area, so I felt immune from that.Carol Greider: It’s all the companies that have to worry about that kind of expectations because we never really said as scientists that there was going to be that kind of therapy to come in tomorrow because we didn’t have the vested interest to be doing that.Elizabeth Blackburn: I think it is good to have these avenues explored for sure and I think that the fact that it hasn’t gone all that fast is actually not to do with the science or other sorts of things. In the meantime it’s really important to try and understand what is going on because any therapeutic is going to be all the better for having a better sense of what underlies the usefulness and where its danger points might be. It’s not clear how we think about these issues of long term diseases that affect huge numbers of people, you don’t necessarily put everybody on statins, that’s a common thing, but perhaps that equivalent isn’t necessarily the best way to go either, although we tend to be a very ‘take a pill’ oriented society and nothing wrong with that, I mean. I am all for western medicine, believe me, but I am just saying that we don’t want to limit our thinking I think to that …Jack Szostak: And jump into something too quick and not recognize a problem.Elizabeth Blackburn: Exactly, that’s right. |
| Q43 | I wanted to end just by dealing with these questions of staying with your subject or not. You two have stayed with the subject … |
|  | Carol Greider: That’s debatable, the subject really has changed continuously |
| Q43 | I am sorry, the subject expands… |
|  | Carol Greider: Yes, I was a biochemist you know and now I am working on recombination and human disease and various other things.Elizabeth Blackburn: I work with clinicians on chronic psychological stress, but the point is I am not the expert. I bring my expertise and they bring theirs, so it stays very fresh by keeping one’s expertise that you really have. Now interfacing with other expertise’s so it’s actually a very broad topic. Anything that says our cells are going to be able to keep replenishing got a lot of broad implications even though we are focused on one part of it. |
| Q45 | Maybe I will discover my questions completely redundant, but let’s say you two are at least following the questioning in the same general vein and yes, it’s taking you to new places. You, on the other hand, have seemed to jump from one question to another, but there is almost a clear break between one question and the next and they seem from the outside the two different ways to do science. One is to say, There is a problem, I will work on it for a while and then I will look for another problem, actively go and find a different problem. Would that be fair to say? |
|  | Jack Szostak: I think you could find lots of examples of people who you know have one system and they use it to address lots of different questions and that can be extremely productive and then there are other people who just like to find interesting questions in different areas and go for it. |
| Q45 | But what I was going to ask was what for you is the attraction of jumping from question to question. |
|  | Jack Szostak: Well its fun to think about new things, get into an area where you don’t really know very much so you don’t have to be fooled by the preconceptions that might dominate the field so you might have a chance of making a contribution in a different way. So that is part of the attraction. |
| Q45 | Is there also an attraction in going to less populated places? |
|  | Jack Szostak: For me, I don’t like to be working in an area where there are a lot of other people who are going to do the same experiment at the same time or a few months later. I find it more fun to be doing something that is probably unique.Elizabeth Blackburn: And that’s what telomeres were initially to. Nobody was asking these questions and it is a the most fun way to do science actually. I agree with you.Jack Szostak: In the mid or late 1980s I think the implications of all the telomere work were becoming clear and it was I think clear that a lot of people would be going into that field and so I think that helped to make me look around for other areas and all the stuff about ribozymes was very new and exciting and I was very surprised that there were very few people going into that area so I thought that we might …Carol Greider: You had already got the Nobel Prize by that time?Jack Szostak: That was 1989 and we started working on it in actually -85.Elizabeth Blackburn: And how life begins, I mean that’s a pretty important question.Jack Szostak: It’s a lot of questions when you start to break it into pieces, it’s a lot of interesting questions, so that has come to dominate what we do today. |
| ID | 0537 |
| Biographical | I greatly enjoy reading the biographies of scientists, and when doing so I always hope to learn the secrets of their success. Alas, those secrets generally remain elusive. Now that I find myself in the surprising situation of having to write my own biography, and thus to reflect on my career, I find the same mystery. I do not know why I have always been fascinated by science, or why I have been driven by the intense desire to make some original contribution. And although I have had some degree of success as a scientist, it is hard to say precisely why. Nevertheless, I have attempted to identify some of the incidents and decisions that helped or hindered me at various times, in the hope that these anecdotes might be helpful to those embarking on a scientific career.I have generally sought to work on questions that I thought were both interesting and approachable, yet not too widely appreciated. To struggle to make discoveries that would be made by others a short time later seems futile to me. This, coupled with a distaste for direct competition, attracts me to areas of science that are less densely populated. On multiple occasions, I have been led into these new areas by talking to people working in fields quite different from mine. The confluence of ideas from distinct fields seems to create a kind of intellectual turbulence that is both exciting and productive.My knowledge of the details of my family history is rather sketchy. My paternal great-grandfather was born near Cracow, and emigrated to New York City in the late 19th century, but ultimately settled in a small farming town in Saskatchewan, Canada where my father was born. Eager to escape the small town isolation, my father left as soon as he could by joining the Royal Canadian Airforce (RCAF) towards the end of World War II. He was trained as a pilot but fortunately the war ended before he could serve in combat, and he was then posted to Ottawa. My mother’s family came from England but settled in Ottawa, where my mother was raised and met my father after the war. Shortly after they married my parents moved to England for my father’s continued training in aeronautical engineering at Imperial College, London. I was born in London, England during the great fog of 1952, but survived the coal-fueled air pollution with no ill effects and after less than a year in England was carried to Canada by my parents. My father continued to work as an aeronautical engineer for the RCAF for the next twenty years, and our house was always decorated with models of the airplanes he worked on. After he retired my father joined the civil service, and for a time studied issues of Arctic transportation; I remember him telling me about the complex properties of Arctic sea ice. Some of my work has an engineering flavor, in that we build structures and test their properties, and it’s possible that it may reflect some influence of my early home life. But a more direct influence stems from the fact that my father was often unhappy with his job, chafing at both his superiors and his subordinates. This I am sure made me seek out the academic life for its more egalitarian aspects. I have never felt like I worked for a boss or had employees who worked for me, just colleagues who like me were interested in learning more about the world around us. My childhood was punctuated by frequent moves, as my father was transferred to different Air Force postings in Germany, Montreal, and Ottawa (Figure 1). At the time many school systems encouraged students to advance as rapidly as possible; as a consequence I was often the youngest in my class. Although socially difficult, this was more than compensated for by making my classes more interesting than they would otherwise have been. Some of my earliest recollections involve grade school math. Learning about fractions was for some reason surprising enough to have stuck with me for the rest of my life; similarly, my discovery of quadratic equations in grade 5 was a revelation. Later, at Riverdale High School in suburban Montreal I was fortunate to have some exceptional teachers. Don Hall struggled to answer my strange science questions, and Irene Brun (now Winston) inspired a life-long love of biology. At the same time, my interest in science was encouraged at home. My father built a basement chemistry lab for me, and the experiments I conducted there often made use of remarkably dangerous chemicals that my mother was able to bring home from the company where she worked. My mother also helped me to get my first summer job, in a chemical testing laboratory at the same company. This was a good window into the importance of quantitative analysis, but the repetitive nature of the work was not at all interesting. Some of the experiments carried out in my basement lab were much more dramatic. For example, with my father’s assistance, shortly after the tragic Apollo 1 fire, we prepared and collected a jar of pure oxygen. We then carefully lowered a small quantity of methanol into the oxygen reservoir. The transformation of the barely visible pale blue flame in air into an intense jet of fire in oxygen was amazing, but also horrifying in the context of the recent Apollo fire. Less carefully supervised experiments frequently led to explosions, which made chemistry seem much more dramatic than one would guess from the textbooks. My failure to carefully separate the hydrogen evolved during electrolysis from ambient air led to an impressive explosion which resulted in a glass tube being embedded in a wooden ceiling rafter. I also participated in more biologically oriented projects with my high school friend Joachim Sparkuhl. In the basement of his house we constructed a small hydroponics garden, inspired, I believe, by the idea that astronauts living on some future space station would need or want to grow their own fresh food.  In 1968 I began my undergraduate studies at McGill, at the age of 15. My first laboratory work at McGill involved helping a chemistry graduate student to purify cholesterol, the starting material for the synthesis of sterols. We started with large sacks of gallstones, which we would dissolve in hot solvent, and then recover the iridescent crystals of pure cholesterol after the solution cooled. While this was a useful experience, it did not inspire me to remain in chemistry, and the pull of biology increased as new opportunities opened up. To my surprise I was accepted into a summer research program for undergraduates at the Jackson Laboratories, a renowned mouse genetics institute on Mt. Desert Island off the coast of Maine. The environment was idyllic, and the program combined intense scientific education and hands-on experimental work with outdoor activities such as hiking up Cadillac Mountain and observing the beautiful organisms that populated the nearby tidal pools. The Jackson labs are a mouse genetics research facility, and this influenced my future scientific career in an unexpected way. My project, carried out under the guidance of Dr. Chen K. Chai, involved the analysis of thyroid hormones in various mutant strains. This required the careful dissection of the thyroid gland from many mice. Although I was, after much practice, able to remove the thyroid without (at least most of the time) severing any of the many nearby major blood vessels, I strongly disliked the process of killing and dissecting the animals, and by the end of the summer had vowed never again to work on animal models.  Back at McGill the next fall, this time as a resident student (my parents having moved back to Ottawa), I started spending less time in the lectures and more time in the library, and also searching out new labs in which to gain additional experience. I was always surprised when seemingly intimidating Professors welcomed me into their labs and invited me to join in ongoing research projects. During this year and the next I did work in several labs in the Biology and Biochemistry departments, generally on plant biology systems. Field trips with Kurt Meier, a specialist in bryophyte biology, inculcated an enduring affection for the simple mosses and liverworts. I apparently did well enough in a physiology course run by Ron Poole to land a summer job prototyping and testing new lab experiments for the following year’s lab course. Although most of my lecture courses were uninspiring, John Southin’s course in Molecular Biology was an incredible exception. I’ll never forget entering the first class and being handed a thick book of printouts, which I assumed were a set of papers we were supposed to read. In fact the whole book was simply a list of references, which we were expected to read and absorb in the library. These readings from the frontiers of molecular biology were very impressive. We read and discussed the beautiful Meselson-Stahl experiment, which was just over a decade old at the time, and learned how the genetic code had been unraveled only a few years previously. The fact that one could deduce, from measurements of the radioactivity in fractions from a centrifuge tube, the molecular details of DNA replication, transcription and translation was astonishing to me. One of the intellectual highlights of my time at McGill was the open-book, open-discussion final exam in this class, in which the questions were so challenging that the intense collaboration of groups of students was required to reach the answers.  In my senior year, I began a project in Mel Goldstein’s lab, together with my friend Joachim Sparkhul. The subject of our study was the beautiful colonial green flagellate *Eudorina elegans*, a smaller version of the more common *Volvox*. Over the school year and the following summer, we obtained evidence that these algae secreted a peptide hormone that induced spermatogenesis under favorable environmental conditions. This work led to our first scientific publication, which appeared the following year (1).  In the fall of 1972 I started my graduate studies at Cornell University in Ithaca, New York. I decided to attend Cornell in part because the A.D. White Fellowship would fully support me, but also because I would be able to pursue my work on *Eudorina* in the Department of Plant Physiology. At the time, I was enamored with a grandiose plan to develop *Eudorina* as a simple model system for studies in developmental genetics. This plan did not work out, for several reasons, not least the fact that this sort of ambitious program cannot be developed in isolation by an inexperienced student. Lacking the necessary genetic expertise, and because I was either unable or unwilling to seek out the necessary help, my project became mired in frustrating technical difficulties.  However, the periods spent waiting for my *Eudorina* cultures to grow allowed for plenty of time for conversations with my fellow graduate student John Stiles. John was approaching graduation and was thinking about what to do after the completion of his Ph.D., while I was gradually shifting from thinking about *Eudorina* to dreaming up some more productive project. We talked a lot about the emerging methods in molecular biology, which were clearly heading towards the ability to explore the structure and activity of individual genes at the molecular level; cloning and sequencing technologies were just beginning to emerge. John and I eventually came up with a specific proposal for a collaborative experiment. Our idea was to chemically synthesize a DNA oligonucleotide of sufficient length that it would hybridize to a single sequence within the yeast genome, and then to use it as an mRNA and gene specific probe. While conceptually simple, our idea was technically challenging. At the time, there was only one short segment of the yeast genome for which the DNA sequence was known, the region coding for the N-terminus of the iso-1 cytochrome c protein, which had been intensively studied by Fred Sherman for many years. The Sherman lab, in a tour de force of genetics and protein chemistry, had isolated double-frameshift mutants in which the N-terminal region of the protein was translated from out-of-frame codons. Protein sequencing of the wild type and frameshifted mutants allowed them to deduce 44 nucleotides of DNA sequence. John and I thought that if we could prepare a synthetic oligonucleotide that was complementary to the coding sequence, we could use it to detect the cytochrome-c mRNA and gene. At the time, essentially all experiments on mRNA were done on total cellular mRNA, rendering efforts to monitor the expression of individual genes almost impossible.  John and I were sufficiently confident of our ideas to begin contacting labs where we might pursue the work, with me doing the chemistry, and John working on the yeast biology. At Cornell, there was one laboratory that was the obvious place for such an experiment, and that was the lab of Ray Wu in the Department of Biochemistry. Ray was already well known for determining the sequence of the sticky ends of phage lambda, the first ever DNA to be sequenced, and his lab was deeply involved in the study of enzymes that could be used to manipulate and sequence DNA more effectively. John and I approached Professor Wu, who listened to our proposal and allowed that it was an interesting idea worth exploring. However he was reluctant to appear to be ‘poaching’ a graduate student from another lab and department; another complication was that the work would require collaboration with Fred Sherman’s lab. John applied to Fred’s lab in nearby Rochester, New York, for a postdoctoral position, and was accepted. At Cornell, I persisted and eventually Ray allowed me to transfer into his lab and begin the project.  The interlude between wrapping up my work in the Department of Plant Physiology and starting as a transfer student in the Department of Biochemistry provided me with the opportunity for an extended vacation and my first trip to Europe on my own. I began with a visit to Cambridge, England where I was very kindly hosted by Professor Poole (for whom I had worked at McGill), who was on sabbatical at the University of Cambridge. I explored the town and was incredibly impressed by the Chapel of King’s College and the ethereal music therein. Even more impressive was the famous Laboratory of Molecular Biology at the MRC, where I talked with one of the iconic figures of molecular biology, [Sydney Brenner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/). I was asked to wait for Sydney in his office, which I was surprised to notice held two large desks, both piled to the ceiling with papers. When Sydney arrived he told me about his remarkable new project involving the use of the nematode *Caenorhabditis elegans* as a model system for developmental genetics − this was an impressive if somewhat painful lesson on the right way to carry forward such an ambitious project. I also learned why two desks crammed that small office − it turned out that [Francis Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/)!  After a memorable month of art, architecture and music in Paris, I returned to Ithaca to start afresh in a new lab with a new project. My goal was clear − the chemical synthesis of the oligonucleotide needed for our gene detection scheme. At the time, this was still a challenging endeavor for a student such as myself with minimal synthetic skills. Ray had an ongoing collaboration with Saran Narang, who was developing the solution phase phosphotriester approach to oligonucleotide synthesis. Our plan was to use this approach to prepare large quantities of the five trimers needed to make a 15-mer, then link the trimers together to form 6-mers, a 9-mer and finally a 15-mer. I began the work under the tutelage of Chander Bahl, a postdoc who had some experience with this technology. Unfortunately our lab was better equipped for enzymology than synthesis, and we lacked a critical mass of experienced chemists. After a year of work, I was still far from my goal and becoming increasingly frustrated. Fortunately Ray Wu realized that I needed help, and arranged for me to visit Saran Narang’s lab in Ottawa. There I was fortunate to receive training from Keichi Itakura, who later became famous for synthesizing the gene for insulin. After two weeks of intense training, I returned to Ithaca, and attacked my synthesis with fresh energy. A few months later, I was rewarded with several milligrams of our long sought 15-mer. In collaboration with John Stiles and Fred Sherman, who sent us RNA and DNA samples from appropriate yeast strains, we were able to show that we could use the labeled 15-mer as a probe to detect the *cyc1* mRNA, and later the gene itself. This was quite exciting, and seeing our work published in *Nature* (2) was a great boost to my confidence after years of work with little to show. It was also an important lesson in effective research strategy, imprinting on me the value of seeking help from knowledgeable people when faced with difficulties. One of the delights of the world of science is that it is filled with people of good will who are more than happy to assist a student or colleague by teaching a technique or discussing a problem.  The completion of my Ph.D. in 1977 marked the beginning of a major scientific transition for me. Against all commonsense advice, I decided to remain in Ray’s lab for postdoctoral work, but in a very different scientific area. The decision was triggered by the arrival in Ray’s lab of a new postdoc, Rodney Rothstein, from Fred Sherman’s lab in Rochester. Rod was already a seasoned yeast geneticist, but had little experience with molecular biology; in contrast my graduate work was in molecular biology but I had no practical experience with genetics. We hit it off and essentially trained each other through our collaborative work on yeast transformation. Our frequent discussions were long and often loud, sometimes triggering mild protests from Ray who would emerge from his office and ask us to turn it down a notch when he needed a quieter atmosphere in which to work. The combination of the molecular biology I learned in Ray’s lab and the genetics I learned there from Rod prepared me well for the next decade of my work on yeast, first in recombination studies, and later in telomere studies and other aspects of yeast biology. Ray was a wonderful advisor (3), and in addition to his scientific advice I absorbed much of his way of running a lab, which in essence was to be there when advice was needed but otherwise to let creative students and postdocs run with their ideas (Figure 2).  My postdoctoral studies of recombination in yeast were enabled by the discovery, in Gerry Fink’s lab at Cornell, of a way to introduce foreign DNA into yeast (4). These pioneering studies of yeast transformation showed that circular plasmid DNA molecules could on occasion become integrated into yeast chromosomal DNA by homologous recombination. Rod and I began to search for ways of increasing the frequency with which transformants were recovered. Increasing the target size for recombination seemed like a good possibility, and indeed when I transformed yeast with plasmids containing fragments of rDNA, I did recover more transformants, and these contained plasmid DNA integrated at the rDNA locus. These strains allowed me to initiate studies of unequal sister chromatid exchange in rDNA locus, resulting in my first publication in the field of recombination (5). Towards the end of my stay in Ray Wu’s lab, Rod and I came upon the first hints of double-strand break stimulated recombination in yeast. Our preliminary experiments suggested that cutting plasmid DNA within a region of homology to yeast chromosomal DNA led to an increase in the recovery of transformants, presumably reflecting increased recombination of the input DNA with the homologous chromosomal locus. The idea that you could increase transformation frequency by cutting the input DNA was pleasingly counterintuitive and led us to continue our exploration of this phenomenon.  My first independent position was at the Sidney Farber Cancer Institute (now the Dana-Farber Cancer Institute). I owe a great debt to Professor Ruth Sager, who was the main force behind hiring me. She established a terrific group of young investigators in her division, including Richard Kolodner and Gerry Rubin, creating a superb intellectual atmosphere. Ironically, I heard many years later that Ruth was only able to hire me over the objections of some of the senior clinical faculty, who did not believe that studies of yeast had any place in a cancer institute. Times have changed, and fortunately model systems are now much more widely appreciated. My graduate students came from the graduate program at Harvard Medical School, where I had an academic appointment in the Department of Biological Chemistry. These students were wonderful, and together we made rapid progress in setting up a productive yeast genetics lab.  Our initial focus was the study of double-strand breaks in DNA and their repair by recombination. This work was spearheaded by my first graduate student, Terry Orr-Weaver, who is now a Professor at the Whitehead Institute and MIT. Terry’s work, and our continuing interactions with Rod Rothstein, led us to think intensively about the kinds of reactions engaged in by DNA ends (6). There was considerable debate about different models for recombination within the wider DNA repair and recombination community, and seminars and conferences were important means for the exchange of the latest information. For many years, the major international recombination meeting was held in Aviemore, Scotland, which afforded the opportunity to sample diverse single-malts while discussing the intricacies of genetic exchange. I do recall that excessive sampling at one Aviemore meeting did make it difficult for me to present my work the next morning.  I also enjoyed attending Gordon Conferences and Cold Spring Harbor meetings, which were small and highly interactive meetings that provided wonderful opportunities for young scientists to present their work and meet and talk to people doing the best and most important current work. In the summer of 1980, I attended the Nucleic Acids Gordon Conference, expecting to hear the latest advances in DNA synthesis, sequencing and repair. However, for me the high point of the meeting was hearing Liz Blackburn talk about her work on telomeres in *Tetrahymena*. Our subsequent discussion led to the initiation of a collaboration in which we decided to test the ability of *Tetrahymena* telomeres to function in yeast. Those experiments are described in my Nobel Lecture; here I will just say that it was an incredibly exciting time for me. I performed the experiments myself, and experienced the thrill of being the first to know that our wild idea had worked. It was clear from that point on that a door had been opened and that we were going to be able to learn a lot about telomere function from studies in yeast. Within a short time I was able to clone bona fide yeast telomeres, and in a continuation of the collaboration with Liz Blackburn’s lab we soon obtained the critical sequence information that led us to propose the existence of the key enzyme, telomerase.  With the success of the recombination and telomere projects, my lab began to grow. My second graduate student, Andrew Murray, now a Professor at Harvard, began to work on building artificial chromosomes. Andrew was a brilliant and energetic student who was fun to talk with about any conceivable experiment; his colorful personality (and dress) enlivened the lab. My collaboration with Rod and Terry grew to include Frank Stahl, the world’s leading expert on the genetics of meiotic recombination, with whom we had many detailed discussions of the genetic implications of specific physical models. I particularly remember an afternoon I spent at Frank and Mary Stahl’s house in Eugene, Oregon, going back and forth with Frank about different versions of the double-strand break repair model as we worked on our manuscript (7). It was an intense and stimulating experience that I still treasure.  After five very productive years at the Farber, a remarkable opportunity induced me to move to the fledgling Department of Molecular Biology at the Massachusetts General Hospital (MGH). Howard Goodman, the founder of the Department and a major figure in the emerging field of biotechnology, had arranged an extremely interesting and innovative academia/industry collaborative venture. In this deal, the pharmaceutical giant Hoechst AG agreed to fully support all research in the MGH Department of Molecular Biology for a period of about ten years, in return for limited intellectual property rights. This was extremely attractive to me, as it promised to allow me to pursue research in any direction that I found to be of interest, without having to worry about obtaining traditional grant support for novel and hence untried ideas. Thus, in the summer of 1984 I moved my lab from the Farber to our new home in the downtown Boston campus of MGH (humorously referred to by colleagues at MIT’s Whitehead Institute as “one of the finest research institutes in downtown Boston”).  At that time, I was actively exploring the possibility of moving into other fields. By 1984, I had a growing feeling that my work in yeast was becoming less significant, in the sense that other people would inevitably end up doing the same experiments we were doing in a few months or years at the most. To learn more about other fields and to prepare myself to work in a new area I audited several courses at Harvard. A delightful course by Steve Kosslyn on cognitive psychology explored the fascinating correlations between localized brain lesions and cognitive deficits, and highlighted the emerging neuroimaging technologies that were promising to revolutionize studies of brain function. I also audited an applied math course to brush up on the skills I would need should I decide to seriously enter into structural biology. Finally an outstanding course on enzymology and catalytic mechanisms by the late Jeremy Knowles stimulated my interest in catalysis. Later, when Jeremy left science to become Dean of the Faculty of Arts and Sciences at Harvard, I had the good fortune to “inherit” one of his graduate students, Jon Lorsch, who migrated to my lab and did outstanding work on ribozyme selections and mechanistic enzymology.  The combination of Jeremy’s enzymology course and the recent discovery of ribozymes by [Tom Cech and Sid Altman](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1989/) (who shared the 1989 Nobel Prize in Chemistry for their work), ultimately led me to begin a transition to work on ribozymes. This seemed like a reasonably conservative way to switch fields, since the methods used to study ribozymes were largely a combination of molecular biology and chemistry. I was surprised that so few people were entering the field, since I thought that there were major questions to be addressed in terms of understanding the origins of biological catalysis in the hypothetical RNA world that preceded the evolution of protein synthesis.  I began to work with RNA myself, playing around with Cech’s *Tetrahymena* ribozyme, which I obtained from the same piece of DNA that contained the *Tetrahymena* telomeres I had worked on just a few years earlier. The first student to join me in this new area was [Jennifer Doudna](https://www.nobelprize.org/prizes/chemistry/2020/doudna/facts/). Jennifer had actually come to my lab to work on yeast genetics, but I was fortunate to persuade her that the future lay in RNA. Jennifer’s energy and determination drove our efforts to convert self-splicing introns into an RNA replicase. We were soon joined by Rachel Green and several other dedicated students, techs, postdocs, and a memorable sabbatical visitor, François Michel, who impressed everyone with his work ethic, his uncanny ability to intuit structure from phylogeny, and his parallel career in butterfly evolution.  Even as I pushed our gradual transition to a focus on RNA, I maintained a substantial effort in yeast genetics for several years during the mid to late 1980s. My interest in recombination and telomeres had not disappeared, and I wanted to bring our earlier advances to a satisfying conclusion. Recombination remained a large part of the lab, with Doug Treco, Alain Nicolas, Neil Schultes and Hong Sun maintaining a focus on the role of double-strand breaks in meiotic recombination. Most important for the telomere story was Vicki Lundblad’s ground-breaking work on telomere genetics in yeast, which provided a link between telomere maintenance and senescence and aging (8). Barbara Dunn linked the telomere and recombination realms by study the transfer of sub-telomeric repeats between chromosomes by recombination.  By end of the 80s, our yeast work was almost done, and the lab was increasingly focused on RNA. The RNA floodgates really opened with the work of Andy Ellington on *in vitro* selection (9), which ushered in a new era of work on the *in vitro* directed evolution of new functional molecules. Over time we came to feel that we could evolve a binding site for virtually any target molecule, using any kind of nucleic acid. This confidence led us to try to evolve new catalysts, and, returning to the RNA world hypothesis for inspiration, we aimed for the chemistry of nucleic acid polymerization (10). This was the basis of Dave Bartel’s ground-breaking work on the selection of ribozyme ligases, which he subsequently (in his own lab at the Whitehead Institute and MIT) evolved into an RNA molecule with bona fide RNA polymerase activity. Our advances fueled my interest in the role of RNA in early evolution and seemed to bring the resurrection of the RNA world almost within reach. Our ability to evolve new aptamers and ribozymes was so intoxicating that my lab spent most of the 90s exploring the range of possibilities and the limitations of what RNA could do. Our advances began to attract attention, leading to my election to the National Academy of Sciences and appointment as a Howard Hughes Investigator in 1998. At the same time, the Hoechst funding of my department was winding down, making my HHMI appointment particularly welcome as a means of enabling ventures into new scientific areas.  As other labs also started to evolve new and interesting ribozymes, the difficulty of evolving *de novo* proteins began to seem the greater challenge. We entered the field of protein and peptide evolution when Richard W. Roberts, a postdoc in my lab, learned how to trick the translation apparatus into covalently linking a newly translated protein to its own mRNA through the action of the antibiotic puromycin (11). Galvanized by this advance, I encouraged several new lab members to develop and use this mRNA-display technology to address fundamental questions about the origin of protein structure. Most significantly, Tony Keefe used this method to evolve a novel ATP-binding protein from a large library of random sequence polypeptides (12). Remarkably, this non-biological protein looks indistinguishable from any normal biologically derived small protein domain. Postdoctoral fellows John Chaput and Sheref Mansy continued to evolve this protein and study its structure over the following years.  The development of this protein evolution technology led me to co-found a startup biotechnology company, together with Rich and my colleague Brian Seed. Although the company was not a business success, it was a very interesting and educational experience. The collaborative efforts of a team of scientists ranging from protein biophysicists to people with clinical drug development experience allowed us to evolve a small protein domain with therapeutic potential; this artificially evolved protein is now in clinical trials. While I have continued to maintain a focus on fundamental questions in my laboratory, I firmly believe that small startup companies are the best way to develop more applied research to the point that it can eventually be therapeutically useful.  By the year 2000, I started to pay more attention to fundamental questions related to the origin of life. My interest in the role of compartmentalization and cellular structure in the origin of life was stimulated by discussions with Pier Luigi Luisi and David Bartel. A year of debate led to a synthesis of our views on the roles of genetics, compartmentalization and evolution, which we expressed in our 2001 *Nature* paper Synthesizing Life (13). This paper catalyzed my entry into the field of membrane biophysics, for I felt that having proposed a model for early cells in which bilayer membranes played a crucial role, it was incumbent on us to show that such models were physically plausible. I have to admit that I was somewhat surprised to find myself working with lipids and membranes, which are remarkably squishy and ill-defined by comparison with nucleic acids. However, in at least one way, the study of membranes composed of prebiotic building blocks such as fatty acids was perfect for me, since this field was filled with important yet technically addressable questions. When postdoctoral fellow Marty Hanczyc and graduate student Shelly Fujikawa joined the project, we were able to make rapid progress, and within a few years had demonstrated a proof-of-principle path for vesicle growth and division based solely on physical processes. I began to grow more confident that it might ultimately be possible to deduce plausible explanations for at least some of the mysterious steps in the origin of life. My enthusiasm grew when Irene Chen, a brilliant biophysics graduate student, made further progress by demonstrating a pathway for competition between protocells. We worried that our model protocells would not be able to take up nutrients, such as the nucleotides needed for the replication of their genetic material, but Sheref Mansy showed that this was not a problem. Most recently, another graduate student, Ting Zhu has come up with a very attractive pathway for spontaneous, coupled growth and division, so it is beginning to seem that the assembly and replication of protocell membranes is not as difficult as we once thought.  The dramatic progress in the identification of pathways for the self-replication of protocell membranes has encouraged us to focus on the hardest remaining problem, the replication of the genetic material. Here the big question is whether RNA was in fact the first genetic polymer, or whether RNA was preceded by some simpler, easier to make or more robust genetic material. This question has driven the most recent transformation of my lab (Figure 4), into a well equipped synthetic organic chemistry lab. We are synthesizing amino-nucleotides, the building blocks for phosphoramidate polymers, due to their greater reactivity than normal nucleotides. Alonso Ricardo, a postdoc, and Jason Schrum, a graduate student, have recently made very significant progress in the template-directed synthesis of 2′-5′ linked phophoramidate DNA (14), and we are now exploring a series of related polymers in a search for even better self-replicating genetic materials. The complexity and fragility of RNA long made it seem an unlikely candidate for the first genetic material, but this prospect has been revived by the brilliant recent work from John Sutherland’s lab in Manchester (15). With John’s former graduate student Matt Powner now in my lab as a postdoc, we are eagerly exploring new avenues to the chemical replication of RNA. It is thrilling to me to see people in my lab developing new approaches to the synthesis of modified nucleic acids, but the suspense is almost unbearable as we await the results of template-directed polymerization experiments.  From our current vantage point, it is not clear whether there will be many solutions to the problem of chemically replicating genetic polymers, or just one, or none, but in any case it is an exciting quest. Encouraged by our small advances on the way, we are continuing to feel our way towards the tantalizing goal of building replicating, evolving chemical systems. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0537=JS [Jack Szostak] Hello?  [Adam Smith] Good morning. May I speak to Jack Szostak please? This is Adam Smith.  [JS] Yes, this is Jack.  [AS] Oh, hello. Well, congratulations on the award of the Nobel Prize.  [JS] Thank you very much.  [AS] Since you are, presumably in Cambridge, it’s, what, coming up to five a.m. in the morning?  [JS] That’s right, yeah. Although, I live in Boston to be precise.  [AS] Were you awake when the call came?  [JS] Ah, no, actually it woke me up – woke us up!  [AS] That seems a nice way to be woken up.  [JS] It’s a, yeah, very… yes, indeed.  [AS] You have been receiving a great number of awards over the recent years so presumably you had a suspicion that this might be on the way?  [JS] Yeah, well, yes. Especially after the Lasker, people started to say this might happen at some point. But, you know, it’s the sort of think you never know for sure. There are many, many possibilities.  [AS] Exactly, yes. Anyway, happy day. Just looking back at the period of the early 80s when you did the work, together with Elizabeth Blackburn, which is the first part of the citation, you were actually working on DNA recombination then. And, I believe it was at a Gordon conference that you heard her speak and then the idea of this joint experiment, crossing kingdom boundaries was suggested.  [JS] That’s right.  [AS] And, when you showed, together, that telomeres from one species could protect DNA from a totally unrelated species – a very distant species – were you both immediately aware of how fundamental this discovery was?  [JS] Yes, absolutely. The implications that the whole machinery was conserved across kingdoms; that was obvious as soon as we saw that the *Tetrahymena* telomeres worked in yeast. And, basically I could see that it had worked as soon as I saw the results on the jelly. You could tell that we had linear plasmids in yeast and, therefore, that the telomeres were working. So, it was quite an exciting moment.  [AS] Elizabeth Blackburn and Carol Greider, of course, who’s the other co-Laureate, have both stayed with telomere research throughout their careers so far. You’ve tended to move through fields so that you worked on telomeres in the early 80s and you then worked on catalytic RNA and the origin of life. What is it that attracts you to new fields as you move through them? Can you say?  [JS] That’s a hard question. There are just … the world’s full of interesting problems and I think I like to work on problems that aren’t receiving a huge amount of attention.  [AS] And do you tend to feel that … do you like to stay with a problem until you’ve got to some kind of solution and then move out of that?  [JS] Yeah, sure, sure. So, I guess, especially after Vicki Lundblad did her work, which I think was really the first experimental work showing that telomere maintenance was essential for avoiding senescence and therefore all of the other things that would follow from that, it became obvious that a lot of people were going to come into this field and move it forward in mammalian systems and explore the linkage to aging and cancer. You know, I know that that kind of work was important but it was also obvious that a lot of people were going to do it. So, by that time, I really was already moving on; most of my lab had already changed directions to the RNA work.  [AS] Right, right. And, the work you’re currently undertaking, where you’re trying to build artificial cells to see what that can tell us about the origins of life. Is that a relatively sparsely populated area at present?  [JS] It’s a very sparsely populated area. I mean there are relatively few labs working in it for, I think, for a number of reasons. I think that it’s actually unfortunate that there are so few labs working on these problems. And most of the people that are, are doing so for reasons that are related to either biophysical studies of membranes, which are more broadly important, or working on nucleic acid chemistry, which as implications in many fields. But, it’s hard, especially for younger people, to get into the field of the origin of life, just for reasons of funding and because the problems are so long term.  [AS] Long term and so basic that there really isn’t any sort of medical application or anything that one could …  [JS] Yeah, it’s completely basic work. Although, I have to say, it’s the same thing when we started working on telomeres. That was totally basic, there were no applications envisaged at all. And yet, to our surprise, it turned out be … to have important medical implications. And, I think even though the work I’m doing now is totally basic, we always keep our eyes open for possible applications. Because a lot of it is uncovering basic physical phenomena or developing new technologies and you can’t really predict when applications will come up.  [AS] Yes, one can never tell. But basic research is certainly where it appears that you like to live?  [JS] Oh, yes. That’s definitely true.  [AS] So how do you think the day will pan out now? Do you’ll maintain any control of it?  [JS] I was just talking with my wife about how we’re going to start doing things today. Getting the kids to school … and I know my institution, Massachusetts General Hospital, has contingency plans so I’m sure there will be a bunch of press conferences and stuff like that.  [AS] Are the kids awake yet and know what’s going on?  [JS] No, not yet, no.  [AS] Are they of an age where they are going to be able to appreciate all this?  [JS] Yeah, I think they’ll be pretty excited. We had a lot of fun taking them to Amsterdam for the Heineken prize. So, actually, we’ll be looking forward to taking them to Stockholm with us.  [AS] Splendid. Well, we happily get a longer chance to speak to you when you come to Stockholm so I’ll very much look forward to that.  [JS] OK, wonderful.  [AS] And, I wish you a wonderful day.  [JS] Ok, thank you very much.  [AS] Thank you very much. Bye.  [JS] Bye. |
| Interview |  |
| Q13 | Your Nobel Prize is of course associated with a couple of interesting numbers. This is the hundredth time, I am sure you’ve heard, that the Nobel Prize in Physiology or Medicine has been awarded and also this is the first time ever that two women have been co-recipients of the same Nobel Prize in the sciences, and telomere research in general is one where the proportion of women is more normal, if you like, its more representable of the maked up society. Is there a reason for that, do you think? |
|  | Elizabeth Blackburn: I think we should turn it around and ask why everybody else is so aberrant, seriously, because I think that actually might frame the question a little bit more instructively as to why things are not, as you said, the biological or societal representation of women. We can point to various sorts of things such as the fact that some of who have been in the field are females, but actually there are plenty of men in the field as well and I think what stands out is that the numbers are a little different, but certainly, having examples of women who have done well in science – we all know that kind of example does make it more encouraging for others, younger people, to visualize themselves being successful in science – and so I think there has been a kind of perpetuating effect there, but I do like to think that this is the normal way it can be and perhaps we should think about, well, how do we make this more normal in other fields of science. |
| Q13 | We will pick up your question, why is it aberrant in other fields do you think? |
|  | Elizabeth Blackburn: Somebody else can take that one.Jack Szostak: There is obviously a lot of historical reasons, bias, familiar /- – -/ that takes a long time to get rid of and a lot of good role models to get rid of. |
| Q21 | Have you found it difficult being a woman in science? |
|  | Carol Greider: No, I have not found it difficult, but I think that one of the things that I have always done is sort of put blinders on and done what I wanted to do, but it was when I then started to get to the higher levels in ranks that I could then look back and see what the data was. At graduate school there were 50% women, at graduate school there was postdoc fellows usually 50% and then as you get higher and higher up the representation is lower. I didn’t feel like I personally had experienced any big obstacles, I am a scientist, I can look at the data and see that there is something that is not quite representative, as one moves up the higher ranks. I think that role models are one good thing, that the more people there are in the higher ranks the more the younger people can look up and say Yes, there is something that I can do, and it doesn’t seem like an impossible task. |
| Q4 | Is there more that needs to be done than role models? I mean, would it naturally change, or does it have to be aggressively tackled do you think? |
|  | Elizabeth Blackburn: I think aggressive tackling is good. Look at something like smoking, it took very aggressive actions to make smoking less of a wide-spread practice and certain amount of imposition of things. I don’t think it will happen organically completely from within. When you talk to colleagues, individually they are very well disposed to the idea that they see the value of having more women and more diverse groups of people’s insights, because like any enterprise the more diverse sorts of backgrounds come into it, the better way the problems can be solved. I think there is not a lack of good will among a lot of people to do this. It is a question of how do you do it, and then I am sure a mixture of various sorts of strategies will be hopeful, not least education and not least just seeing a woman there sort of makes it more possible. I think we are very visual species, and you look at something and that’s evidence in front of you, that you seem to think Oh, that’s me. If you were a young woman, I could do this.I think further that we have to make the career structure a little bit more flexible because there has been a one size fits all model for careers in science which have been very much that based on a man having a supportive wife or partner or something to take care of life and family and that’s been something that has been daunting, we find, to young women. I personally found it very daunting as a young woman into the career structure, not the science, but the career structure, and so I think we can be much more imaginative about how we make sure women don’t leave sciences during the time when they have preoccupations with family or with elderly parents who need long term care, the sort of things that women often do. |
| Q4 | Yes, that requires one to have really quite a strong support structure within science. |
|  | Jack Szostak: A lot more broadly than that, there are a lot of things done here in Sweden that would be kind of chocking in the United States.Elizabeth Blackburn: Yes, absolutely!Carol Greider: A support in terms of general /- – -/ support.Elizabeth Blackburn: Yes, because I think the seeking point for many women, at least in my personal experience from what I see is, they say “I just can’t see being a scientist and I also do want to have a life” and I think that that is something that we shouldn’t say to young people. “Oh no, you can’t have a life and be a scientist” and yet that is the perception that they have. I think as senior scientists we could do a lot more to try to think of active ways in which this one kind of career structure model that we have could be thought of more imaginatively. And I just know examples of women who have gone part-time as their families and other needs have happened, and then they go back in full time and they just come roaring back and have done really well, and they are not all in the United States unfortunately, which again tells us something about the United States situation and support. |
| Q23 | I think it’s your own phrase … I have heard you say it. They were known in the 1930s, it was known that they had an important protective role of the chromosomes, but people didn’t know what they were. It was you in the late 1970s that sorted out the molecular nature. |
|  | Elizabeth Blackburn: Began to, its still an on-going saga, none of us are out of jobs yet. That’s right. I think it was so wonderful the science that was done /- – -/ genetically in which such deductions were made about what’s going on with chromosomes and their inheritance. Now we look back at it and we say they didn’t know it was DNA and yet the thinking about what was observed, and I particularly enjoyed [McClintock](https://www.nobelprize.org/prizes/medicine/1983/mcclintock/facts/)’s work because that’s what I got more familiar with. It was so elegant and there are so many treasures in there, of insights into what turns out to be going on in meiosis and as it turned out with what’s going on with telomeres, although her fame more broadly was, I think, perhaps more for jumping genes for many years. What she said, something written in 1931, about a telomere being distinctive, and she didn’t call it a telomere, was so clear and I think very important and it was just lack of the research tools of the time.Jack Szostak: Molecular understanding was there …Elizabeth Blackburn: Right they had microscopes, they had genes, phenotypes, they had really wonderful other kinds of thinking, but they were not playing with the same sort of toys in the lab that we have played with. |
| Q11 | Ahead of time … Then you two met at this Gordon conference in 1980 and it’s sort of the way science is supposed to happen, two people meet each other, have an idea, do an experiment and prove something wonderful. |
|  | Elizabeth Blackburn: And then … nobody pays for it, but they do pay for it, no they pay for a broad sort of setting in which you can go and do experiments and explore and ask questions without somebody saying, Oh, is this going to be useful for this year’s economy or for somebody’s /- – -/ medicine. I think that is really important, I mean we thought that was something … we didn’t really think about it at the time, it was such a given that you can do an experiment with broad funding that is never going to be wasted. Scientists don’t throw away money, they work very hard and giving scientists money to ask questions that hadn’t been planned, it’s really important.Jack Szostak: That meeting, or that kind of meeting, it’s great for bringing people together, who are working on different things.Elizabeth Blackburn: These meetings are famous for …Carol Greider: You had met each other before?Jack Szostak: No, that’s how we met. After your talk I came up …Elizabeth Blackburn: We walked across this lawn and just talked and talked.Jack Szostak: Because I was working on broken DNA molecules’ ends and then Liz had these ends that behaved completely differently, and it was just a contrast that was kind of chocking so we had to talk about it and see what we could do to figure out what was going on.Carol Greider: So Liz, you gave your talk first?Elizabeth Blackburn: Yes. |
| Q11 | It was after the talk the two of you teamed up? |
|  | Elizabeth Blackburn: Yes, I talked about what we knew about the molecular nature of these DNA molecules. You know the ends, you could get your hands physically on. |
| Q11 | We will turn to the experiment in a minute, but I just want to ask you in general about choosing companions in science, because it is so important to get the right people to work with. Is there some, and of course one works with lots of different people throughout one’s career, but are there some criteria that you applied choosing companions to work out with? |
|  | Jack Szostak: I think it’s mostly a matter of, you know, is there an interesting experiment that actually can get done?Elizabeth Blackburn: And then if you have the luxury of choice, yes, you do want to work with people who really do rigorous science, I think, and that can be very different kinds of science, can be done with rigour, but I think that’s important as one collaborates with people outside new areas. Jack and I, we were really much in the same sort of area, it was a molecular genetic tradition, but when you collaborate even further out, now you don’t have the deep expertise, then I think you have to have a real respect for that person’s quality of their research.Jack Szostak: And you also need to have someone who is fun to talk to and you can exchange ideas with, each way. Some people are better at that than others. More fun to work with.Elizabeth Blackburn: But you are right, if the scientist is really exciting you will make it happen.Jack Szostak: You will find a way. |
| Q26 | And when you are picking companions who don’t have a track record, students that come in into the lab, what do you look for in them? |
|  | Carol Greider: Really, it’s just the excitement of what they are doing and they simply need to communicate that excitement back and forth and I think if people really are interested and care, just interacting with them over a period of a few weeks, one can tell whether or not there is a compatible set of interest that are there. So usually there is an opportunity to do that when students may be coming into the lab, you have a chance to get to know them a little bit and see where the capabilities are on both sides. It’s not just a mentor choosing a student for a very … there is opportunities for students to go around and choose mentors and make sure that they are compatible with them as well, and I think both of those things are important. |
| Q12 | I was going to go on to ask what do you think are the important characteristics of being a mentor, what do you try and provide for the student? |
|  | Carol Greider: Again, it’s all about the science and it’s about being a /- – -/, sit down and have a conversation and really understand that person’s interest. Some problems are very interesting, but somebody may approach it from a particular angle and somebody else approach it from a different angle and then when those two people talk it may not be as easy to understand, but a third angle, there may be a shared understanding like, you know, languages, if somebody speaks a language that is close to a language, if somebody speaks Italian and Spanish, maybe they will understand each other better than somebody speaking some other languages. So I think that that is true in terms of people in their interpersonal interactions as well, so finding those compatibilities is just a matter of spending some time together and talking about their science. |
| Q12 | I don’t know if you want to add anything? |
|  | Elizabeth Blackburn: And finding their strengths too, which is something I learned not by being clever, but somebody once said to me that Shirley Tilghman, who is now the President of Princeton, but she is a very accomplished molecular geneticist, and somebody who knew her very well in her science days said she always is very good finding what people are good at and then making sure that gets used very well. It’s not an altruistic thing necessarily, she is making sure they thrive and do the best in science and I thought that was a really good hint and I try and look for that as well because some people have real strengths in some areas, some will ask all these questions all the time and they will never do this experiment, but its also important that they are doing that. Others will say, Yes, I will do the experiment but also be critical. Carol was actually somebody in the latter, she said, “I will do the experiment” and be very smart and critical at the same time. But other people will question, question, question, and if you can make use of that and say, this is really good that someone’s bringing into their really critical thinking and not say, Well, I really want you to do it this way and stopping it, and think, Ah this person actually is smart and they probably got some good reasons for what they are thinking about and so try and use what strengths you feel you discern in people is important.Jack Szostak: I like to find people who are pretty independent and have some initiative and the best students are the ones where I can tell them that’s never going to work and then they go and do it and show that it does work.Elizabeth Blackburn: My problem is that I always think that it is going to work, and they are the ones who say, Well actually …. It goes both ways and you have to have both going on and you have to have the sort of Let’s try it, and things that you really have reasoned through very well, that sometimes is the route to doing something new as you reason something very well and you do that and then something new comes of that too, so both ways in biology really can work and you can’t always predict which is going to be the formula. |
| Q12 | Presumably it often takes quite a long time to find out what people are good at, because there must be a lot of graduate students who start and then find they don’t hit the ground running, it takes time to get going. That can be quite a dissolution at time, so it’s important for people to understand it can take time for one to work out what one should be doing. |
|  | Elizabeth Blackburn: I think people’s quality of thinking that emerges relatively easily I think, now as you say what unfolds in the experiment can of course be very slow because you know by definition you are doing things that are difficult. If they are easy someone would have done them, and so that’s I think the hard, unpredictable road for graduate students. Back to your questions of mentoring, that’s were you have to realize that that’s going on and that people will go through periods in science as we all have done, when you’re just seeming to fail all the time and the experiments don’t work, sometimes for reasons that are boring, but sometimes for reasons that are significant. You have to be able to fail a lot of the time, scientists just have to be terrific at getting slapped back on the face by nature all the time.Carol Greider: I have told my students and I am famous in the lab for saying “That’s why they call it research” because somebody would come into my office and we will be talking about an experiment with a great result and I say “Great, go and do it again!” Somebody would come into my office and say “Nothing worked at all, nothing worked at all”. “Great, go and try it again!” And I say that’s why it is called re-search, you always have to do it again.Elizabeth Blackburn: I realized the opposite because somebody said it isn’t research because somebody already searched for the /- – -/ rediscovering it or something. I like yours better.Carol Greider: You have to repeat that good experiment just like you have to try again at the failed experiment. |
| Q23 | Yes, Carol’s is less depressing, yes. So back to the experiment, together you demonstrated that telomeres from one species could protect DNA from an entirely unrelated species and thus the mechanism of the telomere protection was more fundamental than perhaps one might have though initially. And that result was very clear, you understood that immediately so where you aware of what an important piece of information you had just discovered at the time? |
|  | Jack Szostak: I think we knew that it was going to open up a lot of new experiments, because we could use all the tools available in yeast as well as you could do in *Tetrahymena* and then in other organisms. So we knew that it was going to allow more progress.Elizabeth Blackburn: And I think it also felt somewhat fundamental in the sense … you know molecular biology was very dominated by there will be universal solutions for things because we were so influenced by the genetic code, DNA, everything was very universal and so when you saw something crossing lines of phylogenetic divisions … Don’t you think there was a bit of a sense when we found the sequences looked similar and they looked like there is something fairly deeply universal in the eucariotic world.Jack Szostak: That is an important point, because it was already clear that in bacteria and many viruses there were lots of different solutions, so it didn’t have to turn out to be universal.Elizabeth Blackburn: Yes, it was completely nonintuitive what would go on in terms of actually more the replication problem in terms of … and protection too. |
| Q23 | And you also observed that the telomeres in yeast were lengthening and that something had to be causing that lengthening and that’s when you come into the story, because you set out to find the activity that was causing the lengthening. |
|  | Elizabeth Blackburn: By chemically speaking yes, because I thought that was … I am sort of a biochemist, somewhat by training I suppose and I had gone through biochemistry and then molecular biology and so it felt natural to try and say this is very direct, you know, reactions take place in real time sort of more or less in front of your eyes in sort of, you know, biochemical way.Jack Szostak: You had the right organism for doing the right chemistry.Elizabeth Blackburn: And the organism was right and it turned out … There was a biology of the organism that set this burst of telomere synthesis that takes place and there was an abundance, relatively speaking, of telomeres and so that all pointed to, well, this is a good system to try and answer questions and I had been trained in the lab of Joe Gall, which is where I actually did the sequencing of the telomeric ends, as we now call them, the DNA ends of the mini-chromosomes in the ciliated protozoans. Joe had very much always said that you should find this system in which you would answer the question best, what I think is a fundamental idea. Things will be pretty conserved throughout much of life and so this idea that find the good system was very much in my mind so I started out doing a little out of foray into things, got ten years, felt brave and Carol joined the lab and felt really brave. |
| Q40 | She was one of your unusual students who took one of your ideas and said, Yes I can do that and off she went. |
|  | Elizabeth Blackburn: I had actually offered it to a postdoc who turned it down: Very nice Liz, but I think I will do something different. It was very politely, but. |
| Q23 | And you got this now famous Christmas present in 1984, the first indication that you got your hands on the activity that was causing the lengthening of the telomeres. |
|  | Carol Greider: Yes, I was doing experiments, it was about nine months of trying various things. Liz and Jack had proposed that there may be something that would lengthen the telomeres and so, not knowing exactly what that is or what the properties were. We would just try different things and Liz and I would talk to each other every day or so and say, Okay let’s try this, like cooking, you add some ingredients and you taste it and that doesn’t taste so good so you add a little bit more salt. After trying various things there was one particular change that I made in the experiment. I was just interested in … It was an exciting time to do an experiment and then a few days later, it would take several days for the experiment to sit on an autoradiograph and so I went back in on Christmas day to develop the results of the experiment that I had done several days before and that’s when I saw this very clear repeating pattern on the autoradiograph that just looked like a six-base repeating pattern that you would expect of a telomere repeat.That first instinct is like, Wow, this might really be what we think, of course, then after the excitement there is the, Well, are we being fooled? And so then has to follow all of the ways where we would then be our own worst critics in a sense. It’s like how could we be being fooled by this? Maybe it’s really some normal polymerase that is copying something that is a repetitive sequence in the extract. So that is were the real work of the self criticism is very important and so that is why the discovery was Christmas 1984, but the paper was published in December -85.Elizabeth Blackburn: It just shows how fast these things go actually. |
| Q7 | It is an obvious point, but obviously you were enjoying yourself tremendously and going in on Christmas morning was just something that was natural and the enjoyment of what you do is key, is absolutely the essence of it. Its not work, its enjoyable, I presume. |
|  | Elizabeth Blackburn: That’s right, it’s the best kept secret in science. We never tell people what fun we are having and maybe we are a little afraid because somehow society will frown upon the idea that you actually really … And yet at serious play, but it’s completely the element and the resources, I wonder what, because often the trajectory of the experiments, you find out something the next day because something has rather been incubating or autoradiograms exposing, things like this. There is often this thing where you would leave something and the next day come in and I have just been driving to Berkeley and I am driving up university avenue, really impatient because the traffic would get very slow off the free way, and you knew there would be something at the end of that university avenue when you got out of the car and went into the lab.Carol Greider: That’s why I lived up on the hill and I came down on my bike.Elizabeth Blackburn: Yes, you came down on your bike fast, that’s right. And you had a Volkswagen once. At least you were on the bike, that’s good. But I think that’s really an important point because many young people are saying, Oh you know science is so hard, its so true, and we all complain bitterly because we just take completely for granted the fact that we are having such a good time so we sort of have the luxury to complain about the other stuff. But it’s a really good career and very autonomous, nobody tells us what to do in terms of our choice of research and when you think about how many jobs that’s true for it’s a mince and its not as if scientists waste money. We really are so driven, we want to find things.Carol Greider: I remember when I was a graduate student and it was the first time that I was sort of on my own and supporting myself, and I was like, Wow, they are going to pay me to come in and play everyday ,and I was being paid now what would now be you know, but it was great and I thought Wow, this is just amazing. Maybe if I just keep it up, and it’s worked so far.Elizabeth Blackburn: No, it’s true, as an Assistant Professor you’re suddenly given this playground. They really trust me to do this – that was my feeling. And Berkeley was very /- – -/ actually and they sort of really trust you to go out and … I think now mentorship in young peoples careers is much more thoughtfully done and maybe that’s not always good because we had huge freedom just as Assistant Professors, right?Jack Szostak: We just had the resources to go.Elizabeth Blackburn: Yes, you have to gather the resources, but then you work really hard because you are just driven. |
| Q7 | Perhaps it’s too big a question to ask whether its changing for the good or for the bad. Its presumably going in both directions in the same time. |
|  | Elizabeth Blackburn: I think those who love science are still driven in the same way.Jack Szostak: I don’t know, it might be, it probably takes more time and effort to raise the money to support lab. There are more frustrations there, maybe its more bureaucratic than it use to be, but if you really want to do it, you can still do it and then you have the luxury of doing whatever experiments you think are the most interesting. |
| Q23 | Okay, so back to the enzyme, the enzyme you discovered was unusual, it was a reverse transcriptase with extra protein and RNA and it took some time to sort all that out. When you did sort it out, it turned out that it solved the end replication problem because this problem had been laying around for a while unsolved of how DNA polymerase, well the fact that DNA polymerase could not, on its own, synthesize both chains of DNA to the end. And it seems strange that that problem had been there without anybody being able to solve it for quite a long time. DNA polymerase was revealed in 1958 by [Kornberg](https://www.nobelprize.org/prizes/chemistry/2006/kornberg/facts/) and it was pointed out in what 1970 or so, 1972 by [Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/) and others, there was this problem. And it was the late 80s or mid 80s the solution came. |
|  | Carol Greider: There were solutions in other organisms as Jack had alluded to, that various viruses … what wasn’t known was how the eucariotic chromosomes solved the problem and that did wait for the sequences, until Liz found the sequences you couldn’t really ask the question until you had the actual molecular details.Elizabeth Blackburn: And there was some peculiarities about the sequences, there were different numbers of repeats of the ends of different molecules in a population of molecules. This wasn’t like viruses although there are some viruses in which they do have recombination at the ends and they have some end repeats as well, so there were solutions that looked very plausible, that the viruses of bacteria had already evolved to have. It was really various lines of evidence that sort of said, Aha, this does not seem to be the kind of solution that new eucariots have.Jack Szostak: But if you go back and read all our early papers we were through a lot of models, they were mostly based on recombination-like mechanisms and we held on to those to the bitter end until the sequences said that can’t possibility be.Elizabeth Blackburn: Because people could draw beautiful diagrams, right, and the literature was, you did …, I don’t know how to draw beautiful ones. No but there was definitely some ideas out there and some of them have turned out to be quite applicable actually to some viruses and stuff like that, so the ideas were not completely useless.Carol Greider: … applicable to telomerase in theory, as well.Elizabeth Blackburn: Yes!Jack Szostak: Yes, that’s right.Carol Greider: There really were two answers, it’s just that one turned out to be a little bit more dominant then the other.Elizabeth Blackburn: A lot more dominant.Carol Greider: A lot more dominant, yes!Elizabeth Blackburn: As almost universal eucariots, with exceptions, and exceptions are always instructive, that is sort of the richness of the question because there is such a lot that goes on in what seems very simple, but technically a different chromosome, it sounds like you just stick a fortress around and that’s okay, but its much more interesting and dynamic than one had thought, which again makes it fascinating. |
| Q38 | It is fascinating, is it interesting because one tends to tell the story of science in retrospect as being a problem followed by a solution and its not quite that, is it? Its much more complicated. |
|  | Elizabeth Blackburn: And often observations come and then they are what you expect and then you start thinking about them and what they might mean and then realize, Yes, that might be providing a solution to something. You know it doesn’t happen in …Carol Greider: But there are also possible solutions that aren’t correct, or pursue things, that’s not how they found out, that’s not how it works and you go back and pursue a different angle and what you end up hearing about historically is those things that were correct, so it seems like a linear path when actually it was a branch in a tree of which were interesting ideas. They just didn’t turn out to be how it actually worked.Elizabeth Blackburn: Yes! Or at least not in that situation.Carol Greider: Yes, that particular situation.Jack Szostak: And also you get a solution to say the problem that you were thinking very originally, but once you have that solution you realize, Oh, now there is three other problems you hadn’t even thought of before and so it goes. And that is really true in the case of like human telomeres where the biochemistry is unbelievably complicated.Elizabeth Blackburn: And yet there is an inevitability to the complexity because people say, Well, if you want a very robust sort of system it has to be inherently complex and so suddenly it makes sense in a way that we didn’t think of. We really simplified the question where we just said, we are just going to think about the DNA and the enzyme that does it and just so, you have to do that, I think, up to a point, you have to take away the irrelevancy, but always knowing that it is taking place in a cell, an incredibly complex entity which is a cell inside an incredibly complex identity which is, in our case a human, and yet you can take these things and sort of push them up to a point and then you have to realize when you have to take the blinders off, that’s the key. But again, the inherent complexity of it, its not like a curse, its sort of like, This is the way it is, because the really interesting reasons why systems have to be that way and yet we have to, on the other hand, sort of reject the complexity at certain stages in the research. |
| Q37 | 20 years on you are still working on telomeres and telomerase and sorting out the system and one thing that … Oh yes, I am coming to Jack, I’m coming back to that. One aspect that is growing up is the therapeutic implications of the fact that telomere shortening was seen to be associated with the disease states and indeed the maintenance of telomere length in both directions seems to be important, maintained equilibrium is important. What do you feel are the potential therapeutic benefits of studying telomerase and telomeres? |
|  | Elizabeth Blackburn: It is usually divided into two general categories, one is the rather hyperactive telomerase that characterizes the great majority of human cancers, on the other hand the telomerase that is presents in much more regulated form in the natural cells of the body. The normal cells, the telomerase is present in much more regulated form in normal cells of the body and various indications, such as the associations you mentioned of short telomeres with many disease states or risks of it that’s intriguing this genetic data in cases of insufficient telomerase action which says that clearly is not good for humans to not have enough telomerase in their normal cells that have to replenish to decades of adult life if we are fortune enough to move past our re-productive years and we are looking at old age, we are interested in what our health is like for that. So understanding what’s going on in cells at this fundamental level, I think you really do understand this, just to understand what’s going on in the trajectory of humans as we age, because all of the social and other settings are now letting us age, we have this sort of unexpected biological reality to live with, so we are understanding that first of all.Now, are there quick-fixers magic pills? Not tomorrow, but maybe there is interesting things that could keep telomerase a little more active, but you have to be careful and I like to think it’s like aspirin, you take two aspirins – good – take a bottle, that’s bad. Clearly any measure would have to be carefully thought through how you would, if you want to keep telomere maintenance better, not to push it too far, because too much telomerase can help cancer cells, but I mean, really a lot to much. Then the question of course is can you exploit the high telomerase in cancer cells to selectively target cancer cells and there is beginning efforts in industry to do very early stages, to look at these kinds of things. But I think just understanding what’s going on is actually really important in understanding human ageing.Carol Greider: And it’s not just telomerase, because one of the things that we have learned in the research over the years is really that’s the short telomeres that cause the end effect and as Jack has mentioned, any time you ask a question and you find out the answer there is many more other questions to ask. There are various regulatory mechanisms that allow the telomere length to be maintained at a certain equilibrium and telomeres is essential to provide the raw material to do that, but both the telomere is regulated as well as the proteins that are on the telomeres, that the telomeres has to interact with. I think that really understanding those details of all of the components and the complexity that goes in to the regulation will tell us a lot about these diseases, these age related degenerated diseases that may not be just telomerase related but they may be a number of other genes that one can look at that may be associated with these degenerated diseases that aren’t directly the telomerase, so there is a lot of interesting avenues to pursue still, to really understand the different directions these diseases may come from. |
| Q41 | Because there was a great deal of therapeutic excitement about telomerase and telomeres early on and there still is. Was there an initial kind of pressure on you suddenly, that everybody was getting excited about the potential? Does it make life difficult if people’s expectations are a little bit too elevated early on? |
|  | Elizabeth Blackburn: I work in the basic science area, so I felt immune from that.Carol Greider: It’s all the companies that have to worry about that kind of expectations because we never really said as scientists that there was going to be that kind of therapy to come in tomorrow because we didn’t have the vested interest to be doing that.Elizabeth Blackburn: I think it is good to have these avenues explored for sure and I think that the fact that it hasn’t gone all that fast is actually not to do with the science or other sorts of things. In the meantime it’s really important to try and understand what is going on because any therapeutic is going to be all the better for having a better sense of what underlies the usefulness and where its danger points might be. It’s not clear how we think about these issues of long term diseases that affect huge numbers of people, you don’t necessarily put everybody on statins, that’s a common thing, but perhaps that equivalent isn’t necessarily the best way to go either, although we tend to be a very ‘take a pill’ oriented society and nothing wrong with that, I mean. I am all for western medicine, believe me, but I am just saying that we don’t want to limit our thinking I think to that …Jack Szostak: And jump into something too quick and not recognize a problem.Elizabeth Blackburn: Exactly, that’s right. |
| Q43 | I wanted to end just by dealing with these questions of staying with your subject or not. You two have stayed with the subject … |
|  | Carol Greider: That’s debatable, the subject really has changed continuously |
| Q43 | I am sorry, the subject expands… |
|  | Carol Greider: Yes, I was a biochemist you know and now I am working on recombination and human disease and various other things.Elizabeth Blackburn: I work with clinicians on chronic psychological stress, but the point is I am not the expert. I bring my expertise and they bring theirs, so it stays very fresh by keeping one’s expertise that you really have. Now interfacing with other expertise’s so it’s actually a very broad topic. Anything that says our cells are going to be able to keep replenishing got a lot of broad implications even though we are focused on one part of it. |
| Q45 | Maybe I will discover my questions completely redundant, but let’s say you two are at least following the questioning in the same general vein and yes, it’s taking you to new places. You, on the other hand, have seemed to jump from one question to another, but there is almost a clear break between one question and the next and they seem from the outside the two different ways to do science. One is to say, There is a problem, I will work on it for a while and then I will look for another problem, actively go and find a different problem. Would that be fair to say? |
|  | Jack Szostak: I think you could find lots of examples of people who you know have one system and they use it to address lots of different questions and that can be extremely productive and then there are other people who just like to find interesting questions in different areas and go for it. |
| Q45 | But what I was going to ask was what for you is the attraction of jumping from question to question. |
|  | Jack Szostak: Well its fun to think about new things, get into an area where you don’t really know very much so you don’t have to be fooled by the preconceptions that might dominate the field so you might have a chance of making a contribution in a different way. So that is part of the attraction. |
| Q45 | Is there also an attraction in going to less populated places? |
|  | Jack Szostak: For me, I don’t like to be working in an area where there are a lot of other people who are going to do the same experiment at the same time or a few months later. I find it more fun to be doing something that is probably unique.Elizabeth Blackburn: And that’s what telomeres were initially to. Nobody was asking these questions and it is a the most fun way to do science actually. I agree with you.Jack Szostak: In the mid or late 1980s I think the implications of all the telomere work were becoming clear and it was I think clear that a lot of people would be going into that field and so I think that helped to make me look around for other areas and all the stuff about ribozymes was very new and exciting and I was very surprised that there were very few people going into that area so I thought that we might …Carol Greider: You had already got the Nobel Prize by that time?Jack Szostak: That was 1989 and we started working on it in actually -85.Elizabeth Blackburn: And how life begins, I mean that’s a pretty important question.Jack Szostak: It’s a lot of questions when you start to break it into pieces, it’s a lot of interesting questions, so that has come to dominate what we do today. |
| ID | 0538 |
| Biographical | Born in 1936, I experienced the Second World War as a child in the city of Gelsenkirchen-Buer. This area was heavily bombed, but fortunately all members of my family survived the war and post-war period. As a child I remember my own intensive interest in biology, birds, other animals and flowers and was determined at an early age to become a scientist. Since schools were closed due to the bombing raids in 1943, my elementary school training was full of gaps. When I entered “Gymnasium” at the age of 10 in 1946, during the first year these gaps were evident and created some difficulties for me. After the first year there, however, although not being the top pupil, I went to school without any major problems. In 1950 my parents moved to Northern Germany where I finished high school in 1955 with the “Abitur”.After briefly considering whether to study biology or medicine, I opted for medicine and initiated my studies at the University of Bonn. The first two years were particularly hard, since I simultaneously decided to attend lectures and courses in biology as well. The first examination after 5 semesters (“Physikum”) was passed without any problems with remarkably good grades. This created some self-confidence for the forthcoming semesters, which I spent at the University of Hamburg for one year and the (at that time) Medical Academy in Düsseldorf. At the end of 1960 I graduated there in medicine and also finished my MD thesis.Although I remained firmly determined to continue in science, I wanted to receive a licence to practice medicine. This required at that time two years of medical internship. It brought me for short periods of time into surgery, internal medicine and for the remaining time into gynaecology and obstetrics. The last part fascinated me tremendously, although it turned out to be physically highly demanding. When I left the hospital and started to work in Medical Microbiology and Immunology at the University of Düsseldorf, for the first and only time I had some doubts whether this was the correct decision. For a short while I considered returning to the life of a practising physician; after a couple of months, however, I became more fascinated by early experimental studies. Initially I started to work on virus-induced chromosomal modifications and at the same time received relatively solid training in diagnostic bacteriology and virology, both of them at that time in an early stage of development.During my 3½ years in Düsseldorf, I became increasingly aware of the limitations in my scientific education and decided to search for a postdoctoral position elsewhere, preferably in the United States. I received an interesting offer from Werner and Gertrude Henle at the Children’s Hospital of Philadelphia, where Werner headed the Division of Virology. In 1964 I got married and our first son Jan Dirk arrived one year later. Within the same year we decided to accept the offer from Philadelphia; in the end of December 1965 I arrived there and started work at the beginning of 1966. The Henle’s laboratory was deeply interested in the newly discovered Epstein-Barr virus (EBV), and the whole team was actively engaged in developing serological tests for this virus and in studying its epidemiology. They had noted early that Burkitt’s lymphoma patients developed high antibody titres against viral antigens. I felt very much compelled to work with this agent, but noted at the same time my lack of familiarity with the rapidly developing molecular biological methods. I urged Werner Henle to permit me to work with a different agent, namely adenovirus type 12, hoping that this relatively well established system would permit me to become acquainted with molecular methods. He reluctantly agreed. I started to work eagerly on the induction of specific chromosomal aberrations in adenovirus type 12-infected human cells, simultaneously studying a DNA-replication disturbance of individual chromosomes in human lymphoblastoid and lymphoma cell lines, and, to please my mentor, I demonstrated electron microscopically the presence of EBV particles directly in individual serologically antigen-positive Burkitt’s lymphoma cells. During my years in Philadelphia the immortalising function of EBV was demonstrated for human B-lymphocytes, and the role of this virus as a causative agent of infectious mononucleosis was conclusively established.  In 1968 I received an attractive offer from Eberhard Wecker, who headed the newly opened Institute for Virology at the University of Würzburg, Germany. He offered me the establishment of my own independent group and granted me his support for a quick start in the German academic system. I accepted this offer and moved with my family in March 1969 back to Germany. Here I decided to change my topics completely to EBV research. The intention was to prove that EBV DNA persists in every tumour cell of Burkitt’s lymphoma and does not establish a persistent infection there, as assumed at that time by a number of my former colleagues. With the aid of Werner Henle in Philadelphia and George Klein in Stockholm I received a large number of Burkitt’s lymphoma cell lines and tumour biopsies. The biopsies also included material from nasopharyngeal carcinomas, where serological assays also suggested an involvement of EBV infections.  The major problem, the purification of sufficient quantities of EBV DNA from a low number of spontaneously virus-producing cells, was quickly solved. By the end of 1969 I had the first data available that the non-EBVproducing Burkitt’s lymphoma cell line Raji contained multiple copies per cell of EBV DNA. Shortly thereafter it was also possible to demonstrate EBV DNA in Burkitt’s lymphoma and nasopharyngeal cancer biopsies. It seems that this was the first demonstration of persistent tumour virus DNA in human malignancies.  In nasopharyngeal carcinomas, composed of a mixture of epithelial tumour cells and lymphocytic infiltrates, it was intensively discussed whether the EBV DNA might rest in the lymphocytic infiltrates. By using in-situ hybridisations, in 1973 we were able to document the presence of EBV DNA in the epithelial tumour cells.  In 1972 I was appointed chairman of the newly established Institute of Clinical Virology in Erlangen-Nürnberg. With the move to this city I planned to change my scientific direction. Cervical cancer had long been suspected of being caused by an infectious agent. In the late 1960s Herpes simplex type 2 (HSV-2) emerged as the prime suspect based on some seroepidemiological observations. Since our previous EBV work led to the identification of EBV DNA in specific human cancers, I had asked my colleague Heinrich Schulte-Holthausen to use the same technique to search for HSV-2 sequences in cervical cancer biopsies. All attempts, however, failed.  During the previous years I had studied a large number of anecdotal reports describing malignant conversion of genital warts into squamous cell carcinomas. Since genital warts had been shown to contain typical papilloma-virus particles, this triggered the suspicion that the genital wart virus might represent the causative agent for cervical cancer. Based on this hypothesis we initiated our papillomavirus programme in Erlangen. With the aid of the local Dermatology Hospital we received a large number of wart biopsies. Viral particles could be extracted from plantar warts and in 1974 we published our first report, demonstrating a cross-hybridisation of the plantar wart virus DNA with some warts, but by far not with all of them. Genital warts and cervical cancer biopsies were negative. This was our first hint that there exist different types of papillomaviruses. In the following years our group, as well as the group around Gérard Orth in Paris, were able to identify the plurality of the human papillomavirus family by isolating a steadily increasing number of novel types.  In 1977 I was appointed as chairman of the Institute of Virology of the University of Freiburg, Germany. Most members of my group in Erlangen joined me in moving to Freiburg. Here we continued intensively our studies on human papillomaviruses.  Late in 1979 my co-workers Lutz Gissmann and Ethel-Michele de Villiers successfully isolated and cloned the first DNA from genital warts, HPV-6. It was initially disappointing not to detect this DNA in cervical cancer biopsies. HPV-6 DNA, however, turned out to be helpful in isolating another closely related genital wart papillomavirus, HPV-11, initially from a laryngeal papilloma. By using HPV-11 as a probe, one out of 24 cervical cancer biopsies turned out to be positive. In addition, in other biopsies some faint bands became visible, permitting the speculation that they might represent hints of the presence of related, but different HPV types in these cancers. Two of my former students; Mathias Dürst and Michael Boshart, were asked to clone these bands. Both of them were successful. In 1983 we were able to document the isolation of HPV-16, in 1984 the isolation of HPV-18 DNA. We noted from the beginning that HPV-16 DNA was present in about 50% of cervical cancer biopsies, HPV-18 in our early experiments in slightly more than 20%, including several cervical cancer cell lines, among them the HeLa line.  Within the first two years after isolating HPVs 16 and 18 it became clear that these viruses must play an important role in cervical cancer development: viral DNA was commonly found in an integrated state, indicating the clonality of the tumour. In addition, part of the viral genome frequently became deleted in the process of integration. Two viral genes, E6 and E7, were consistently transcribed in the cancer cells. Precursor lesions of cervical cancer also contained these viruses and expressed the respective genes. Early contacts with pharmaceutical companies for the development of HPV vaccines failed, in view of a market analysis conducted by one of them which indicated that there would be no market available. Fortunately, this changed in later years.  My period in Freiburg permitted me to also work on other aspects of tumour virology: I discovered the potent activity of some phorbol esters in inducing latent Epstein-Barr virus DNA. This procedure also proved to be successful for other persistent Herpes-type viruses. In addition, I isolated a novel lymphotropic polyomavirus from African Green Monkey lymphoblasts. Up to 20% of sera from human adults also revealed neutralising antibodies to this virus. Our attempts to isolate a human correlate, however, failed. I also identified a novel adeno-associated virus, now labelled AAV-5, from my own skin scrapings. In collaboration with my colleague Jörg Schlehofer, we were also able to demonstrate that herpes simplex virus, but also other herpes-, adeno-, and vaccinia virus infections of polyoma- or papillomavirus DNA harbouring cells, resulted in amplification of the DNA of the latter.  The early hypothesis that cervical cancer was caused by papillomaviruses, the successful isolation and characterisation of the two most frequent HPV types in this cancer and the subsequent steps leading to a better understanding of the mechanism of HPV-mediated carcinogenesis and eventually to the development of a preventive vaccine were cited as the prime reasons for awarding one half of the Nobel Prize for Medicine or Physiology to me in 2008.  In 1983 I was appointed as the Scientific Director of the German Cancer Research Centre (Deutsches Krebsforschungszentrum) in Heidelberg, a national research centre. Besides the major task of reorganising this research centre, I tried to maintain some time for laboratory research and continued jointly with Frank Rösl to analyse intracellular and extracellular control mechanisms preventing the activity of viral oncogenes in proliferating epithelial cells.  In 2003, after 20 years, I retired from the scientific directorship of the German Cancer Research Centre. Subsequently, I kept a laboratory in the virus building of the Cancer Centre and continue up to now to act as Editor-in-Chief of the International Journal of Cancer. I started this commitment at the beginning of 2000.  In retrospect, I have devoted my scientific life mainly to the question to what extent infectious agents contribute to human cancer, trusting that this will contribute to novel modes of cancer prevention, diagnosis and hopefully later on also to cancer therapy. I am of course pleased to see that at least part of this programme has been successful. I am grateful to a large number of my former co-workers, who skilfully contributed to the programme. In addition, I most gratefully acknowledge the contributions of my wife, Ethel-Michele de Villiers, who is also a scientist and tumour virologist, for her never-ending support. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0538= [Harald zur Hausen] zur Hausen.  [Adam Smith] Oh hello, Professor zur Hausen.  [HzH] Yes.  [AS] This is Adam Smith from the web site of the Nobel Foundation … Hello. Would you mind if we recorded a very brief telephone interview with you?  [HzH] No, it’s fine.  [AS] Thank you.  [HzH] I was informed that this would come through.  [AS] Thank you very much. Well first of all, of course, many congratulations on the award of the Nobel Prize.  [HzH] Well, thank you very much. I’m of course totally surprised. And it’s of course a great pleasure for me.  [AS] Where were you when you received the news?  [HzH] Here in the Institute, in my office.  [AS] This is in the DKFZ?  [HzH] In the DKFZ, indeed. Well I am an Emeritus as you may know, but I still kept my office. I’m still Editor-in-Chief of the *International Journal of Cancer*, and also keep a laboratory here.  [AS] Yes, yes indeed. So, if we may turn to the discovery. When you first suggested that human papilloma virus caused cervical cancer, the prevailing view was that it was herpes simplex virus.  [HzH] Yes.  [AS] So how was your suggestion at first received?  [HzH] Well it was not very welcome, let’s say it this way. Because in the early phase indeed, quite a number of scientists believed that herpes simplex type 2 would do it. There were a number of reports which seemed to confirm that there are increased antibody titres to herpes simplex type 2 in cervical cancer patients. And I reported it for the first time in public in 1974 at a meeting in Key Biscayne in Florida, when there was a meeting which was specifically scheduled for herpes simplex type 2 in cervical cancer. And at that time I reported our negative results in trying to find herpes simplex type 2 DNA in cervical cancer cells. And at the same time I stated that it would be very worthwhile to look rather into genital papilloma viruses, because the reasoning for me was that I had surveyed the literature and found a number of anecdotal reports on malignant conversion of genital warts.  [AS] So I imagine, since the meeting was organised around herpes simplex virus, you were the unwelcome guest on that occasion.  [HzH] Almost. You are almost exactly stating it in the right way because my statements were not well received, and I felt as a lonely voice in that meeting.  [AS] And it took about 10 years before you discovered the main disease-causing genotypes, HPV16 and 18.  [HzH] Well it’s true, let’s say in the meantime, between – I started to work on papilloma viruses in 1972 myself – but in the meantime we could identify the, individual … excuse me, I’m still a little bit nervous at the moment.  [AS] Understandable, yes.  [HzH] Well, we could demonstrate that there exists a plurality of papilloma virus types. So there was not, as initially assumed, only one single papilloma virus type, but a multitude of different types, which was also confirmed by the group of Gérard Orth in Paris. And, but we concentrated ourselves on trying to isolate the viruses from genital warts because initially we suspected that that virus may be responsible for cervical cancer development. In 1979/1980 we could finally – it was mainly in collaboration with my co-worker Lutz Gissmann – that we could identify HPV6, and Ethel-Michele de Villiers was cloning it subsequently, with Gissmann. And subsequently we could identify another one – that was HPV11, which was also in genital warts and laryngeal papillomatosis. In fact, in the subsequent period, we were initially disappointed not to find HPV6 and 11 in cervical cancer, without one rare exception. But, the probes helped us to identify HPV16 and 18 subsequently. In 1983 and 1984 this was published, by two of my students, Mattias Dürst and Michael Boshart. And, so that was in a way for us a breakthrough because at that time period, of course, interest was awakening very substantially, and quite a large number of groups were collaborating there, and starting to work on papilloma viruses, and ask us for the probes, so we dispersed them very freely throughout the world.  [AS] Yes, I understand that you gave them to anybody who asked …  [HzH] Right.  [AS] … and indeed then others went on and claimed patents on some of them, but that’s another story, perhaps.  [HzH] Alright.  [AS] It’s perhaps surprising that vaccine development didn’t immediately follow your discoveries.  [HzH] Well, I mentioned it some time ago – in Stockholm, even – that, I tried to contact very early the German, particularly German pharmaceutical companies. And one of the companies, the Behring company in Marburg, became quite interested in it initially, and so they even funded our research for a certain period of time, with the expectation that we could collaborate on the development of vaccines. But then they did, at the same time, a market analysis and according to this market analysis there would be no market for such a vaccine. And then they stopped the funding. And it stopped for a certain period of time, indeed, at our place, intention to work on vaccines.  [AS] It shows how wrong market analysis can be.  [HzH] Well, it was totally wrong of course, as seen today. But, I mean, there’s a little bit of an excuse for these companies, because at that time the PCR technology was developed, and many people started to work with this technology, and there was – quite a wide variation in data had been obtained in this time period. And, so they … from 0–100% in supposedly negative tissues turned out to be positive, and so on. So this confused industry too.  [AS] Right.  [HzH] And, in addition…  [AS] And, so what eventually changed?  [HzH] Well, eventually it changed basically as the continuation of some molecular studies, which demonstrated indeed that the virus must be closely involved, but also the epidemiology studies, which in the end clarified the situation in demonstrating that HPV16 and 18 were so-called high-risk viruses, and indeed major risk factors for the development of cervical cancer.  [AS] And the results of the vaccination trials that have so far been reported have been enormously promising. Do you think that vaccination programmes should be widened now?  [HzH] Yes. From my viewpoint, yes, clearly so. I think the vaccination is extremely successful. It is presently – the major disadvantage at this stage is that it is too expensive for those parts of the world which most badly need the vaccine; namely, the developing world. And so the prices have to go down in the future in order to enable those people to receive the vaccine. From my personal experience, what I hear is that, in Africa, for instance, and also other parts of the developing world, the willingness to be vaccinated is remarkably high, so it’s more a question of how do we get it to those people and how do we get a drastic reduction of the present price.  [AS] One final scientific question. Do you think that in general we’re going to see more link between infectious disease and cancer in the future?  [HzH] Well, if you ask me this way, yes. My personal feeling is, yes, we will see more links. One came up this year only – the so-called Merkel cell carcinoma polyoma virus, which – the virus is called Merkel cell polyoma virus – which has been found in Merkel cell carcinomas, and every evidence at this stage points to the fact that this is indeed aetiologically involved. I think it’s, I hope indeed, that this Nobel Prize will of course create more awareness of the role of infectious agents in human cancer, and I’m so pleased that the HIV part is also awarded.  [AS] Yes, it’s a fascinating linkage. What do you think gave you the dedication to stay with the studies of HPV’s link with cervical cancer for so long?  [HzH] Well, my personal conviction that there must be … first of all there must be an infectious aetiology of this type of malignant disease, but secondly also I was in-between always encouraged – in spite of the fact that we didn’t find directly this virus – by the fact that I saw how many questions there remained open in the papilloma virus field. But, maybe I should mention it; I was not from the beginning mainly interested in papilloma virus, I was mainly interested in infectious agents in human cancer. So papilloma viruses came up as the most likely candidate from my viewpoint.  [AS] But yes, infectious agents had been the lifelong pursuit.  [HzH] Yes, indeed. Indeed.  [AS] So I shouldn’t keep you on the telephone for too long, you have many other things to do, but may I just ask you if you have any plans for how you might celebrate this?  [HzH] I don’t know yet. It was so surprising I really have to sleep about it for one night or so before I make any decisions.  [AS] I fear the chances of getting any sleep for the next little while may be rather small.  [HzH] Yes, there’s a risk indeed. Alright …  [AS] Anyway, my congratulations …  [HzH] Thank you once again.  [AS] Thank you for talking to us.  [HzH] Thank you. Bye bye.  [AS] Bye bye. |
| Interview |  |
| Q19 | The work for which the prize has been awarded was done a good quarter of a century ago, and so I imagine you’ve all allowed yourselves the luxury of imagining yourself here once or twice, so is it a huge surprise to find yourselves here? |
|  | Françoise Barré-Sinoussi: For me yes, yes it is, I never thought before, to be here one day. Surely because working on the HIV/AIDS I thought that probably you will need a vaccine to have a Nobel Prize one day for this disease. |
| Q38 | Again, something we’ll come to in a little while. This year’s prize has been awarded for work on two viruses, human papilloma virus, HPV, and human immunodeficiency virus, HIV, and the work on these two viruses indicates two very different timelines of research for discovery. in HPVs case it took you, Professor zur Hausen, a full decade to convince the community that your hunch that HPV was responsible for most cervical cancers was correct. How did it feel to have a hunch that you had to keep for ten years while working on it? |
|  | Harald zur Hausen: Let me say it this way, it’s true what you said, I mean it took about ten years or so before we were able also to prove our point, but in a way there’s some, in my opinion, there’s some similarity between AIDS and cervical cancer research said this way. It’s of course a problem of enormous magnitude, particularly in the ECS right now, killing an enormous number of people. Cervical cancer has been a problem of enormous magnitude over decades, a million year really, because it’s probably with us since the early time of mankind. In a way these are both conditions which are quite important, the agents causing them are quite different, I mean they are really different, and so research followed different pathways in a way, but I think looking at it from the viewpoint of public health these are both problems of certain importance. |
| Q38 | Certainly, yes, that unites the discoveries. But just getting back to this timeline thing, were there times during your ten-year search for the proof that you thought of abandoning the project? |
|  | Harald zur Hausen: No, not really, because I must say I was very convinced that we were on the right track from the beginning really, because first of all we had seen that the existing number of anecdotal reports are from malignant conversion of genital warts, and secondly already since the 1930s there are examples available where at least in animal systems papilloma virus has caused cancer. So it was not that farfetched to research carefully in human cancers as well, and cervical cancer was a good example. It was not well received in the early days it’s true, because another virus had been suspected at that time, namely inner genital herpes simplex type II infections, but I must say really we were convinced during this period that this was the right way to go and so we pursued it intensively. |
| Q37 | It became, as many people have reported, quite a competitive area later on, but at that point, when the epidemic was just beginning, was it a very collaborative field to be in? Were people helping each other? |
|  | Luc Montagnier: Yes, I think it was actually, we had a very good relationship with Dr Gallo and his colleagues at the NIH in the United States, and we had access to his reagent to show this virus was different from HTLV-I for the first human T-cell leukaemia virus found in men. And also we had as Françoise said, a good contact with clinicians who we are working now on AIDS, there were very few in France because in that time maybe there were other cases of AIDS, but not in France. We had also the collaboration of a very good electron microscopist, could see the first viral particle one month after we had the culture, and after that we extended our collaboration with immunologists and epidemiologists so that we could have a group which could concur to find this virus as /- – -/ because it was the main … of course /- – -/ virus is good, but was it passenger virus, was it something else, where did it go, this is where the main problem, and in that of course, and my /- – -/ colleagues also quickly contributed. |
| Q10 | What have we learnt so far from those patients? |
|  | Françoise Barré-Sinoussi: We already learn the patients that are called HIV controllers is less than 2% of people that are infected, they control perfectly well their viral load, and we already learned that at least some of these controllers have developed a sub-population of T cells which are capable to eliminate infected cells. We know that this sub-population of T cells is less activated that the cells that we found in most HIV patients that progress to disease. What we don’t know yet is why this proportion of patients are developing this response, what are the signals that in use this sub-population of efficient CD8 cells, we know that there is some genetic factors that are probably associated, genetic factor does not explain all of it because not all HIV controllers are HLAB 27, B57, and to speak into English, into scientific language, but whatever, that means that genetic factors are probably involved. |
| Q36 | Right. Thank you. A question for any and all of you, do you think that viruses will come to play a more important role in cancer in the future? Do you think that we don’t yet fully understand how important viruses are in causing cancer? |
|  | Luc Montagnier: I think the candidates retroviruses is also for breast cancer, prostate cancer, it’s possible, and probably also we have to look at infectious bacteria, the microbes, not only the viruses, because cancer to be some factors, you know, to be termed not the only factor, but since cancer is multifactorial probably there are some infectious agents probably like the stomach cancer where you’ve got *Helicobacter pylori* also. Also a Nobel Prize …  Luc Montagnier: … two years ago, so I think yes, we should look for more infectious agents in cancer, it’s a way also to protect because we have needs to counteract the effect on viruses, vaccine but also antiviral drugs so there are many possibilities to find viruses and micro variations as well by antibiotics for instance.  Harald zur Hausen: I agree with what Luc Montagnier said a moment ago. Indeed, in my opinion too there are good chances that additional cancers will be linked to viruses in the future. If you look into the discovery of new viruses potentially linked to human cancer it becomes apparent that during the past two years four new types in the papilloma virus group popped up, one by the way here in Sweden. One of them is also linked to a specific type of human cancer, namely the so-called Merkel cell tumours, a relatively rare tumour arising on the immune suppression in the skin and your endocrine tumour. I personally believe that besides breast cancer I also strongly feel that there’s very good reason to search very intensively for viral etiology, leukemias, lymphomas, really cancers where you have very good reasons to search for agents, so right now from epidemiological grounds.  I also feel, which relates to what Professor Montagnier said a moment ago, to look more carefully in cancers where we know already since a long time that genetic modifications play a major role, because there’s no infections linked to cancer at this moment without additional genetic modifications in the host cell, that’s an interplay between the infections and modifications of the host cell genome. For those reasons I personally also suspect that cancer of the colon is interesting and looking for it for quite a number of variety, in fact I will allude to this in my Nobel Lecture a little bit, and I think it’s still an open question to which extent that it affects a link to human cancer. If you look at it globally and if you include the old /- – -/ cancers right now identified besides *Helicobacter pylori* in gastric cancer also 10% of gastric cancers are linked to /- – -/ bowel infections you come up to a figure of about 20-21% of the global cancer incidents. I personally believe that this is not the end of the story, and that we are still in for further surprises.  Françoise Barré-Sinoussi: I totally share with what has been said and we have already a lot of viruses that are related to cancer and we will discover more in the future. I just would like maybe one point that we have to consider with the virus HIV, under treatment. For example there is more and more complications that we could see in HIV patients including cancer, and I personally believe that we have to understand better what’s’ going on, why when a patient restores an immunity that he develops cancer, and probably we will discover also several agents that are responsible for cancer.  Harald zur Hausen: I mean to add one point, if you identify infectious agents of human cancer then of course as Professor Montagnier said before, we have not only a better possibility in prevention but also for therapy because in many of these cancers we can identify exactly the molecules that are responsible for the malignant growths. In cervical cancer for instance, if you switch off the two viral genes which are active the cells revert to a quasi-normal state, and so these are, you identify targets and you can much better cope with those types of diseases in the end if you try to develop a targeted chemotherapy in those cases. |
| Q43 | You mentioned the search for infective agents, is there a sufficiently good apparatus in place do you think to search for the agents? |
|  | Harald zur Hausen: In my opinion it’s an underdeveloped area in the research on the whole, I mean globally, because there are a couple of laboratories working on these questions, but on the whole the interest decreased rapidly in the 1970s, between 1970s and 80s, with the discovery of onco-genes and tumour suppressor genes, because at that time quite a number of scientists believed there was no need any more for infectious agents. You could explain cancer quite readily by a failing interplay between oncogenes and chemo suppressive genes, but that story turns out to be not as simple as it was thought during this period, and many of the former virologists turned into cell biologists during this period. I think it’s a gradually now an awakening interest again in these questions and I hope it will go on in the future.Luc Montagnier: Yes, we have a much better technology now to identify new agents than we had in the 80s, much more powerful.Françoise Barré-Sinoussi: We will probably learn from the genomics I think, the new technology will be very helpful to discover new agents responsible for disease.Luc Montagnier: We don’t intercultivate viruses anymore, it’s /- – -/ in the case, because we can cultivate the papilloma viruses in vitro but all the /- – -/ techniques you can …Harald zur Hausen: Without molecular biology we wouldn’t have been able to identify the HIVs /- – -/ than without techniques. |
| Q12 | So as some last thoughts, what advice would you offer to young people who want to come into the area and search for causative agents for these diseases? |
|  | Luc Montagnier: The very first to say there are still plenty of things to find, new /- – -/ objects, which already exist, we don’t know. Actually probably some people say we know only 10% of the virus world, and so there are many other viruses to come, new epidemics perhaps but also plenty of work to do, and probably quicker, in a much quicker than we did in the past. I think it’s a very interesting field, and also for helping humankind because cancer is the main cause of death and disease and it’s a very terrible disease and we have to find all the agents including viruses and microbes.Harald zur Hausen: If you ask me, I will say develop original and slightly unorthodox ideas, avoid to believe too much in dogmas, and be persistent, and either prove or disprove your own hypothesis.Françoise Barré-Sinoussi: I totally agree, about dogma, and be very persistent, but also don’t be afraid to work in multi-disciplinary approaches, this is a road for success indeed. |
| ID | 0539 |
| Biographical | I was born in July 1947 in the 19th arrondissement of Paris, the city which remains my home today. My childhood holidays were, however, spent in the Auvergne countryside in central France, where I was content to spend my days outdoors, observing the wonders of the natural living world. Even the smallest of insects could capture my attention for hours. This fascination for the natural world was perhaps the earliest indication of the future direction my life would take.During my school years, my passion for science was reﬂected in my grades, which were by far better in scientific subjects than in languages and philosophy. Having completed my baccalauréat in 1966, I was initially undecided between medicine and biomedical sciences as the subject for my university studies. I finally decided to opt for an undergraduate degree at the Faculty of Sciences at the University of Paris. My choice was ultimately dictated by the pragmatic reasoning that a degree in Natural Sciences was shorter and less expensive than a degree in Medicine, and I was keen to not have to burden my family with unnecessary further expenses to support me during my studies. Towards the end of my degree, I seriously questioned the possibility of research as a career option. It was therefore important for me to gain laboratory experience to clarify these doubts about my future. I contacted a large number of both private and public laboratories offering to volunteer part-time at the bench. My search for a host laboratory proved fruitless for many months. It was only when a friend of mine from university suggested contacting a group with whom she had been collaborating that I finally found a laboratory willing to host me as a volunteer. The group was led by Jean-Claude Chermann at the Institut Pasteur site at Marne-la-Coquette. Chermann was studying the relationship between retroviruses and cancers in mice. Very early on he transmitted so much passion and enthusiasm for the research I was doing, that, although I was supposed to continue attending classes for my degree, I spent all my time in the lab and only made an appearance at the university site to pass the necessary exams. Very quickly after my arrival in the Chermann group, Jean-Claude proposed a PhD project. My project analysed the use of a synthetic molecule which inhibited the reverse transcriptase to control leukaemia induced by Friend virus. This synthetic molecule, named HPA23, proved capable of inhibiting reverse transcriptase activity of Friend virus in culture. Pre-clinical tests showed that the molecule was capable of delaying the progression of the disease in mice. I completed my PhD relatively rapidly, as [Jacques Monod](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1965/), director of the Institut Pasteur at the time, had decided to move all external sites of the institute (including the Marne-la-Coquette site) back to the main campus in the 15th arrondissement of Paris. The move of the laboratory to the main campus would have proved a confusing time, and I was eager to complete my PhD before the move. I was awarded my PhD in 1974 by the Faculty of Sciences at the University of Paris.During my time as a PhD student, the group was visited by Dr Dan Haapala and Dr Robert Bassin, two researchers from the National Cancer Institute (NCI) of the National Institutes of Health (NIH) in the United States, for a sabbatical research period. Furthermore, a member of this lab had been in our group teaching us the technique for the detection of reverse transcriptase, soon after the discovery of this enzyme by [David Baltimore and Howard Temin](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1975/). Following these contacts, I decided to join Bob Bassin for a post-doctoral research fellowship at the NIH in Bethesda in the mid-70s. My research project was a challenging one, aiming to identify the viral target of the Fv1 gene product implicated in the genetic restriction of murine leukaemia virus replication. Although the project was difficult, my experience at the NIH was a truly enriching one, albeit relatively short. I only remained one year in the United States, as during my PhD I had met my future husband, whom I later married in 1978. In addition, while in the US I discovered that I had been awarded an INSERM (National Institute for Health and Medical Research in France) position to return to Jean-Claude Chermann’s laboratory (which had in the meanwhile moved to the central Pasteur campus) in the unit of Professor Luc Montagnier.The group, which was slowly expanding in size in the late 70s and early 80s, was one of the few groups which continued to study the link between retroviruses and cancers. Indeed, many others had turned their attention to oncogenes, whose crucial role had been illustrated in the mid-70s by [J. Michael Bishop and Harold Varmus](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1989/). My research project at the time was to study the natural control of retroviral infections in the host, in particular the role of interferon in controlling endogenous retroviruses, and the functional implication of retroviral sequences on the metastatic potential of tumour cells in mouse models.In late 1982, Luc Montagnier was contacted by Françoise Brun-Vézinet, a virologist working at the Bichat Hospital in Paris. Françoise Brun-Vézinet was working closely with Willy Rozenbaum, one of the first clinicians in France to observe the alarming new epidemic, which seemed to be affecting certain homosexuals. Willy had observed a number of cases in his ward, and had made the link with the Centres for Disease Control (CDC) report which had been published in 1981. After this first contact, Luc Montagnier asked me whether I was interested in working on this new project to determine whether a retrovirus could be responsible for the disease. After discussion with Jean-Claude Chermann, we accepted the proposal. We had previously detected mouse mammary tumour virus (MMTV) sequences in the lymphocytes of breast cancer patients, and we were familiar with the technique of reverse transcriptase activity detection. It would have been a relatively routine procedure to detect the presence of a retrovirus, and we were obviously keen to determine whether a retrovirus was present in patients affected by this newly described disease (later to be known as AIDS). In late December 1982, meetings were held between our group at the Institut Pasteur and Willy Rozenbaum and Françoise Brun-Vézinet. The clinical observations suggested that the disease attacked the immune cells, but the strong depletion of CD4 lymphocytes greatly hindered the isolation of the virus from these rare cells in patients with AIDS. We therefore decided to use a lymph node biopsy from a patient with generalised lymphadenopathy. We waited until the new year to obtain the first patient biopsy from which lymphocytes were isolated and cultured. The cell culture supernatant was regularly tested for reverse transcriptase activity. The first week of sampling did not show any reverse transcriptase activity, but in the second week I detected weak enzymatic activity, which increased significantly a few days later. The reverse transcriptase activity level dropped dramatically however, as the T lymphocytes in the culture were dying. To save the culture, with the hope of preserving the virus, we decided to add lymphocytes from a blood donor to the cell culture. This idea proved successful, and as we had hoped, the virus − which was still present in the cell culture − started to infect the newly added lymphocytes and we were soon again able to detect significant reverse transcriptase activity. We named this newly isolated virus lymphadenopathy associated virus (LAV). At this point it was important to visualise the retroviral particles, and Charles Dauguet, in charge of the microscopy platform at Pasteur, provided the first images of the virus in February 1983.  The isolation, amplification and characterisation of the virus rapidly ensued, and the first report was published in *Science* in May 1983. In the same month, I presented our findings at the annual Cold Spring Harbor Meeting, after which I was invited by researchers at the CDC and by others at the NIH in Bethesda to discuss the results in further detail. During the following months, we continued to characterise this newly isolated virus, and a collaboration with molecular biologists at the Institut Pasteur determined the genome sequence. The collective efforts by researchers in our group and others, and by clinicians, brought together sufficient data to convince the scientific community and the relevant authorities that LAV (later to be named human immunodeficiency virus, HIV) was the etiological agent of AIDS.  The year 1983 marked the beginning of my career in HIV research at the Institut Pasteur, which still continues to this day. I remained at the Institut Pasteur, even after the departure of Jean-Claude Chermann in 1987, and I was finally appointed as head of the Biology of Retroviruses Unit in 1992. My professional life has been intrinsically linked with collaboration with resource-limited countries. My first visit to an African country was in 1985, on the occasion of a World Health Organisation (WHO) workshop in Bangui (Central African Republic). This visit was an eye-opening experience. The culture shock and dire conditions impressed me greatly and instilled in me a desire and necessity to collaborate with resource-limited countries. My first visit to Vietnam in 1988 was the first of many visits, and the first collaborative steps with Asian countries. This long-lasting collaboration with Africa and Asia has resulted in continual exchanges between young scientists from the respective countries and researchers in Paris.  My unit at the Institut Pasteur was re-confirmed in 2005 and re-named the Regulation of Retroviral Infections Unit. The unit hosts approximately 20 people at any one time, consisting of students, post-docs and permanent research staff. Currently the unit is interested in defining the immune correlates of protection against HIV infection for vaccine research and the correlates of protection against AIDS for immunotherapy. Along these lines, the unit is focusing its research on the mechanisms of host control of HIV infection, both at the cell level and at the level of the immune response. We are studying examples of natural protection against infection, such as HIV-exposed but uninfected individuals (EU) and the placental barrier against HIV in-utero transmission; or of natural protection against disease, such as HIV controllers (HIC) and animal models of non-pathogenic infection (African Green Monkey, AGM /SIVagm).  Although I anticipate continuing my professional endeavours largely unchanged by the Nobel Prize, I hope that this recognition will provide the necessary spark to spur international efforts in the fight against HIV/AIDS. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0539=FB-S [Françoise Barré-Sinoussi] Hello.  [Adam Smith] Ah, hello, Professor Barré-Sinoussi.  [FB-S] Yes.  [AS] This is Adam Smith from the Nobel Foundation web site.  [FB-S] Okay.  [AS] We have a tradition of recording very short telephone interviews with new Nobel Laureates after the award, so would you mind if we spoke very briefly?  [FB-S] No, not at all, that’s fine.  [AS] Thank you. Many congratulations, of course, on the award.  [FB-S] Thank you.  [AS] I gather that you are in Cambodia, and how did you hear the news?  [FB-S] I got the news indeed by a journalist from the French radio, the national radio, who called me in the afternoon in Cambodia for an interview, and I didn’t know about the news before.  [AS] And …  [FB-S] It was a big surprise.  [AS] I can imagine. It’s, indeed, it’s 25 years after the publication of those two papers in which you describe the first lentivirus found in humans. Looking back at those experiments where you first identified retroviral activity in – coming from the cells of – cultured from patients, do you remember the sense of excitement when you found that result?  [FB-S] Ah, you know, the excitement was really in different phases, because first it was the isolation of the virus from a patient that was with symptoms associated with AIDS, but he had no AIDS yet. And regulate the virus on lymph node. And, of course it was the surface fragment to get this virus out of the cell culture. But at this time, it was the first isolate only, and secondly we had to compare if the virus had any relationship with HTLV-1, which was the second retrovirus known at that time. And, we obtained reagents from Gallo’s lab to compare, and the second excitement was when we realised that the cross-activity, as we say, with HTLV-1 was negative. That was really for us, telling us that it’s not a known virus up to now. Then we had electron microscopy pictures showing that the morphology was different, and so on. So, it was, I would say, a progressive excitement. Also the fact that each time that we make an hypothesis; for example, of course, we hypothesized that the virus was targeting CD4+ T cells, and then make the experiment, and the answer was, yes, this virus has a tropism mostly for CD4+ T cells, and also was killing the CD4+ T cells. So, you know, all the evidences were really in favour of the virus. Then, we developed diagnostic tests to make several epidemiological studies, and found out that only patients that were with AIDS or with pre-AIDS had antibodies against this virus, and not patients with other disease, or blood donors. So, all the evidence were going together to the role of this virus in this newly identified disease. So, again, it’s a step-by-step excitement phase, I would say.  [AS] And what gave you the idea of looking for a retrovirus in the first place; the original hypothesis?  [FB-S] First thing is because most of the virus family were already explored. For example, some scientists thought that it could be viruses related to hepatitis virus, or to cytomegalovirus, and so on. The – almost the only family that was not explored was retrovirus. Secondly, as I mentioned before, the only known retrovirus at that time was HTLV-1, and it was reported that HTLV could infect T-lymphocytes. And, of course in this disease, in AIDS, we knew that T-lymphocytes were affected in the disease, characterized by immune deficiency in the patients. Thirdly, I will say that we knew also from the literature that cats, when they are infected by a retrovirus, called feline leukaemia virus, most of the cats are dying from immune deficiency before dying of leukaemia. So, it was several line of arguments telling us that we should look for retrovirus really. So the reason, since we were working on mammalian retroviruses at Pasteur at that time, we said, okay, look, we have all the reagents, we have the technique, and so let’s try.  [AS] Yes, and the award of the Nobel Prize will focus attention on the discovery, and on AIDS in general. What would you like the message of the Prize to be? Is there anything in particular you would like people to note at this point?  [FB-S] The main message I will say today is, first of all, that this success in the discovery of the AIDS virus is really a success of a world team with different expertise. And I think, for the future, it’s also important, especially when working on infectious disease, to have a world network of clinicians, virologists and microbiologists, working in the hospitals and basic sciences. This was really essential for me in the discovery of the AIDS virus. And I think it’s essential also for tomorrow for discovering new, emerging, or re-emerging agents responsible for infectious disease.  [AS] And, you find yourself now in Cambodia, so how do you intend to celebrate the award of this Prize?  [FB-S] Right now I must say I’m very, very busy by different phone calls from the media. I’m at the Pasteur Institute in Cambodia, and we try to answer as much as we can. Then, I will probably leave Cambodia earlier to go back to France tomorrow night. And we will certainly celebrate with my own laboratory. We have already started to celebrate with our collaborators here in Cambodia. For me it’s important that the announcement was made at the moment that I was in a developing country because I’ve been working with developing countries since the mid-1980s and it’s really working with those countries that gives me another view, or another way, of orienting my research after the discovery of HIV/AIDS, of the HIV virus. It’s important to really know what’s going on in those countries strongly affected by these kinds of disease.  [AS] Yes, and I know your laboratory has many, many links with developing countries. So …  [FB-S] That’s right.  [AS] … When you come to Stockholm to receive the award in December, perhaps we can explore that in greater detail then. But for now I should let you get on. Thank you very much indeed for taking the time to speak to us.  [FB-S] Thank you, thank you very much.  [AS] Okay, and congratulations again.  [FB-S] Bye bye.  [AS] Bye bye.  [FB-S] Thank you. Bye. |
| Interview |  |
| Q19 | The work for which the prize has been awarded was done a good quarter of a century ago, and so I imagine you’ve all allowed yourselves the luxury of imagining yourself here once or twice, so is it a huge surprise to find yourselves here? |
|  | Françoise Barré-Sinoussi: For me yes, yes it is, I never thought before, to be here one day. Surely because working on the HIV/AIDS I thought that probably you will need a vaccine to have a Nobel Prize one day for this disease. |
| Q38 | Again, something we’ll come to in a little while. This year’s prize has been awarded for work on two viruses, human papilloma virus, HPV, and human immunodeficiency virus, HIV, and the work on these two viruses indicates two very different timelines of research for discovery. in HPVs case it took you, Professor zur Hausen, a full decade to convince the community that your hunch that HPV was responsible for most cervical cancers was correct. How did it feel to have a hunch that you had to keep for ten years while working on it? |
|  | Harald zur Hausen: Let me say it this way, it’s true what you said, I mean it took about ten years or so before we were able also to prove our point, but in a way there’s some, in my opinion, there’s some similarity between AIDS and cervical cancer research said this way. It’s of course a problem of enormous magnitude, particularly in the ECS right now, killing an enormous number of people. Cervical cancer has been a problem of enormous magnitude over decades, a million year really, because it’s probably with us since the early time of mankind. In a way these are both conditions which are quite important, the agents causing them are quite different, I mean they are really different, and so research followed different pathways in a way, but I think looking at it from the viewpoint of public health these are both problems of certain importance. |
| Q38 | Certainly, yes, that unites the discoveries. But just getting back to this timeline thing, were there times during your ten-year search for the proof that you thought of abandoning the project? |
|  | Harald zur Hausen: No, not really, because I must say I was very convinced that we were on the right track from the beginning really, because first of all we had seen that the existing number of anecdotal reports are from malignant conversion of genital warts, and secondly already since the 1930s there are examples available where at least in animal systems papilloma virus has caused cancer. So it was not that farfetched to research carefully in human cancers as well, and cervical cancer was a good example. It was not well received in the early days it’s true, because another virus had been suspected at that time, namely inner genital herpes simplex type II infections, but I must say really we were convinced during this period that this was the right way to go and so we pursued it intensively. |
| Q37 | It became, as many people have reported, quite a competitive area later on, but at that point, when the epidemic was just beginning, was it a very collaborative field to be in? Were people helping each other? |
|  | Luc Montagnier: Yes, I think it was actually, we had a very good relationship with Dr Gallo and his colleagues at the NIH in the United States, and we had access to his reagent to show this virus was different from HTLV-I for the first human T-cell leukaemia virus found in men. And also we had as Françoise said, a good contact with clinicians who we are working now on AIDS, there were very few in France because in that time maybe there were other cases of AIDS, but not in France. We had also the collaboration of a very good electron microscopist, could see the first viral particle one month after we had the culture, and after that we extended our collaboration with immunologists and epidemiologists so that we could have a group which could concur to find this virus as /- – -/ because it was the main … of course /- – -/ virus is good, but was it passenger virus, was it something else, where did it go, this is where the main problem, and in that of course, and my /- – -/ colleagues also quickly contributed. |
| Q10 | What have we learnt so far from those patients? |
|  | Françoise Barré-Sinoussi: We already learn the patients that are called HIV controllers is less than 2% of people that are infected, they control perfectly well their viral load, and we already learned that at least some of these controllers have developed a sub-population of T cells which are capable to eliminate infected cells. We know that this sub-population of T cells is less activated that the cells that we found in most HIV patients that progress to disease. What we don’t know yet is why this proportion of patients are developing this response, what are the signals that in use this sub-population of efficient CD8 cells, we know that there is some genetic factors that are probably associated, genetic factor does not explain all of it because not all HIV controllers are HLAB 27, B57, and to speak into English, into scientific language, but whatever, that means that genetic factors are probably involved. |
| Q36 | Right. Thank you. A question for any and all of you, do you think that viruses will come to play a more important role in cancer in the future? Do you think that we don’t yet fully understand how important viruses are in causing cancer? |
|  | Luc Montagnier: I think the candidates retroviruses is also for breast cancer, prostate cancer, it’s possible, and probably also we have to look at infectious bacteria, the microbes, not only the viruses, because cancer to be some factors, you know, to be termed not the only factor, but since cancer is multifactorial probably there are some infectious agents probably like the stomach cancer where you’ve got *Helicobacter pylori* also. Also a Nobel Prize …  Luc Montagnier: … two years ago, so I think yes, we should look for more infectious agents in cancer, it’s a way also to protect because we have needs to counteract the effect on viruses, vaccine but also antiviral drugs so there are many possibilities to find viruses and micro variations as well by antibiotics for instance.  Harald zur Hausen: I agree with what Luc Montagnier said a moment ago. Indeed, in my opinion too there are good chances that additional cancers will be linked to viruses in the future. If you look into the discovery of new viruses potentially linked to human cancer it becomes apparent that during the past two years four new types in the papilloma virus group popped up, one by the way here in Sweden. One of them is also linked to a specific type of human cancer, namely the so-called Merkel cell tumours, a relatively rare tumour arising on the immune suppression in the skin and your endocrine tumour. I personally believe that besides breast cancer I also strongly feel that there’s very good reason to search very intensively for viral etiology, leukemias, lymphomas, really cancers where you have very good reasons to search for agents, so right now from epidemiological grounds.  I also feel, which relates to what Professor Montagnier said a moment ago, to look more carefully in cancers where we know already since a long time that genetic modifications play a major role, because there’s no infections linked to cancer at this moment without additional genetic modifications in the host cell, that’s an interplay between the infections and modifications of the host cell genome. For those reasons I personally also suspect that cancer of the colon is interesting and looking for it for quite a number of variety, in fact I will allude to this in my Nobel Lecture a little bit, and I think it’s still an open question to which extent that it affects a link to human cancer. If you look at it globally and if you include the old /- – -/ cancers right now identified besides *Helicobacter pylori* in gastric cancer also 10% of gastric cancers are linked to /- – -/ bowel infections you come up to a figure of about 20-21% of the global cancer incidents. I personally believe that this is not the end of the story, and that we are still in for further surprises.  Françoise Barré-Sinoussi: I totally share with what has been said and we have already a lot of viruses that are related to cancer and we will discover more in the future. I just would like maybe one point that we have to consider with the virus HIV, under treatment. For example there is more and more complications that we could see in HIV patients including cancer, and I personally believe that we have to understand better what’s’ going on, why when a patient restores an immunity that he develops cancer, and probably we will discover also several agents that are responsible for cancer.  Harald zur Hausen: I mean to add one point, if you identify infectious agents of human cancer then of course as Professor Montagnier said before, we have not only a better possibility in prevention but also for therapy because in many of these cancers we can identify exactly the molecules that are responsible for the malignant growths. In cervical cancer for instance, if you switch off the two viral genes which are active the cells revert to a quasi-normal state, and so these are, you identify targets and you can much better cope with those types of diseases in the end if you try to develop a targeted chemotherapy in those cases. |
| Q43 | You mentioned the search for infective agents, is there a sufficiently good apparatus in place do you think to search for the agents? |
|  | Harald zur Hausen: In my opinion it’s an underdeveloped area in the research on the whole, I mean globally, because there are a couple of laboratories working on these questions, but on the whole the interest decreased rapidly in the 1970s, between 1970s and 80s, with the discovery of onco-genes and tumour suppressor genes, because at that time quite a number of scientists believed there was no need any more for infectious agents. You could explain cancer quite readily by a failing interplay between oncogenes and chemo suppressive genes, but that story turns out to be not as simple as it was thought during this period, and many of the former virologists turned into cell biologists during this period. I think it’s a gradually now an awakening interest again in these questions and I hope it will go on in the future.Luc Montagnier: Yes, we have a much better technology now to identify new agents than we had in the 80s, much more powerful.Françoise Barré-Sinoussi: We will probably learn from the genomics I think, the new technology will be very helpful to discover new agents responsible for disease.Luc Montagnier: We don’t intercultivate viruses anymore, it’s /- – -/ in the case, because we can cultivate the papilloma viruses in vitro but all the /- – -/ techniques you can …Harald zur Hausen: Without molecular biology we wouldn’t have been able to identify the HIVs /- – -/ than without techniques. |
| Q12 | So as some last thoughts, what advice would you offer to young people who want to come into the area and search for causative agents for these diseases? |
|  | Luc Montagnier: The very first to say there are still plenty of things to find, new /- – -/ objects, which already exist, we don’t know. Actually probably some people say we know only 10% of the virus world, and so there are many other viruses to come, new epidemics perhaps but also plenty of work to do, and probably quicker, in a much quicker than we did in the past. I think it’s a very interesting field, and also for helping humankind because cancer is the main cause of death and disease and it’s a very terrible disease and we have to find all the agents including viruses and microbes.Harald zur Hausen: If you ask me, I will say develop original and slightly unorthodox ideas, avoid to believe too much in dogmas, and be persistent, and either prove or disprove your own hypothesis.Françoise Barré-Sinoussi: I totally agree, about dogma, and be very persistent, but also don’t be afraid to work in multi-disciplinary approaches, this is a road for success indeed. |
| ID | 0540 |
| Biographical | I was born on August 18, 1932 in Chabris, a “bourg”, larger than a village but smaller than a town, located in Berry south of the Loire Valley. This was – and still is – a region of agriculture with some renowned products such as welsh rabbit, goat cheeses and white asparagus. It was the place where my mother had grown up but, in fact, I never lived there.On my father’s side, his parents came from Auvergne, a province in the centre of France, made of rich plains and old volcanoes, the latter probably being at the origin of my family name: Montagnier, the man living in mountains.In his youth, my father had caught a terrible disease: streptococcal arthritis, ending in irreversible lesions in the aortic valves. He was therefore declared unfit for military service and had to find a sedentary job: he became an accountant and excelled in this profession, which implied, at that time, mainly hand-written work. He started working in the Poitiers area and then moved a little farther north to Châtellerault, a small city between Tours and Poitiers.As an only child, I was cherished by my mother, a housewife, but two events dominated this pre-war period, of which I keep a vivid memory:I was badly injured by a high speed car while crossing a main road: multiple wounds of which I keep some visible scars. After two days in a coma, I emerged as if I was born again, at the age of 5 (Figure 1).… and two years later came the declaration of war in 1939, while the whole family was harvesting grapes in the vineyards of my mother’s brother. I still remember the images in a newspaper of Warsaw ruins after a bombing by German planes.And then, in 1940, came the “real” war: the German invasion, my parents and I leaving their house (close to a risky railway station), fleeing on the roads in a little car, and finally more exposed to German bombing during this “exodus” than if we had stayed home.The first year of German occupation was terrible, in that we had no food reserves and most of the time we were starving. I was a rather puny boy and during the four years of the war did not gain a gram! The “ersatz” did not stimulate my appetite, when I was dreaming of chocolate and oranges! My father had chronic enterocolitis and, worse, my grandfather (his father) was diagnosed with rectal cancer. He died in 1947 after terrible suffering and each time I visited him, I could see the inexorable progression of the disease. This affected me so much that it is probably one reason why I decided later to study medicine and to start research on cancer.In June 1944, our house (so close to the railway) was partly destroyed − this time by an Allied bombing. I keep a mixed feeling of this year of the liberation of France. It was a great relief but I could not forget also the vision of so many dead people, civilians and soldiers, and the images of skinny deportees released from concentration camps. I will hate wars and their atrocities for the rest of my life.At high school I did well, being usually ahead of my classmates. This is when I became curious about scientific knowledge, having left behind my religious Catholic belief.Following the example of my father, who was tinkering in his leisure days with electric batteries, I set up a chemistry laboratory in the cellar of the new house which was requisitioned to accommodate us. There, I enthusiastically produced hydrogen gas, sweet-smelling aldehydes and nitro compounds (not nitro-glycerine!) that had the unfortunate habit of blowing up in my face.I was delighted to read – in popularised books – the impressive progress of physics, especially atomic physics. Being good in physics and chemistry – but not as good in maths – I decided not to prepare to compete for the “Grandes Ecoles” but instead to register both at the School of Medicine and the Faculty of Sciences in Poitiers. My goal was in fact to start a research carrier in human biology, but there was no such specialty in Poitiers, either in Medicine or in Sciences. Since both the Faculty and School were within walking distance, I could spend the morning at the hospital and the afternoon attending courses in botany, zoology and geology, which were the main disciplines of the degree course in Sciences.Fortunately the new Professor of Botany, Pierre Gavaudan, was a very atypical professor in that his scientific interests went far beyond the classification of plants. In fact, I owe him for having opened me a large window on what was the beginning of a new Biology, the DNA double helix, the *in vitro* synthesis of proteins by ribosomes and the structure of viruses.At the same time, I was installing at home a device combining a time-lapse movie camera and a microscope, thanks to a gift by my father. This allowed me to do my first research work. I was studying a phenomenon known since 1908 as the phototaxy of chloroplasts: the property of some algae living at the surface of ponds to orient their large unique chloroplast according to the intensity of light; if the light was too intense, the chloroplast turned inside the tubular cell to present its edge. In dark or weaker light, the chloroplast, a flat plate, exposed its larger surface. The phenomenon took a few minutes, which could be analysed by time-lapse cinematography. Using different glass filters, I could show that it was not the wavelength absorbed by the chlorophyll (red light) which regulated the orientation of the chloroplasts but indirectly some yellowish pigments absorbing the blue light. I was very proud, at the age of 21, to defend this work as a small thesis at the Faculty of Sciences of Poitiers. I was asked by my mentor, Pierre Gavaudan, to do research also on a literature-based subject: the L-forms of bacteria. This allowed me to make my first incursion – not the last – into the world of filtering bacteria. I could only find the references on this controversial subject at the library of the Institut Pasteur in Paris. This was indeed the time when I left Poitiers for Paris, where I was able to complete my medical studies as well as explore some aspects of biology closer to human beings, particularly neurophysiology, virology and oncology.Having been hired as an assistant at the Sorbonne at the age of 23, I started learning old-fashioned technologies derived from [Alexis Carrel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1912/)‘s work on chick embryo heart cultures, as well as that of human cell lines in monolayers. Although my research was not productive at all, I keep from this period a solid expertise of Pasteurian technologies for working in perfectly sterile conditions without the use of antibiotics.In 1957, the first description of infectious viral RNA from the tobacco mosaic virus by Fraenkel-Conrat and Gierer and Schramm determined my vocation: to become a virologist using the modern approach of molecular biology.I started with the foot and mouth virus and then, in Kingsley Sanders’ laboratory at Carshalton near London, I was proud to identify for the first time an infectious double-stranded RNA from cells infected with the murine encephalomyocarditis virus, a small single-stranded RNA virus. This demonstrated for the first time that RNA could replicate like DNA by making a base-paired complementary strand.In order to perfect my knowledge of oncogenic viruses, I moved from Carshalton to Glasgow where a new Institute of Virology had been recently inaugurated, headed by a remarkable virologist, Michael Stocker, and where many high-ranking visitors, among them [Renato Dulbecco](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1975/), were spending sabbatical years.Working on a small oncogenic DNA virus, polyoma, I could show there, with I. Macpherson, a new property of transformed cells, that of growing in soft agar. Using this technique, it was easy to detect the transforming capacity of polyoma virus and its DNA. We showed that naked DNA alone carried all the oncogenic potential of the virus. This now looks pretty obvious, but it was not so at that time.Back to France at the Institut Curie, I extended this finding to a number of cancer cells, transformed or not by oncogenic RNA or DNA viruses. However, this property allowed me to distinguish some *in vitro* steps in the process of transformation, which were correlated with some modifications of the plasma membrane and of the carbohydrate layer surrounding it.A great mystery remained at that time: that of the replication of the oncogenic RNA viruses, now known as retroviruses. [Howard Temin](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1975/) (Figure 2) had proposed the hypothesis of a DNA intermediate, but other possibilities could be considered. I myself tried to find a double-stranded RNA specific of the Rous sarcoma virus, a virus able to infect and transform chick embryo cells. I indeed isolated double-stranded RNA sequences, but they were of cellular origin and existed at the same level in non-infected cells! With Louise Harel, I later showed that this RNA was partly coming from repetitious sequences of DNA. In retrospect, it could at least in part represent the recently identified interfering RNAs involved in the negative control of messenger RNA translation.In 1969–70, the isolation of an RNA-polymerase associated with the viral particles of the vesicular stomatitis virus led to the idea that perhaps a key enzyme was also associated with the oncogenic RNA viruses. Indeed, Howard Temin and Mizutani, and independently [David Baltimore](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1975/), discovered in 1970 a specific enzyme associated with Rous sarcoma virus (RSV), the reverse transcriptase (RT), capable of reversely transcribing the viral RNA into DNA.At about the same time, Hill and Hillova in Villejuif, France, demonstrated that the DNA extracted from RSV transformed cells was infectious and carry the genetic information of the viral RNA, confirming that the enzyme was working faithfully in infected cells.I myself, with P. Vigier, confirmed and extended this discovery by showing that the infectious DNA was associated with the chromosomal DNA of the cells, showing integration of the proviral DNA, as earlier postulated by Temin.Work on the chicken RSV was extended to similar viruses in mammals, so that many researchers at that time believed that RT activity was a new, highly sensitive tool for detecting similar viruses in human leukaemia and cancer. This was stimulated by the generously funded virus-cancer program launched by America’s National Institutes of Health. Unfortunately, the hunt for human retroviruses was basically unsuccessful but led to important basic work on the molecular biology of animal retroviruses.In 1972, I was asked by [Jacques Monod](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1965/), then head of the Institut Pasteur, to create a research unit in the newly created Department of Virology of the Institute. I accepted, and this new laboratory allowed me to develop new avenues of research within the general theme of Viral Oncology, the ultimate goal remaining the detection of viruses involved in human cancers.Thus, I became interested in the mechanism of action of interferon and its role in its expression of retroviruses. I came into this field after having demonstrated the biological activity of interferon messenger RNA in collaboration with two world-renowned experts in the field, Edward and Jacqueline De Maeyer.From 1973 on, Ara Hovanessian and his co-workers joined my unit and brought a new dimension: the complex biochemical mechanism sustaining the antiviral activity of this remarkable group of cellular proteins.In 1975, two other researchers joined my unit and brought their expertise on murine retroviruses: J. C. Chermann and his collaborator, Françoise Barré-Sinoussi (Figure 3). The latter mastered particularly the detection of retroviruses by their RT activity. I convinced them to participate in a joint study inside the unit to look again for retroviruses in human cancers. We started in 1977 with blood samples coming from different Paris hospitals and biopsy specimens.Two advances made in other laboratories boosted this search:In Villejuif, France, Ion Gresser had prepared a potent antiserum neutralising any molecule of alpha endogenous interferon produced by individual cells. This interferon, we realised, was produced by mouse cells induced to express some of their endogenous retroviruses. Its blockade by the antiserum increased by up to 50 times the production of endogenous retroviruses in the culture medium. We could conclude that, despite the fact that endogenous retroviruses have been integrated in the genome of vertebrates for millions of years, their expression is still controlled by the interferon system, like that of exogenous viruses.At about the same period, the discovery by Denis Morgan and Frank Ruscetti in Dr. Gallo’s laboratory of a growth factor allowing the *in vitro* multiplication of human T lymphocytes (TCGF, then named interleukin 2, Il2) made it possible to propagate T lymphocytes in sustained cultures.We knew at that time that some retroviruses involved in mouse mammary tumour formation (MMTV) could not only be expressed in the tumour cells but also in the circulating lymphocytes.Taking advantage of these two advances, we started a search for retroviruses in human cancers. Using anti-interferon serum and Il2, we focused particularly on the T lymphocyte cultures from breast cancer patients.Indeed, in 1980, we were able to detect a DNA sequence close to that MMTV, not only in the cells of an inflammatory breast cancer (from a North African woman), but also in her cultured T lymphocytes. A second patient showed similar results.Unfortunately, the molecular tools we had at that time could not tell us whether we were dealing with endogenous retroviral sequences or with an exogenous virus. Nowadays, having access to more powerful technologies, I am planning to reinitiate these studies.But in 1983, the same approach, the use of anti-interferon serum, and the use of long term cultures of T lymphocytes greatly facilitated the isolation of HIV.My involvement in AIDS began in 1982, when the information circulated that a transmissible agent – possibly a virus – could be at the origin of this new mysterious disease. At that time there were only a few cases in France, but they attracted the interest of a group of young clinicians and immunologists. They were looking for virologists, especially retro-virologists, as a likely hypothesis was that HTLV – the only human retrovirus known so far, recently described by R. C. Gallo – could be involved. Retrovirus causing leukaemia in rodents often also causes a wasting syndrome, which could be the result of secondary immune depression. This was also the case of patients suffering from leukaemia induced by HTLV.A member of the working group, Françoise Brun-Vézinet, was a former student of the virology course that I was then directing. She called me up to organise the search for the putative retrovirus from a patient presenting with an early sign of the disease, lymphodenopathy. The patient was a young gay man who had been travelling to the USA and who was consulting Dr. Willy Rozenbaum – one of the leaders of the working group – for a swollen lymph node in the neck.The reasoning was that if we were to find a virus at this early stage of the disease, it could be more a cause than a consequence of the immune depression.Another incentive to start this research was a request from the producers of hepatitis B virus vaccine in the industrial subsidiary of the Institut Pasteur. They were using plasmas from American blood donors and were concerned by the risk of transmission of the AIDS agent through their procedure of viral antigen purification.The lymph node biopsy arrived on January 3, 1983, a date which I remember well because it was also the first day of the virology course at the Institut Pasteur, which I had to introduce. I could only dissect the small hard piece at the end of the day. I dissociated the lymphocytes with a Dounce glass homogeniser and started their stimulation in culture with a bacterial mitogen, Protein A, known as an activator of B and T lymphocytes, since I did not know which fraction of lymphocytes could produce the putative virus. Three days later, I added the T cell growth factor I had obtained from a colleague working in the laboratory of [Jean Dausset](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1980/).The T cells grew well. As previously established in a protocol for the search of retrovirus in human cancers, it was decided with my associates, Françoise Barré-Sinoussi and Jean-Claude Chermann, to measure the RT activity in the culture medium every 3 days. On day 15, Françoise showed me a hint of positivity (incorporation of radioactive thymidine in polymeric DNA), which was confirmed the following week.We had evidence of a retrovirus, but this was just the beginning of a series of questions: • Was it close to HTLV or not? • Was it a passenger virus or, on the contrary, the real cause of the disease?In order to answer these basic questions, we had to characterise the virus biochemically and immunologically, and to do that, we needed to propagate it in sufficient amounts. Fortunately, the virus could be easily propagated on activated T lymphocytes from adult blood donors. No cytopathic effect was observed with this first isolate, but unlike HTLV infected cultures, no transformed immortalised cell lines could emerge from the cultures, which always died after 3–4 weeks as do normal lymphocytes.By contrast, subsequent isolates I made from culture of lymphocytes of sick patients with AIDS were cytopathic for T lymphocytes culture and – we discovered later – could be cultivated in larger amounts in tumour cell lines derived from leukaemia.Shortly after the virus isolation, my co-workers and I were able to show that it was not immunologically related to HTLV, and in electron microscopy, it was very different from HTLV viral particles. In fact, as soon as June 1983, I noticed the quasi-identity of our virus with the published electron microscopy pictures of the visna virus in sheep, the infectious anaemia virus in horses and the bovine lymphocytic virus: it was a retrolentivirus, a sub-family of viruses causing long-lasting disease in animals without immunodeficiency.This indicated clearly that we were dealing with a virus very different from HTLV, and my task was now to organise a team of researchers to accumulate evidence that this new virus was indeed the cause of AIDS.It was an exciting period, since every Saturday morning when we had a meeting in my office, new data were brought by my associates favouring the causative role of the virus. The viral isolates were called LAV, for Lymphadenopathy Associated Virus, when it was isolated from patients displaying swollen lymph nodes, a frequent sign of the early phase of infection. The isolates made from patients with full-blown AIDS were called Immuno Deficiency Associated Viruses (IDAV). The latter generally grew better in T lymphocyte culture and induced the formation of large syncitia, resulting from the fusion between several infected cells. Some of them – we found out later – could also multiply in continuous cell lines of B or T cell origin. The latter property greatly facilitated the mass production of the virus for commercial use.By September 1983, I was able to make a synthesised presentation of all our data favouring a causal link between the virus and the disease at a meeting on the HTLV organised by L. Gross and R. Gallo at Cold Spring Harbor.This presentation was received with scepticism by a small audience (it was a late night session) and the HTLV theory still prevailed. Mentally, most attendants were not prepared to accept the idea of a second family of retroviruses (lentiretroviruses) existing in humans and causing immune deficiency, and having no counterpart in animals!This situation is not infrequent in science, since new discoveries often raise controversy. The only problem is that it was a matter of life and death for blood transfused people and haemophiliacs, since a serologic blood test using our virus antigen was already working at laboratory scale but awaited industrial and commercial development.This came in 1985, after two other teams of researchers, first that of Dr. Gallo at the NIH in early 1984 and that of Jay Levy in San Francisco, confirmed and extended our findings. In particular, Dr. Gallo and his associates gave more strength to the correlation between the virus and the disease, improved the detection of the antibody response and were able to grow several viral strains, including ours, in T cell lines of cancer origin. Meanwhile, my co-workers showed the tropism of the virus for CD4T cells and identified the CD4 surface molecule as the main receptor to the virus.The rest of the story is described in the next chapter. I would just like to illustrate how I discovered what I believe are two important phenomena for explaining the destruction of the immune system induced by HIV.During the latent phase of the infection, no virus is found in the blood. It is mostly localised in lymphocytes of lymphatic tissues and yet, we found that most of the lymphocytes present in the blood are sick! In 1987, a young visitor from Sweden, Jan Alberts, came to my lab. He wanted to cultivate human lymphocytes in a serum-free synthetic medium and to learn some technologies about HIV culture. The surprise came when we compared the viability in his medium of lymphocytes from healthy donors and those from HIV infected patients, even in their early asymptomatic stage of infection. While the former could survive several days without dying, the majority (more than 50%) of the latter died very quickly. Addition of interleukin 2 partially prevented their death.When we used normal culture medium supplemented with foetal calf serum, the same difference was observed, although the survival time of the lymphocytes from infected patients was longer.It did not take very long before three of my collaborators found the reason for such deaths: apoptosis. This is an active process by which the cell “decides” to die in a clean way, without releasing too many toxic compounds into the medium.It is a physiological way of preventing abnormal proliferation of activated lymphocyte clones, but here the phenomenon was enormous and bore not only on the main cellular target of HIV infection, CD4+ T-lymphocytes, but also on cells which were not infectable by the virus, such as CD8+ T-lymphocytes, B-lymphocytes, monocytes, natural killer cells … Clearly, it was a general phenomenon, the culture simply revealing a predisposition to apoptosis of the majority of circulating blood cells, although most of them were not infected. Indeed, my collaborator Marie-Lise Gougeon found a very good relation between *in vitro* apoptosis and the *in vivo* observed drop of CD4 T cells in patients.We have spent a lot of time trying to find the origin of this massive apoptosis, without finding a completely satisfactory explanation: the most likely is the intensive oxidative stress existing in patients since the beginning of their infection. This is also a finding I am very proud of: although oxidative stress has been – and still is – completely overlooked by AIDS researchers, it is likely to aggravate the wrong activation of the immune system at the origin of its decline and also it triggers inflammation through the production of cytokines.Of course, the next question arises: what are the factors causing oxidative stress: viral proteins, fragments of viral DNA, co-infection with mycoplasmas? Even after 25 years, we still do not know the complete answer. But the phenomenon does exist and needs to be treated, while most AIDS clinicians do not care about it at all!The treatment by combined antiretroviral therapy has, without doubt, changed the prognosis of this lethal disease, from a death sentence to an almost “normal” life. However, the virus is still there, ready to multiply when the treatment is interrupted, and not all HIV infected patients in the developing world have access to it. And the epidemics still kill 2–3 million people each year. It is thus absolutely necessary to resolve these problems. Basic research, as well as clinical research, has to be continued.In addition, I realised in the 1990s that research should not only be localised in the wealthy laboratories of the developed countries, but also in southern countries where a lot of patients were suffering from AIDS and many other diseases like tuberculosis and malaria.Too many examples showed that collaboration between northern and southern research laboratories is unequal, the south providing serum samples to be analysed in the north. This “safari” concept is wrong. There are now many young researchers trained in northern laboratories who would like to return to their own countries, but are prevented from doing so because laboratories and adequate structures are missing. Moreover, one has to be in the regions where disease proliferates to realise how complex the reality is.This is why I joined with the former Director General of UNESCO, Federico Mayor, in initiating a foundation aimed at creating centres for research and prevention in African countries. Although the task was difficult, this concept was met with enthusiasm from colleagues and medical doctors and also found the support of governments, particularly in Côte d’Ivoire and Cameroon.I wish that based on these pilot experiments, a whole network of similar centres could cover all the countries of the developing world where the populations are badly hit by epidemics.Another lesson I drew from my AIDS experience was the weakening effect of oxidative stress on the immune system and its pro-inflammatory role in many chronic diseases, such as Parkinson’s, Alzheimer’s and rheumatoid arthritis: a likely consequence of chronic infections? Or both consequence and cause? There are many questions, which can be resolved only by hard work and innovative thinking. I hope to be able to continue both. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0540=LM [Unknown] Hallo.  [Adam Smith] Hello, is it possible to speak to Professor Montagnier yet?  [Unknown] Yes, I’m going to bring him to you, okay?  [AS] Thank you very much indeed.  [Unknown] If you can hold on.  [AS] Yes, of course.  [Unknown] Thank you.  [AS] Thank you.  [Unknown] Professor … Professor … Professor. Sorry, there’s so many people around him right now.  [AS] I can imagine.  [Unknown] Can you hear me?  [AS] I can hear you very well, yes, thank you.  [Luc Montagnier] Hallo.  [AS] Hello, Professor Montagnier, can you hear me?  [LM] Yes, speaking.  [AS] My name is Adam Smith. I’m calling from the Nobel Foundation web site. Congratulations on the award of the prize.  [LM] Thank you. Thank you very much.  [AS] And I understand you are in the Ivory Coast at the moment?  [LM] Yes, I’m in a meeting of the … Hello?  [AS] Hello, yes?  [LM] I’m in a meeting on AIDS, which will be chaired by the President of the Republic of Ivory Coast, and he’s going to arrive at any time now – we are waiting for him.  [AS] Okay, I won’t take very long. Your discovery for which you have been awarded the Nobel Prize was made in 1983, and this is 25 years later.  [LM] Yes.  [AS] What do you think is the main message that you would like to send out after this award?  [LM] Well, the main message I will convey that even after 20 years we are still fighting this virus, very strongly, and the AIDS epidemic – I am now in an African country – is still spreading in Africa in [inaudible], so the fight is not finished. And I appreciate that the Nobel Committee has put on the air this important disease which is not finished, and my message is that we should continue the research. And myself I’m working on a vaccine – not a preventive vaccine but on a therapeutic vaccine which is aimed at completing the antiretroviral therapy which is now given to many patients even in Africa, but which does not cure. So the idea is to eradicate the virus infection. I think this is the main step now.  [AS] Yes, and what is the most urgent research need, do you think, in AIDS nowadays?  [LM] Well, the important research should be done on completing the treatments which are given to patients, for life. And I know that in Africa it’s not possible to give a treatment for life. Because we give up before. So the idea is to buy a treatment which, like for tuberculosis, could be given for a short period of time – 6 to 9 months – and then stopped. And then vaccinate the people by a combination of viral protein, which I’m working on, so that the immune system of the host, of the person which is infected, will defend himself. Nature has shown us a few percent of people which are in this stage. They are infected, they are not sick. So the idea is to make most of these people, infected people, never sick, for life. So I think this would be very important, but I’ve tried to quantify all the forms of the virus. So I’m also working on that. There are probably some very small forms of the virus which escape [inaudible] and the immune system. So we have to identify those foremost. I think the AIDS epidemic is caused by a very old virus. And probably the virus was in Africa for a long period of time, as shown in some recent papers.  [AS] Yes.  [LM] But, what is new in Africa, like in the North America, is the epidemic. The AIDS epidemic started about the same time in Africa, in big cities, in Africa and North America. And we have to explain why. I think there are factors; I’ve been promoting a virical cofactor for a long time. But I’m beginning now to think those cofactors may act indirectly by inducing mutations – oxidative stress, free radicals which can induce mutations in the virus. What they have shown the virus is the enormous potential to change all the time. This is new, quite new, and was the cause of the epidemic. So we have to put back the virus in this Pandora’s box, you know. And for that we have to not only find physically treatments but also improve the hygiene conditions, especially in Africa, and these conditions are so very important so that the immune system will be very active.  [AS] Yes. So my last question. If you remember the day on which you first saw reverse transcriptase activity in the cultured cells from patients. Did you have any idea on that day in 1983 of the size of epidemic that you might be looking at?  [LM] Well not in the beginning of course, no. I was actually working on a possible viral cause of breast cancer. I’m still interested in cancer virus so I appreciate that the Nobel Committee also has awarded the Prize to Harald zur Hausen who has worked for a long time on this. But, when I realised that the virus could be the cause of AIDS and was present not only in gay men in France and the United States, and haemophiliacs, but also in African nations – so this was in September 1983 – I realised it could be big, okay?  [AS] Yes, yes.  [LM] Okay.  [AS] Okay, thank you.  [LM] Thank you.  [AS] It’s been a pleasure to speak to you.  [LM] Good bye.  [AS] Good luck. Good bye. |
| Interview |  |
| Q19 | The work for which the prize has been awarded was done a good quarter of a century ago, and so I imagine you’ve all allowed yourselves the luxury of imagining yourself here once or twice, so is it a huge surprise to find yourselves here? |
|  | Françoise Barré-Sinoussi: For me yes, yes it is, I never thought before, to be here one day. Surely because working on the HIV/AIDS I thought that probably you will need a vaccine to have a Nobel Prize one day for this disease. |
| Q38 | Again, something we’ll come to in a little while. This year’s prize has been awarded for work on two viruses, human papilloma virus, HPV, and human immunodeficiency virus, HIV, and the work on these two viruses indicates two very different timelines of research for discovery. in HPVs case it took you, Professor zur Hausen, a full decade to convince the community that your hunch that HPV was responsible for most cervical cancers was correct. How did it feel to have a hunch that you had to keep for ten years while working on it? |
|  | Harald zur Hausen: Let me say it this way, it’s true what you said, I mean it took about ten years or so before we were able also to prove our point, but in a way there’s some, in my opinion, there’s some similarity between AIDS and cervical cancer research said this way. It’s of course a problem of enormous magnitude, particularly in the ECS right now, killing an enormous number of people. Cervical cancer has been a problem of enormous magnitude over decades, a million year really, because it’s probably with us since the early time of mankind. In a way these are both conditions which are quite important, the agents causing them are quite different, I mean they are really different, and so research followed different pathways in a way, but I think looking at it from the viewpoint of public health these are both problems of certain importance. |
| Q38 | Certainly, yes, that unites the discoveries. But just getting back to this timeline thing, were there times during your ten-year search for the proof that you thought of abandoning the project? |
|  | Harald zur Hausen: No, not really, because I must say I was very convinced that we were on the right track from the beginning really, because first of all we had seen that the existing number of anecdotal reports are from malignant conversion of genital warts, and secondly already since the 1930s there are examples available where at least in animal systems papilloma virus has caused cancer. So it was not that farfetched to research carefully in human cancers as well, and cervical cancer was a good example. It was not well received in the early days it’s true, because another virus had been suspected at that time, namely inner genital herpes simplex type II infections, but I must say really we were convinced during this period that this was the right way to go and so we pursued it intensively. |
| Q37 | It became, as many people have reported, quite a competitive area later on, but at that point, when the epidemic was just beginning, was it a very collaborative field to be in? Were people helping each other? |
|  | Luc Montagnier: Yes, I think it was actually, we had a very good relationship with Dr Gallo and his colleagues at the NIH in the United States, and we had access to his reagent to show this virus was different from HTLV-I for the first human T-cell leukaemia virus found in men. And also we had as Françoise said, a good contact with clinicians who we are working now on AIDS, there were very few in France because in that time maybe there were other cases of AIDS, but not in France. We had also the collaboration of a very good electron microscopist, could see the first viral particle one month after we had the culture, and after that we extended our collaboration with immunologists and epidemiologists so that we could have a group which could concur to find this virus as /- – -/ because it was the main … of course /- – -/ virus is good, but was it passenger virus, was it something else, where did it go, this is where the main problem, and in that of course, and my /- – -/ colleagues also quickly contributed. |
| Q10 | What have we learnt so far from those patients? |
|  | Françoise Barré-Sinoussi: We already learn the patients that are called HIV controllers is less than 2% of people that are infected, they control perfectly well their viral load, and we already learned that at least some of these controllers have developed a sub-population of T cells which are capable to eliminate infected cells. We know that this sub-population of T cells is less activated that the cells that we found in most HIV patients that progress to disease. What we don’t know yet is why this proportion of patients are developing this response, what are the signals that in use this sub-population of efficient CD8 cells, we know that there is some genetic factors that are probably associated, genetic factor does not explain all of it because not all HIV controllers are HLAB 27, B57, and to speak into English, into scientific language, but whatever, that means that genetic factors are probably involved. |
| Q36 | Right. Thank you. A question for any and all of you, do you think that viruses will come to play a more important role in cancer in the future? Do you think that we don’t yet fully understand how important viruses are in causing cancer? |
|  | Luc Montagnier: I think the candidates retroviruses is also for breast cancer, prostate cancer, it’s possible, and probably also we have to look at infectious bacteria, the microbes, not only the viruses, because cancer to be some factors, you know, to be termed not the only factor, but since cancer is multifactorial probably there are some infectious agents probably like the stomach cancer where you’ve got *Helicobacter pylori* also. Also a Nobel Prize …  Luc Montagnier: … two years ago, so I think yes, we should look for more infectious agents in cancer, it’s a way also to protect because we have needs to counteract the effect on viruses, vaccine but also antiviral drugs so there are many possibilities to find viruses and micro variations as well by antibiotics for instance.  Harald zur Hausen: I agree with what Luc Montagnier said a moment ago. Indeed, in my opinion too there are good chances that additional cancers will be linked to viruses in the future. If you look into the discovery of new viruses potentially linked to human cancer it becomes apparent that during the past two years four new types in the papilloma virus group popped up, one by the way here in Sweden. One of them is also linked to a specific type of human cancer, namely the so-called Merkel cell tumours, a relatively rare tumour arising on the immune suppression in the skin and your endocrine tumour. I personally believe that besides breast cancer I also strongly feel that there’s very good reason to search very intensively for viral etiology, leukemias, lymphomas, really cancers where you have very good reasons to search for agents, so right now from epidemiological grounds.  I also feel, which relates to what Professor Montagnier said a moment ago, to look more carefully in cancers where we know already since a long time that genetic modifications play a major role, because there’s no infections linked to cancer at this moment without additional genetic modifications in the host cell, that’s an interplay between the infections and modifications of the host cell genome. For those reasons I personally also suspect that cancer of the colon is interesting and looking for it for quite a number of variety, in fact I will allude to this in my Nobel Lecture a little bit, and I think it’s still an open question to which extent that it affects a link to human cancer. If you look at it globally and if you include the old /- – -/ cancers right now identified besides *Helicobacter pylori* in gastric cancer also 10% of gastric cancers are linked to /- – -/ bowel infections you come up to a figure of about 20-21% of the global cancer incidents. I personally believe that this is not the end of the story, and that we are still in for further surprises.  Françoise Barré-Sinoussi: I totally share with what has been said and we have already a lot of viruses that are related to cancer and we will discover more in the future. I just would like maybe one point that we have to consider with the virus HIV, under treatment. For example there is more and more complications that we could see in HIV patients including cancer, and I personally believe that we have to understand better what’s’ going on, why when a patient restores an immunity that he develops cancer, and probably we will discover also several agents that are responsible for cancer.  Harald zur Hausen: I mean to add one point, if you identify infectious agents of human cancer then of course as Professor Montagnier said before, we have not only a better possibility in prevention but also for therapy because in many of these cancers we can identify exactly the molecules that are responsible for the malignant growths. In cervical cancer for instance, if you switch off the two viral genes which are active the cells revert to a quasi-normal state, and so these are, you identify targets and you can much better cope with those types of diseases in the end if you try to develop a targeted chemotherapy in those cases. |
| Q43 | You mentioned the search for infective agents, is there a sufficiently good apparatus in place do you think to search for the agents? |
|  | Harald zur Hausen: In my opinion it’s an underdeveloped area in the research on the whole, I mean globally, because there are a couple of laboratories working on these questions, but on the whole the interest decreased rapidly in the 1970s, between 1970s and 80s, with the discovery of onco-genes and tumour suppressor genes, because at that time quite a number of scientists believed there was no need any more for infectious agents. You could explain cancer quite readily by a failing interplay between oncogenes and chemo suppressive genes, but that story turns out to be not as simple as it was thought during this period, and many of the former virologists turned into cell biologists during this period. I think it’s a gradually now an awakening interest again in these questions and I hope it will go on in the future.Luc Montagnier: Yes, we have a much better technology now to identify new agents than we had in the 80s, much more powerful.Françoise Barré-Sinoussi: We will probably learn from the genomics I think, the new technology will be very helpful to discover new agents responsible for disease.Luc Montagnier: We don’t intercultivate viruses anymore, it’s /- – -/ in the case, because we can cultivate the papilloma viruses in vitro but all the /- – -/ techniques you can …Harald zur Hausen: Without molecular biology we wouldn’t have been able to identify the HIVs /- – -/ than without techniques. |
| Q12 | So as some last thoughts, what advice would you offer to young people who want to come into the area and search for causative agents for these diseases? |
|  | Luc Montagnier: The very first to say there are still plenty of things to find, new /- – -/ objects, which already exist, we don’t know. Actually probably some people say we know only 10% of the virus world, and so there are many other viruses to come, new epidemics perhaps but also plenty of work to do, and probably quicker, in a much quicker than we did in the past. I think it’s a very interesting field, and also for helping humankind because cancer is the main cause of death and disease and it’s a very terrible disease and we have to find all the agents including viruses and microbes.Harald zur Hausen: If you ask me, I will say develop original and slightly unorthodox ideas, avoid to believe too much in dogmas, and be persistent, and either prove or disprove your own hypothesis.Françoise Barré-Sinoussi: I totally agree, about dogma, and be very persistent, but also don’t be afraid to work in multi-disciplinary approaches, this is a road for success indeed. |
| ID | 0541 |
| Biographical | In 1996, as a Kyoto Prize laureate, I was asked to write an autobiographical sketch of my early upbringing. Through this exercise, shared by all of the laureates, the hope was to uncover potential influences or experiences that may have been key to fostering the creative spirit within us. In my own case, what I saw was that, despite the complete absence of an early nurturing environment, the intrinsic drive to make a difference in our world is not easily quenched and that given an opportunity, early handicaps can be overcome and dreams achieved. This was intended as a message of hope for those who have struggled early in their lives. As I have previously noted, our ability to identify the genetic and environmental factors that contribute to talents such as creativity are too complex for us to currently predict. In the absence of such wisdom our only recourse is to provide all children with the opportunities to pursue their passions and dreams. Our understanding of human development is too meager to allow us to predict the next Beethoven, Modigliani, or [Martin Luther King](https://www.nobelprize.org/nobel_prizes/peace/laureates/1964/).The content of the autobiographical sketch was based on my own memories, on conversations with my aunt and uncle, who raised me once I arrived in the United States, and on conversations with my mother. Because of the added exposure resulting from the winning of the Nobel Prize, I have received letters from people who knew me in Italy during those formative early years. In addition members of the press have taken an interest in my story and have sought independent corroboration. An amazing and wonderful surprise is that they have discovered a half-sister of whom I was completely unaware. She is two years younger than I, and was given up for adoption before she was one year old. Most recently I had the opportunity to meet my half-sister. She was a very nice person, as a sister should be. I am grateful for all of these new sources of information and revelation. Where appropriate, I will weave the new information into this retelling of my story.Autobiographical Sketch I was born in Verona, Italy on October 6, 1937. Fascism, Nazism, and Communism were raging through the country. My mother, Lucy Ramberg, was a poet; my father, Luciano Capecchi, an officer in the Italian Air Force. This was a time of extremes, turmoil and juxtapositions of opposites. They had a passionate love affair, and my mother wisely chose not to marry him. This took a great deal of courage on her part. It embittered my father. I have only a few pictures of my mother. She was a beautiful woman with a passion for languages and a flair for the dramatic (see Figure 1). This picture was taken when she was 19. She grew up, with her two brothers, in a villa in Florence, Italy. There were magnificent gardens, a nanny, gardeners, cooks, house cleaners, and private tutors for languages, literature, history, and the sciences. She was fluent in half a dozen languages. Her father, Walter Ramberg, was an archeologist specializing in Greek antiquities, born and trained in Germany. Her mother was a painter born and raised in Oregon, USA. In her late teens, my grandmother, Lucy Dodd, packed up her steamer trunks and sailed with her mother from Oregon to Florence, Italy, where they settled. My grandmother was determined to become a painter. This occurred near the end of the 19th century, a time when young women were not expected to set off on their own with strong ambitions of developing their own careers.  My grandmother became a very gifted painter. Let me share with you a couple of her paintings, which also illustrate the young lives of her children. These paintings are very large, approximately seven feet by five feet. The first painting (Figure 2) is the center panel of a triptych depicting my mother and her two brothers Walter and Edward (both of whom became physicists) surrounded by olive trees at the villa in Florence. The influence of the French impressionist painters is evident. The second painting (Figure 3) is of my mother, age 8, and her younger brother Edward, age 6, having a tea party, again at the villa in Florence. Their father, the German archeologist, was killed as a young man in World War I. My grandmother finished raising her three children on her own by painting, mostly portraits, and by converting the family villa into a finishing school for young women, primarily from the United States.  My mother’s love and passion was poetry. She published in German. She received her university training at the Sorbonne in Paris and was a lecturer at that university in literature and languages. At that time, she joined with a group of poets, known as the Bohemians, who were prominent for their open opposition to Fascism and Nazism. In 1937, my mother moved to the Tyrol, the Italian Alps. Figure 4 shows the chalet north of Bolzano, in Wolfgrübben, with my mother in the foreground. We lived in this chalet until I was 3½ years old. In the spring of 1941, German officers came to our chalet and arrested my mother. This is one of my earliest memories. My mother had taught me to speak both Italian and German, and I was quite aware of what was happening. I sensed that I would not see my mother again for many years, if ever. She was incarcerated as a political prisoner in Germany.  I have believed that her place of incarceration was Dachau. This was based on conversations with my uncle Edward, my mother’s younger brother. During World War II, my uncle lived in the United States. Throughout these war years, he made many attempts to locate where my mother was being held. The most reliable information indicated that the location was near Munich. Dachau is located near Munich and was built to hold political prisoners. My mother survived her captivity, but after the war, despite my prodding, she refused to talk about her war experiences.  Reporters from the Associated Press (AP) have found records that my mother was indeed a prisoner during the war in Germany. In fact, they have found records of German interest in my mother’s political activities preceding 1939. In that year, they had her arrested by the Italian authorities and jailed in Perugia and subsequently released. However, the AP reporters did not find records indicating that my mother was incarcerated in Dachau. Though Germans were noted for their meticulous record keeping, it would be difficult now to evaluate the accuracy of the existing war records, particularly for cases where data is missing. It is clear, however, that exactly where in Germany my mother was held has not yet been determined. Regardless of which prison camp was involved, her experiences were undoubtedly more horrific than mine. She had aged beyond recognition during those five years of internment. Following her release, though she lived until she was 82 years old, she never psychologically recovered from her wartime experiences.  My mother had anticipated her arrest by German authorities. Prior to their arrival, she had sold most of her possessions and gave the proceeds to an Italian peasant family in the Tyrol so that they could take care of me. I lived on their farm for one year. It was a very simple life. They grew their own wheat, harvested it, and took it to the miller to be ground. From the flour they made bread which they took to the baker to be baked. During this time, I spent most of my time with the women of the farm. In the late fall, the grapes were harvested by hand and put into enormous wooden vats. The children, including me, stripped, jumped into the vats and mashed the grapes with our feet. We became squealing masses of purple energy. I still remember the pungent odor and taste of the fresh grapes. Most recently, members of the Dolomiten Press have located this farm and I had the opportunity to visit it. It is still owned by the same family that occupied it when I was there. The old farm house has been taken down and a new one erected. However, the pictures of the old farm house, as well as the surrounding land are remarkably consistent with my memories.  World War II was now fully under way. The American and British forces had landed in Southern Italy and were proceeding northward. Bombings of northern Italian cities were a daily occurrence. As constant reminders of the war, curfews and blackouts were in effect every night; no lights were permitted. In the night we could hear the drone of presumed American and British reconnaissance planes which we nicknamed “Pepe.” One hot afternoon, American planes swooped down from the sky and began machine gunning the peasants in the fields. A senseless exercise. A bullet grazed my leg, fortunately not breaking any bones. I still have the scar, which, many years later my daughter proudly had me display to her third-grade class in Utah.  For reasons that have never been clear to me, my mother’s money ran out after one year and, at age 4½, I set off on my own. I headed south, sometimes living in the streets, sometimes joining gangs of other homeless children, sometimes living in orphanages, and most of the time being hungry. My recollections of those four years are vivid but not continuous, rather like a series of snapshots. Some of them are brutal beyond description, others more palatable.  There are records in the archives of Ritten, a region of the Southern Alps of Italy, that I left Bozen to go to Reggio Emilia on July 18, 1942. AP reporters exploring this history have suggested that my father came to the farm, picked me up, and that we went together to Reggio Emilia where he was living. I have no memory of his coming to the farm, nor of having travelled with him to Reggio Emilia. I have recently received a letter from a man who remembers me as the youngest member of his street gang operating in Bolzano, which is on the way to Reggio Emilia.  I did end up in Reggio Emilia, which is approximately 160 miles south of Bolzano. I knew that my father lived in Reggio Emilia and I have previously noted that I had lived with him a couple of times from 1942-1946, for a total period of approximately three weeks. The question has been raised why I didn’t live with him for a much longer period. The reason was that he was extremely abusive. Amidst all of the horrors of war, perhaps the most difficult for me to accept as a child was having a father who was brutal to me.  Recently, I have also received a very nice letter from the priest in Reggio Emilia who ran the orphanage in which I was eventually placed. I remember him because he was one of the very few men I encountered in Reggio Emilia who showed compassion for the children and took an interest in me. I am surprised, but pleased, that after all these years he still remembers me among the thousands of children he was responsible for over the years. Further, I believe I was at that orphanage for only several months, the first time in the fall of 1945, after which I ran away, followed by a second period, in the same orphanage, in the spring of 1946. But his memory is genuine, for he recounts incidents consistent with my memories that could only have been known through our common experience.  In the spring of 1945, Munich was liberated by the American troops. My mother had survived her captivity and set out to find me. In October 1946, she succeeded. As an example of her flair for the dramatic, she found me on my ninth birthday, and I am sure that this was by design. I did not recognize her. In five years she had aged a lifetime. I was in a hospital when she found me. All of the children in this hospital were there for the same reasons: malnutrition, typhoid, or both. The prospects for most of those children ever leaving that hospital were slim because they had no nourishing food. Our daily diet consisted of a bowl of chicory coffee and a small crust of old bread. I had been in that hospital in Reggio Emilia for what seemed like a year. Scores of beds lined the rooms and corridors of the hospital, one bed touching the next. There were no sheets or blankets. It was easier to clean without them. Our symptoms were monotonously the same. In the morning we awoke fairly lucid. The nurse, Sister Maria, would take our temperature. She promised me that if I could go through one day without a high fever, I could leave the hospital. She knew that without any clothes I was not likely to run away. By late morning, the high, burning fever would return and we would pass into oblivion. Consistent with the diagnosis of typhoid, many years later I received a typhoid/paratyphoid shot, went into shock, and passed out.  The same day that my mother arrived at the hospital, she bought me a full set of new clothes, a Tyrolean outfit complete with a small cap with a feather in it. I still have the hat. We went to Rome to process papers, where I had my first bath in six years, and then on to Naples. My mother’s younger brother, Edward, had sent her money to buy two boat tickets to America. I was expecting to see roads paved with gold in America. As it turned out, I found much more: opportunities.  On arriving in America, my mother and I lived with my uncle and aunt, Edward and Sarah Ramberg. Edward, my mother’s younger brother was a brilliant physicist. He was a Ph.D. student in quantum mechanics with Arnold Sommerfeld and translated one of Sommerfeld’s major texts into English. Among Edward’s many contributions was his discovery of how to focus electrons, knowledge which he used in helping to build the first electron microscope at RCA. Edward’s books on electron optics have been published in many languages. During my visit to Japan to celebrate the Kyoto Prize, several Japanese physicists approached me to express how grateful they were for my uncle’s texts from which they learned electron optics. Another achievement, of which he was less proud was being a principal contributor to the development of both black and white and color television. While I grew up in his home, television was not allowed. Figure 5 shows a photograph of my uncle working in his laboratory.  My aunt and uncle were Quakers and they did not support violence as solutions to political problems anywhere in the world. During World War II, my uncle did alternative service rather than bear arms. He worked in a mental institution in New Hampshire, cleared swamps in the south, and was a guinea pig for the development of vaccines against tropical diseases. After the war he settled in a commune in Pennsylvania, called Bryn Gweled, which he helped found. People of all races and religious affiliations were welcomed in this community. It was a marvelous place for children: it contained thick woods for exploration and had communal activities of all kinds – painting, dance, theater, sports, electronics, and many sessions devoted to the discussion of the major religious philosophies of the world. Every week there were communal work parties, putting in roads, phone lines, and electrical lines, building a community center and so on.  The contrast between living primarily alone in the streets of Italy and living in an intensely cooperative and supportive community in Pennsylvania was enormous. Time was needed for healing and for erasing the images of war from my mind. I remember that for many years after coming to the United States I would go to sleep tossing and turning with such force that by morning the sheets were torn and the bed frame broken. This activity disturbed my aunt and uncle to the extent that Sarah would take me from one child psychologist or psychiatrist, to another. These professionals were not very helpful, but the support of the community was. The nightly activity eventually subsided. There may be lessons to be learned from such experiences for the treatment of the children from Darfur, the Congo, and now Kenya.  Sarah and Edward took on the challenge of converting me into a productive human being. This, I am sure, was a very formidable task. I had received little or no formal education or training for living in a social environment. Quakers do not believe in frills, but rather in a life of service. My aunt and uncle taught me by example. I was given few material goods, but every opportunity to develop my mind and soul. What I made of myself would be entirely up to me. The day after I arrived in America, I went to school. I started in the third grade in the Southampton public school system. Sarah also took on the task of teaching me to read, starting from the very beginning.  The first task was to learn English. I had a marvelous third grade teacher. She was patient and encouraging. The class was studying Holland, so I started participation in class functions by painting a huge mural on butcher block paper with tulips, windmills, children ice skating, children in Dutch costumes, and ships. It was a collage of activities and colors. This did not require verbal communication.  I was a good, but not serious, student in grade school and high school. Academics came easily to me. I attended an outstanding high school, George School, a Quaker school north of Philadelphia. The teachers were superb, challenging, enthusiastic, competent, and caring. They enjoyed teaching. The campus was also magnificent, particularly in the spring when the cherry and dogwood trees were bursting with blossoms. An emphasis on Quaker beliefs permeated all of the academic and sports programs. A favorite period for many, including me, was Quaker meeting, a time set aside for silent meditation, and taking stock of where we were going. My wife and I sent our daughter to George School for her own last two years in high school so that she might also benefit from the personal virtues it promotes, and we think she has.  Sports were very important to me at George School, and physical activity has remained an important activity for me to this day. I played varsity football, soccer, and baseball, and wrestled. I was particularly proficient at wrestling. I enjoyed the drama of a single opponent, as well as the physical and psychological challenges of the sport. After George School, I went to Antioch, a small liberal arts college in Ohio.  At Antioch College I became a serious student, converting to academics all of the energy I had previously devoted to sports. Coming from George School, I carried the charge of making this a better, more equitable world for all people. Most of the problems appeared to be political, so I started out at Antioch majoring in political science. However, I soon became disillusioned with political science since there appeared to be little science to this discipline, so I switched to the physical sciences – physics and chemistry. I found great pleasure in the simplicity and elegance of mathematics and classical physics. I took almost every mathematics, physics, and chemistry course offered at Antioch, including Boolean algebra and topology, electrodynamics, and physical chemistry.  Although I found physics and mathematics intellectually satisfying, it was becoming apparent that what I was learning came from the past. The newest physics that was taught at Antioch was quantum mechanics, a revolution that had occurred in the 1920’s and earlier. Also, many frontiers of experimental physics, particularly experimental particle physics, were requiring the use of larger and larger accelerators, which involved bigger and bigger teams of scientists and support groups to execute the experiments. I was looking for a science in which the individual investigator had a more intimate, hands-on involvement with the experiments. Fortunately, Antioch had an outstanding work-study program; one quarter we studied on campus, the next was spent working on jobs related to our fields of interest. The jobs, in my case laboratory jobs, were maintained all over the country, and every three months we packed up our bags and set off for a new city and a new work experience. So one quarter off I went to Boston and the Massachusetts Institute of Technology (MIT).  There I encountered molecular biology as the field was being born (late 1950’s). This was a new breed of science and scientist. Everything was new. There were no limitations. Enthusiasm permeated this field. Devotees from physics, chemistry, genetics, and biology joined its ranks. The common premises were that the most complex biological phenomena could, with persistence, be understood in molecular terms and that biological phenomena observed in simple organisms, such as viruses and bacteria, were mirrored in more complex ones. Implicit corollaries to this premise were that whatever was learned in one organism was likely to be directly relevant to others and that similar approaches could be used to study biological phenomena in many organisms. Genetics, along with molecular biology, became the principal means for dissecting complex biological phenomena into workable subunits. Soon all organisms came under the scrutiny of these approaches.  I became a product of the molecular biology revolution. The next generation. As an Antioch college undergraduate, I worked several quarters in Alex Rich’s laboratory at MIT. He was an x-ray crystallographer, with very broad interests in molecular biology. While at MIT I was also fortunate to be influenced by [Salvador Luria](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1969/), Cyrus Leventhal and Boris Magasanik, through courses, seminars, and personal discussions. At that time Sheldon Penman and Jim Darnell were also working in Alex Rich’s laboratory. When placed in the same room, these two were particularly boisterous, providing comic relief to the fast moving era.  After Antioch, I set off for what I perceived as the “Mecca” of molecular biology, Harvard University. I had interviewed with Professor [James D. Watson](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/), of “Watson and Crick” fame, and asked him where should I do my graduate studies. His reply was curt and to the point: “Here. You would be fucking crazy to go anywhere else.” The simplicity of the message was very persuasive.  James D. Watson had a profound influence on my career (see Figure 6). He was my mentor. He did not teach me how to do molecular biology; because of my Antioch job experiences, I had already become a proficient experimenter. Jim instead taught me the process of science – how to extract the questions in a field that are critical to it and at the same time approachable through current technology. As an individual, he personified molecular biology, and, as his students, we were its eager practitioners. His bravado encouraged self-confidence in those around him. His stark honesty made our quest for truth uncompromising. His sense of justice encouraged compassion. He taught us not to bother with small questions, for such pursuits were likely to produce small answers. At a critical time, when I was contemplating leaving Harvard as a faculty member and going to Utah, he, being familiar with my self-sufficiency, counseled me that I could do good science anywhere. The move turned out to be a good decision. In Utah I had the luxury to pursue long-term projects that were not readily possible at Harvard, which, in too many cases had become a bastion of short-term gratification.  Doing science in Jim’s laboratory was exhilarating. As a graduate student, I was provided with what appeared to be limitless resources. I could not be kept out of the laboratory. Ninety-hour weeks were common. The lab was filled with talented students, each working on his or her own set of projects. Represented was a mixture of genetics, molecular biology, and biochemistry. We were cracking the genetic code, determining how proteins were synthesized, and isolating and characterizing the enzymatic machinery required for transcription. At this time, Walter Gilbert was also working in Jim’s laboratory. He was then a member of the physics department, but had also been bitten by the molecular biology bug. Jim and Wally complemented each other brilliantly, because they approached science from very different perspectives. Jim was intuitive, biological; Wally quantitative, with a physicist’s perspective. They were both very competitive. As students, we received the benefit of both, but also their scrutiny. They were merciless, but fair. You had to have a tough hide, but you learned rigor, both with respect to your science and your presentations. Once you made it through Jim’s laboratory, the rest of the world seemed a piece of cake. It was excellent training. Despite the toughness, which at times was hard, Jim was extremely supportive. He also made sure that you, the student, received full credit for your work. Despite the fact that Jim was responsible for all of the resources needed to run his laboratory, if you did all of the work for a given paper, then you were the sole author on that paper. Among all of the laboratory heads in the world, I believe that Jim Watson was among very few in implementing this policy.  The summer before I started graduate school, [Marshall Nirenberg](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1968/) had announced that polyU directs the synthesis of polyphenylalanine in a cell free protein synthesizing extract. That paper was a bombshell! I decided I would generate a cell-free extract capable of synthesizing real, functional proteins. Jim’s laboratory had started working on the RNA bacteriophage, R17. Its genome also served as messenger RNA to direct the synthesis of its viral proteins. That would be my message. The cell-free protein synthesizing extract worked beautifully. Authentic viral coat protein and replicase were shown to be synthesized in the extract[1](https://www.nobelprize.org/prizes/medicine/2007/capecchi/biographical/#not1). Further, the coat protein was functional, it bound to a specific sequence of the R17 genome, thereby modulating the synthesis of the replicase. To this day, the high affinity of the viral coat protein for this RNA sequence is exploited as a general reporter system to track RNA trafficking within living cells and neuronal axons. In collaboration with Gary Gussin, also a graduate student in Jim’s laboratory, this system was used to determine the molecular mechanism of genetic suppression of nonsense mutations[2](https://www.nobelprize.org/prizes/medicine/2007/capecchi/biographical/#not2). In collaboration with Jerry Adams, another graduate student in Jim’s laboratory, the system was also used to determine that initiation of the synthesis of all proteins in bacteria proceeded through the use of formyl-methionine-tRNA[3,4](https://www.nobelprize.org/prizes/medicine/2007/capecchi/biographical/#not3). A similar mechanism is involved in the initiation of protein synthesis in all eukaryotic organisms. Finally, I used the same *in vitro* system to show that termination of protein synthesis unexpectedly utilized protein factors, rather than tRNA, to accomplish this end[5,6](https://www.nobelprize.org/prizes/medicine/2007/capecchi/biographical/#not5). Jim Watson would later offer the very complimentary comment “that Capecchi accomplished more as a graduate student than most scientists accomplish in a lifetime.” It was, indeed, a productive time, but it wasn’t work; it was sheer joy.  While a graduate student in Jim’s laboratory, I was invited to become a junior fellow of the Society of Fellows at Harvard. Being a junior fellow was very special. The society’s membership, junior and senior fellows, represented a broad spectrum of disciplines; all the members were talented, and most of them were much more verbal than I. Social discourse centered around meals, prepared by an exquisite French chef and ending with fine brandy and Cuban cigars. Frequent guests at these dinners were the likes of Leonard Bernstein. Surreal maybe, but also very special.  From Jim’s laboratory, I joined the faculty in the Department of Biochemistry at Harvard Medical School, across the river in Boston. During my four years at Harvard Medical School I quickly rose through the ranks, but then, I unexpectedly decided to go to Utah. I was looking for something different. There were excellent scientists in the department I was in at Harvard Medical School, but the department was not built with synergy in mind. Each research group was an island onto itself. At that time, they were also unwilling to hire additional young faculty and thereby provide the department with a more youthful, energetic character. At the University of Utah, I would be joining a newly formed department that was being assembled by a very talented scientist and administrator, Karl G. Lark (Figure 7). He had excellent taste in scientists and a vision of assembling a faculty that would enjoy working together and striving together for excellence. I could be a participant in the growth of that department and help shape its character. Furthermore, the University’s administration, led then by President David P. Gardner, was in synchrony with this vision and a strong supporter. Gordon had already attracted Baldomero (Toto) Olivera, Martin Rechsteiner, Sandy Parkinson, and Larry Okun to Utah. After I arrived at Utah, we were able to bring to Utah such outstanding scientists as Ray Gesteland, John Roth, and Mary Beckerle. Utah also provided wide open space, an entirely new canvas upon which to create a new career (see Figures 8). These are views from one of the homes in Utah which I have shared with my wife, Laurie Fraser, and daughter, Misha. The air is clean, and I can look for long distances. The elements of nature are all around us. What a place to begin a new life! |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0541=MC [Unknown] – Hello.  [Adam Smith] – Hello, my name’s Adam Smith, may I speak to Mario Capecchi please.  [Unknown] – Yes, just a minute please.  [AS] – Thank you.  [Mario Capecchi] – Hello.  [AS] – Hello, my name is Adam Smith and I’m calling from the Nobel Foundation’s official website, Nobelprize.org. We have a tradition of recording very brief interviews with new Laureates, so would it be alright if I asked you a few questions.  [MC] – Sure, please.  [AS] – Thank you. First of all, very many congratulations on the award.  [MC] – Thank you very much.  [AS] – I imagine that, it being early, the call may have come while you were still asleep.  [MC] – Sound asleep.  [AS] – And were you able to gather your thoughts, and have some reaction to the call?  [MC] – No, it’s a marvellous call, and it’s a wonderful surprise. And also I’m very happy that my colleagues Martin Evans and Oliver Smithies both, are also receiving the Nobel Prize.  [AS] – Yes, the three of you have been united in several prizes now, and …  [MC] – Yeah, we’re good friends and it’s been, there’s a small amount of competition but also mostly good friendship all the way along the way.  [AS] – That’s nice. Yours might be considered a particularly inspiring path to the Nobel Prize since, am I right in saying that you didn’t go to school until you were nine years old, having been a child wandering in war-time Italy?  [MC] – That’s correct.  [AS] – And is it right, am I right in saying that you didn’t read and write until you were 9?  [MC] – That’s correct.  [AS] – So what did that experience teach you? Is it possible to summarize?  [MC] – Well I think what it provided was resourcefulness, and I think just the drive to keep yourself, maintain yourself, and survive. I think it led me to be able to use my own resources, to be able to get through life. And I think now I’m also very grateful, in a sense it’s fantastic. I mean most children didn’t make it, I think I was extremely lucky.  [AS] – Does it also say something about the potential of young people, that they …?  [MC] – Oh, certainly, no, that’s the one thing that I think is extremely important, is that anyone can do it, if given a chance, if given the opportunity.  [AS] – Shortly after graduating from University you found yourself studying with [Jim Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/) …  [MC] – That’s correct.  [AS] – … of DNA fame. What did you learn from him?  [MC] – He was a fantastic mentor, I consider him … essentially he helped me enormously with science and I used him as an example. It was a marvellous opportunity to be in his laboratory and also actually [Wally Gilbert](https://www.nobelprize.org/prizes/chemistry/1980/gilbert/facts/) was in the same laboratory at the same time. So there were actually two people that received the Nobel Prize. So I consider myself a second generation.  [AS] – Presumably they taught you resilience as well because in your initial experiments, where you were attempting to prove that it was possible to use homologous recombination to produce specific gene targeting in cultured cells, there was some resistance to that idea. And I believe it was somewhat hard to obtain funding to do that research.  [MC] – That’s correct. No, our first grant was actually refused with respect to that project, mainly because they didn’t think it was possible. The probability that an exogenous piece of DNA would be able to find the cognate sequence in three-thirty base pairs was thought to be not a significant possibility. So I think that was the resistance, and I think we just had the feeling that if we could make the assay sensitive enough, we knew it was going to be a rare event, but if we could make the assay sensitive enough then we knew we might be able to detect it. And the other thing to keep in mind is that this is actually before the yeast system was working, so we had no precedent. We did know that it could happen in bacteria.  [AS] – Then you happened upon Martin Evans, whose embryonic stem cells provided the vehicle for transmitting these genetic alterations into the germline of mice.  [MC] – Right.  [AS] – How did that meeting come about?  [MC] – Well, I’d heard about the results at a Gordon conference the previous summer and so I actually called him and my wife and I went there, and spent actually a couple of weeks in Christmas, right before Christmas, to learn about ES cells. So that was extremely important for us to do that and get first hand experience in how to grow them, how to manipulate them, and also how to inject them into pre-implantation embryos so that I’d be able to use them to generate mice. So we actually got direct instructions from the people that actually worked them out. That included Martin and also Liz Robertson.  [AS] – Between you, the work you did then and the discoveries you made then has led to the development of many thousands of knock-out and knock-in mice. What’s your hope for what this technology can deliver in the future?  [MC] – I think what it will do in the future is that there now are better and better techniques for manipulating the genome in more and more sophisticated ways, both using conditional mutagenesis, also using much more sophisticated reporters. And my guess is also, it will become multiplex, so that you will not only be working with a few genes but many genes at the same time. You will be able to manipulate their expression, and place of expression as well as time of expression, and probably also modulate how much gene product is being made. So I think, my own feeling is that even though, to me it was always a gamble, you know, how complicated is a mouse and is it actually penetrable by this kind of technology and then at the same time can we make the technology sophisticated enough to be able to handle essentially very complex questions. Eventually what we would like to do is be able to extend it to studying other mammalian organisms so we aren’t simply restricted with respect to finding out how does a mouse work, and its analogy to humans, but also be able to utilize it to study more processes in evolution and how different traits have come up during evolution. So those are the kind of questions we’re looking forward to in the future.  [AS] – Thank you very much indeed. Well, we interview Laureates again when they come to receive their Nobel Prizes in Stockholm in December, so hopefully we’ll have a chance to speak again then.  [MC] – Thanks.  [AS] – Thank you very much indeed. Bye, bye.  [MC] – Thank you, bye, bye. |
| Interview |  |
| ID | 0542 |
| Biographical | I was born on the first day of January 1941 in the front bedroom of my grandparents’ house in Rodborough near Stroud in Gloucestershire where my mother had come to escape the bombing in London. “A fine strapping lad” was the news my grandfather received as Dr Mold came to the top of the stairs. Later my father’s factory was bombed out and evacuated from East London to Hertford where they continued to manufacture military transport vehicles. My parents found a tiny rural cottage to live in near Wareside. It was here that I have my first memories. We had mains water but nothing else. I remember the grand acquisition of a paraffin stove for easier cooking and also after the war helping my father to install some 12 volt battery operated lights and a generator. The switches were from motor vehicles and the wires were ex army telephone cable. In the few hours he was not at work my father ran the local communication signals for the Home Guard. Starting with nothing eventually they had their own telephone network covering Hertfordshire and run from our living room. I remember a slit trench in front of the house as an emergency shelter and seeing the local fields being tilled by prisoners of war. It was here that I remember what I have described as my first experiment – covert mixing of sand cement and water because I couldn’t understand how adding water could make it become solid. It didn’t work (as any good experimental first attempt!) because I added too much water; but it is a vivid memory.After the war we moved to live in Raynes Park and it was there that, on what should have been my first day at school, I suffered a burst appendix and had it not been for the first antimicrobial drugs (M&B 693) would not have survived. I remember vividly seeing the low winter sun, red through the darkened glass of the ambulance, and hearing its shrill bell. I was awakened by a beautiful nurse with a sip of juice – of elixir! Maybe that’s why I have since always loved nurses.I contracted mumps in hospital and thereafter throughout the next 18 months suffered most available childhood infections. I hardly got to school and spent long periods in bed with various books and toys including meccano. When I was seven we moved to Orpington and in my new school I was kept in for extra lessons to learn “joined-up” writing instead of playing football. I still think that my poor handwriting and lack of soccer skills date from that period.When I try to think back to my favourite toys, books and activities I do see now that perhaps I did naturally become a scientist. I made pressed flower collections at about the age of eight, later I learned about wild orchids and became adept at finding all the species in Kent. I loved old science books – e.g. “Moving things for Lively Youngsters”. I was bought a job – lot of very early wireless construction materials from a house sale including a crystal and catswhisker and beautifully-made hexagonal, plug-in, air filled coils bearing the inscription “What are the Wild Waves saying?”; my father and I were able to make a working crystal set from these. We had an old model steam engine “Puffing Billy” and I still remember the smell of the methylated spirit burner. One Christmas I was fortunate enough to be given the electric experimental set for which I had yearned and in which the main item was an induction coil to generate high voltage shocks for all. I build a tesla coil and other static electric gadgets. I kept aquaria. My father had a mechanical workshop and trained me in operating the metalwork lathe. I used it to make cannons and first of all filled them with matchheads for powder. Then one of my greatest amateur passions began with a chemistry set of the sort which is nowadays (on account of Health and Safety!) unobtainable and I slowly learnt quite a bit of basic chemistry. It was possible to buy supplementary chemicals from helpful chemist shops and I even had a can of metallic sodium. The weak cannon filling matcheads were replaced by a variety of improved explosives and I spent a long time trying to perfect a rocket – most of my attempts failed to lift off and several underwent spectacular explosive failures! I was, however, careful with these explosive mixtures but probably my most dangerous experiment was when I attempted to make a large batch of urea formaldehyde resin in the fireplace of my bedroom; the reaction suddenly took off and overheated, nearly suffocating me. In this and other aspects – when only 10 or 12 I was able to spend all day alone miles from home collecting fresh water fish and specimens, with no-one worrying – my personal explorations seem to have been remarkably fostered and unfettered compared with today’s children who are often constrained by our safety-conscious society. I was a boy who dreamt long and hard and could spend all day wondering how to join two cans to make a cylinder.By the time, therefore, in the middle school of St Dunstan’s College we started Chemistry and Physics lessons I was ready, I was keen. I even remember the sudden shock of hearing some of the technical words I had only up to that time read being actually pronounced.In the prep school I had been taught biology by the Reverend Toller, a wonderful man who used his classes to give us foundation in plant and animal science and cosmology. I still remember the start of one term of lessons when he said “Go out tonight and look up at the stars – look carefully they are not all the same colour”. In the middle school we didn’t do Biology before the sixth form but in my year we had the opportunity to start by dropping Maths after the O level exam in the fourth year. Although my main subjects were Chemistry and Physics I chose to do Biology probably just because it had been denied. This meant that because I had dropped the Maths the only choice I had for advanced level in the sixth form was Chemistry with Botany and Zoology.I won a major scholarship to Christ’s college in Cambridge. The Cambridge Natural Science Tripos has the great advantage of allowing breadth and choice. I embarked on Zoology, Botany and Chemistry with the clear intention of following specialisation in Chemistry. After the first term, however, I found that the Zoology course which was a dry systematics was not for me, whereas the Botany in which plant physiology and function illuminated the adaptive radiation and speciation lit my fire. I took a drastic change in my planned courses, dropped Zoology started Biochemistry and doubled the Botany. Chemistry, my erstwhile love, was becoming less of an option for although my Maths and Physics could just manage to mid degree level I was probably going to struggle too much at Part 2. Biochemistry part 2 was the option I had never anticipated but suited me perfectly. In the days I was there it was taught magnificently at the highest level. Enzyme function was taught by the world expert Malcolm Dixon, by then seemingly a quiet, mumbling old man. (Younger then than I am now!) One day I arrived late for the 9am lecture and had to sit in the front row. I heard what he was saying fully for the first time and he was giving us the most exquisite analysis of a paper published that week in *Nature*! Ever after I made sure of a front seat! Molecular Genetics was just starting, [Sanger](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1958/) had sequenced Insulin, the principles of protein synthesis were being established and the genetic triplet code was being solved. [Jacob](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1965/) and [Monod](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1965/) won the Nobel Prize and Monod gave an illuminating series of lectures which together with a seminar series organised by [Sidney Brenner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/) in his College rooms in Kings, inspired me in the new concepts of control of genetic readout through messenger RNAs.Sadly, I was never able to sit my final exams for which I had been working so avidly as I succumbed to Glandular Fever. This effectively scuppered my chances of acquiring the postgraduate position and grant I wanted and so I took a post as a research assistant with Dr Elizabeth Deuchar at University College in London – a most fortunate choice. She was an excellent supervisor who encouraged but didn’t direct, a policy I have myself followed in supervising graduate students. For some it works most excellently and I am justly proud of many of my students. It was just what I needed. It did result in my taking a long time to complete the PhD and in a lot of non realised innovation. I experimented, I developed techniques, I learnt skills – viewed coldly I probably wasted a lot of time but I was not under the pressure that so many are today.My ambition was to isolate developmentally controlled m-RNA but at that time none of the cloning tools or probes upon which we now rely were available. All I could look at were double reciprocally labelled (14C and 3H) profiles of polyribosomes and messenger RNA from dissected blastula and gastrula ectoderm by Sucrose Density Gradient centrifugation and RNA by agarose electrophoresis. In modern terms I was looking at animal cap development in culture before induction and after commitment to either a neural or an epidermal ectoderm.At that time I saw two impediments to further progress: the difficulty of getting enough material for biochemical analysis, and the lack of any foreseeable genetics. In discussion with Robin Weiss and Ann Burgess I cast around for a more tractable system and Robin suggested looking at mouse teratocarcinomas. In 1966 Leroy Stevens and Barry Pierce both published reviews of their formative studies. Stevens had developed a strain of mice with a high incidence of spontaneous testicular teratomas (129 Sv) and demonstrated that the tumours depended upon “Pluripotent embryonic cells (that) appear to give rise to both rapidly differentiating cells and others which, like themselves, remain undifferentiated.” Pierce had, importantly, demonstrated the clonality of these multiply differentiating tumours. Stevens generously sent me stocks of mice and tumours and Robin, who was at that time setting the foundations of his pivotal studies on retroviral tumour viruses, together with Pavel Veseley, who was visiting from Prague, taught me tissue culture.When I was in Cambridge I had met Judith and we were now married with two small boys. I am blessed with a wonderful, interesting, intelligent, independent and supportive wife. By then I had become an assistant lecturer and was teaching an intensive course in molecular developmental biology. I have always found during my academic career that investment in home and family life together with the imperatives of teaching provide the necessary counterbalance to the inevitable slow progress of research. One is doing a good job, at the University, at home and can therefore take the extensive rough with the occasional smooth of research.The science progressed towards every goal and is related elsewhere. Memorable highlights include my trips to Oxford visiting Richard Gardner to make chimaeras. On one occasion I remember our workshop had rigged up an old black wax-oven with a huge battery connected by curly red wires as a temperature-controlled transport vessel and I carried this object, which had all the appearance of a cartoon bomb, home on the crowded tube – with no notice taken, or complaints, by fellow passengers. This was at the height of bomb attacks by the IRA!When I was approaching the salary bar from lecturer to senior lecturer at UCL I was wondering about my future and I applied for a post at the Genetics department in Cambridge. I remember at the interview under extensive cross examination by the whole department that I told them that I would be aiming to use mouse teratocarcinoma stem cells as a vector to mouse genetics. I don’t think they believed that it would become possible. After many months and when I had virtually forgotten about my application I received a phone call assuming I would take the job, which (after a little hesitation) I did. I later learnt that I was not their first choice – I don’t know who got away! Cambridge was a difficult move for me but eventually good. It was a good time to move my children. The boys had not yet started secondary school and we were very worried by the available schools where we lived in London. Clare was just four and therefore needed to start primary. Judith had been working in family planning in London but there were virtually no positions available in Cambridge so when the opportunity came she moved into general practice nursing. This was a newly developing field and over the years she was instrumental in helping to set up local groups and training. It was a very proud moment for us all when she was awarded an MBE for services to practice nursing.It was at Cambridge that I met Matt Kaufman who provided the vital trick of using delayed blastocysts for our isolation of ES cells. This was a very productive collaboration of the best sort where we were able to combine our complementary approaches and expertise and I was later sorry to see him go when he left to take the prestigious chair of Anatomy in Edinburgh.I had an excellent laboratory including Robin Lovell-Badge, David Latchman, Liz Robertson and Allan Bradley among others. Later, when they had all left, I remember a colleague saying, “… you’ll never be able to rebuild it now …”. It was a challenge, but slowly and in particular with Bill Colledge and Mark Carlton we started to be able to use the genetic promise of the ES cells. Because we mutated, trapped and targeted somewhat eclectically we were drawn into a number of fascinating fields of biology and medicine. I am glad to have seen our work with cystic fibrosis and breast cancer moving from mouse models to potential therapeutic application but I do feel that the major contributions are in fundamental understanding of biology.I have always been interested – indeed waylaid – by the leading edges of technology even during my PhD years when I pioneered (but did not publish) agarose gel electrophoresis for RNA fractionation. Also, much later, I was instrumental in showing that Green Fluorescent Protein and RNAi could be made to work in mammalian cells.I have spent a long time with personal computers starting with the Olivetti programmer 101 which was a programmable calculator with (as far as I remember) a memory of eight numbers in an acoustic delay loop and the ability to store its programme on a magnetic card. I was able to program this to replace the use of the University’s IBM mainframe to normalise dual label results with only two separate entries of the data compared with preparation of a suite of punched cards. I later progressed through machine language programming to the use of Basic on a Hewlett-Packard calculator – an amazing advance. Hooked, I used an Apple II with an attached CP/M card as a word processor and later was responsible for Cambridge University using the Torch box addition to the BBC microcomputer as the standard word processing system. This came about from a fairly drunken presentation where on the basis of an order for just two units I persuaded the manufacturers to give the University a main dealer discount! I subsequently became enamoured with (and wasted a lot of time on) UNIX on the desktop.When I took ES cells to Oliver Smithies he introduced me to PCR and his own amazing thermal cycling system. I needed to source the Taq Polymerase and make my own thermal cycler. It was then that I made acquaintance with Dr Peter Dean who has since become a lifelong friend. He was just in the process of setting up his own molecular biologicals supply company and I was able to find him a source of Taq Polymerase and together in discussion we invented a much neater thermal cycler which, by using a low heat capacity block was able to be heated rapidly by a quartz halogen lamp and cooled by a fan. We established a company and went into manufacture and it was, for some years, the best thermally performing machine on the market. This was an adventure into commerce. I was also a co-founder of a biotechnology company with much larger aspirations (Animal Biotechnology Cambridge Ltd) and here learnt a lot about business management.At a time when funding was at a very low ebb I was visited by Michael Morgan of the Wellcome Trust and in conversation asked him how, if ever, will we be able to retain the best postdocs in the UK? Would it be possible to set up an institute of developmental biology? To my amazement he just said, “Send the Welcome Trust an outline proposal”. Brigid Hogan and I had discussed the need for an institute of mammalian developmental biology and so together with her we put together a proposal. Although I didn’t know it at the time and Michael was quite unable through confidentiality to tell me there was a potential institute in discussion and the one component missing was mammalian. Brigid in London kept getting rumours that [John Gurdon](https://www.nobelprize.org/prizes/medicine/2012/gurdon/facts/) was planning something and eventually these rumours became so insistent that, although it appeared that there was nothing whatsoever happening in Cambridge, I phoned him. There was a long pause and John then said – “you’d better come to talk with me”. It transpired that he together with Ron Laskey had prepared a proposal which, when we cautiously swapped them, proved to be closely comparable to ours. This was the start of the Welcome/ CRC Institute for Cancer and Developmental Biology which became such a success and which was such a joy to be part of.In 1999, I moved from leading a personal research group in a scientifically buzzing Institute to heading a large and newly formulated School of Biosciences in Cardiff University. This was a huge change of role but one which I found I was rather better prepared for than I might have anticipated. All my experience both in Cambridge Departmental and University committees as well as my wrangles with commercial management had prepared me well. I was also pleased to be able to help facilitate scientific careers on a wider scale than hithertofore and to help lead and develop a newly re-energised Welsh University into the 21st century. It was hard but extremely rewarding.A Lasker Prize, Knighthood and now the Nobel Prize brings recognition and quiet, unexpected satisfaction. I have always been a bit outside the mainstream and I have been outspoken and opinionated with a wide interest in science but I’m still at heart that small thoughtful enquiring boy. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0542=ME [Unknown] – Hello, [name inaudible] speaking.  [Adam Smith] – Oh, hello, this is Adam Smith calling from the Nobel Foundation’s website. May I speak to Martin Evans please?  [Unknown] – Yes, of course, just hold on please.  [AS] – Thank you.  [Martin Evans] – Hello.  [AS] – Oh, hello, this is Adam Smith from the Nobel Foundation’s website, Nobelprize.org.  [ME] – Yes.  [AS] – We have a tradition of recording these short interviews with new Laureates. Would you mind if I asked you a few questions?  [ME] – Absolutely.  [AS] – Thank you very much. First of all, needless to say, many congratulations …  [ME] – Well, thank you very much.  [AS] – … on the award. I gather that they caught you on the telephone only just before the public announcement.  [ME] – Yes, yes, five minutes before I think.  [AS] – Was it a surprise to you?  [ME] – Of course it was, yes. Yes, it was. I mean, I’ve been asked this repeatedly today and I have to admit that I knew that there was a possibility. I was sort of in the frame and had the Lasker Prize some years ago and clearly it’s a possibility but I had no idea whatsoever that this was going to happen. So, yes, wow!  [AS] – And speaking to Professors Capecchi and Smithies …  [ME] – Yes.  [AS] – … they’ve both been emphasizing the fact that all three of you are friends.  [ME] – Yes, I would agree. Absolutely. I’m delighted to be awarded it with them.  [AS] – How did the three of you meet?  [ME] – So I went to work for a month in the States, in Richard Mulligan’s laboratory at the Whitehead Institute. Now, because I had a short time and was definitely going to learn technology there, I had said “No, I will give no seminars, no I’ve got to do no visiting, no, I will not see or speak to anybody else. I will get in the lab.” However, I got a phone call through from Oliver Smithies. I remember to this day, I said to him “Oliver, you are the only person who I will come and visit.” And I …  [AS] – And he recalls you bringing the cells in your pocket, I think.  [ME] – I did, I went over the weekend with the cells in my pocket, and so that was my real contact with him and I would concur, I would call him a very good friend. And then, when I got back from the states, I think it was probably about a week or so later, I’m not quite sure, quite soon, Mario Capecchi had got in touch with us and he came over for a week with his wife to learn how to deal with the cells.  [AS] – Right, right. You’ve described your self previously as being something of an outsider. Do you think that’s an important appellation, do you think it’s important to march against the tide if you want to be successful?  [ME] – I know what you’re referring to. It’s true. I don’t know, I mean, if you do, then you do things which other people don’t, but maybe it’s … who says that it’s going to be an effective way of doing things. But yes, I think that is partly true.  [AS] – Is it possible to say that if one is an outsider, the value of the prize is perhaps a little greater?  [ME] – Well, I don’t know if it’s greater or not but it is such a valuable honour that, I don’t know if you can … you know, you get to infinity and you can’t go any further, can you?  [AS] – That’s a nice idea.  [ME] – It is another … for so many years I’ve being saying it’s a boyhood dream, which it is. Obviously in my career I’ve known a lot of Nobel Prize winners and, you know, they’ve always been the tops of the tops, amazingly. And, as I say it’s a boyhood dream. And someone said “Is that like scoring the goal in the FA cup?” and I said, “No, it’s like scoring a goal in the world cup!” You know, it is that sort of one-off, sort of amazing …  [AS] – It’s as good as it gets I imagine.  [ME] – Yes.  [AS] – And you’ve been a scientist since boyhood indeed.  [ME] – Yes, I would think so. I think in my deepest recesses I’ve always been a scientist.  [AS] – And what are your hopes for the future potential of the embryonic stem cells you developed?  [ME] – Well I think it’s very interesting that embryonic stem cells, which can be grown in culture and which can differentiate in a mouse, they can also differentiate *in vitro*. And that has actually given them two platform technologies that they’ve established. One is the one we’re talking about here, the ability to manipulate the mouse genome. But the other of course is the one that’s come through in recent years, which the opportunity, maybe, to use the human embryonic stem cells as a platform for regenerative medicine. And I think that all of the (I mean I’m sure you’re well up with the situation), all of the ethical angst and anxiety is going to melt away once we’ve got the reprogramming going properly.  [AS] – If one just concentrates on the mouse side of things, do you think that there’s more to be done on that side?  [ME] – If you look at the numbers of known, well-described knockouts they’re well under the interesting loci that there are out there. No, I think there’s a long way to go and people are starting to use the technology more subtly now too. You know, using conditional knockouts and this sort of thing which is just opening-up whole new areas.  [AS] – Yes, the ability to spatially and temporally segregate …  [ME] – Absolutely.  [AS] – OK, well it sounds as if I may already be interrupting celebrations that are going on in the background, but do you have special plans for celebration tonight?  [ME] – No, no we don’t. We’re probably going out to the pub for a quick pub meal, since all is chaos here.  [AS] – Sounds a down to earth way to celebrate the goal in the world cup.  [ME] – Yes. OK, thank you very much.  [AS] – Thank you, bye, bye.  [ME] – Bye then. |
| Interview |  |
| ID | 0543 |
| Biographical | My fraternal twin, Roger, and I were born prematurely on June 23rd, 1925, in Halifax, England, an industrial town in the West Riding of Yorkshire, although we lived outside Halifax at 2, Woodhall Crescent on Wakefield Road, a row house rented from the town. My father, William Smithies, was at that time working for his father, Fred Smithies, who paid him erratically. My mother, *neé* Doris Sykes, was a college graduate and taught English at the Halifax Technical College (where she met and fell in love with my father who was one of her students and younger than she). Not long after our birth, my father found a regularly paying job selling small life insurance policies to local farmers and their families. He was a kind and gentle man with a natural mechanical aptitude that he had inherited or learned from his father. A car was needed for a person selling insurance to scattered customers. So we were unusual in our neighborhood in the 1930s in having one. Not that the car was very special; it was a two cylinder Jowett and was in constant need of repair. I have vivid memories of “helping” my father, when I was about 8 or 9 years old, to select the least worn exhaust valves to use in keeping it running. (The stems of the valves wore badly.)Our sister, Nancy, was 5 years younger than us, and a welcome addition to the family. She was a beautiful fair-skinned ginger-haired baby, and we 5 year old twins suggested naming her “Buttercup”. All three of us were generally healthy and happy, although Nancy would not have survived infected tonsils without the then newly discovered miracle antibiotic drug “Prontosil” – the first of the sulfonamide drugs. I had a similar incident at age 7, but without the Prontosil, and was bedridden for 10 weeks after a bout with “rheumatic fever”. This illness left me with what I now know was a trivial mitral valve murmur. However at that time the condition was considered serious, and I was not allowed to take part in sports for the next 7 years. But in the time that I might otherwise have spent in competitive sports I learned to enjoy reading and making things. And sometime before I was 11, I read a comic strip in which an inventor was the major character. This was what I wanted to be – an inventor! (I didn’t know the word “scientist”.)Our mother introduced us joyfully to English literature by reading out loud to us, which she did beautifully, while we waited for my father to come home for the midday meal (“dinner”). Kenneth Grahame’s “Wind in the Willows” and Lewis Carroll’s “Through the Looking Glass” were favorites. And we heard and enjoyed Chaucer’s “Canterbury Tales” spoken in middle English. We were often happy when our father was late. A dictionary was a part of our everyday life as children, and continues to this day to be a constant companion in our house.The location of the house on Wakefield Road was ideal for children. Behind it was a long oak wood that covered several square miles. In the spring the wood was carpeted with blue bells, and in the fall with acorns. At other times it was a place for children, and lovers. It was also a source of the leaf mold that my maternal grandfather, Ben Sykes, and I collected for his garden. He was a highly intelligent but somewhat short tempered man who lost his job as a company manager because he couldn’t get on with the son of his employer, who inherited the business when his father died. When I knew him, Grandfather Sykes was working as a paid gardener, which he enjoyed greatly. To keep his mind active, he began learning to speak French at age 70 plus. He enjoyed keeping bees too, and taught our father to love this activity. Later, when father was away in the army, we looked after his bees, and recovered their swarms. Roger kept bees for the rest of his life, and was still harvesting honey from hives that he had in his garden in a London suburb at age 81 shortly before he died.Across Wakefield Road from our house was a large field from which we twins would help ourselves to rhubarb – illegally, of course. Beyond the rhubarb field was the Calder Valley canal and the Calder river, both heavily polluted when we lived there – but now recovering well. The Calder valley was even better for children than the long wood. It had caves in disused quarries; and our childhood girl friends, Margaret and Joan Smith, had a farm on the side of the valley. Above the valley was the village of Norland on the edge of a wild heather-covered moor. This moor was another of our playgrounds, and was where my father took his bees for them to collect the heather honey.My father must have enjoyed mathematics, because I have a particularly vivid memory of him introducing me to decimals at an early age, writing with his finger on the condensate covering the wall above the bath that I was taking. I even remember the color of the wall as being blue. The same love of mathematics was deeply ingrained in Dr. G. E. (“Oddy”) Brown who later taught me mathematics at Heath Grammar School. He conveyed enough of the logic and principles of mathematics that I didn’t need to take any math courses at the University. Indeed, the examiners of my entrance examination to Oxford University commented that my mathematics was “very promising for a person so young.” I suspect that they liked the comment I added to my answer to their question “How much does a Spitfire slow down when it fires its 8 machine guns?” Using their data on muzzle velocities, weight of a bullet, rate of firing, mass of aircraft, etc., etc., I calculated that the aircraft would slow down 150 miles per hour. I tried to calculate this again in several ways, but still got the same result. So I added the comment: “I don’t believe this result. I think that the correct answer might be around 35 mph.”I have an equally but quite different vivid childhood memory of being shown, by my Smithies grandfather, how to straighten a bent nail. He, like me, couldn’t resist picking up anything that he found lying around because “It might come in useful.” This trait was well recognized by Jean Stanier, one of Sandy Ogston’s graduate students at the same time as me. Odds and ends of discarded equipment and the like would be set aside and labeled NBGBOKFO – “No bloody good, but okay for Oliver.” I still make new devices from what most people would call “junk.”My twin Roger and I went to the school in Copley, a village only a 15 minute walk from our Woodhall Crescent house. Our parents decided to let us go to this unpretentious village school rather than send us to a private school, even though the scholastic levels of the village school were less than desirable. It worked out well. Both of us passed the intelligence test used in 1936, as an entrance examination for acceptance of 11 year olds to a higher level of schooling.Partly in preparation for this change, we moved to 33, Dudwell Lane, Halifax, a semi-detached house that was part of a collection of rather well designed but inexpensive new houses. This house was only a 15 minute walk from Heath Grammar School, the school which Roger and I now attended. Shortly after moving to 33, I met Harry Whiteley, the only son of the works manager of a local company that made precision time clocks for factories. Harry’s and my interests matched perfectly, and we became and still are close friends. Harry’s father had set up in the attic of their house (“the loft”) a lathe, a good drill press and the hand tools needed for making many things. Harry knew how to use them, and the loft became our playground. I had somewhere read about a radio controlled boat, and we decided to make one. For the transmitter we used a spark coil from a T-model Ford. For the receiver we used a home made coherer, the same device as the one that [Marconi](https://www.nobelprize.org/nobel_prizes/physics/laureates/1909/) had used in his first wireless telegraphy receiver. This was radio transmission at its basic minimum – and we never got it to work. But, encouraged by my grandfather’s commercially made receiver, which used a crystal in place of the notoriously fickle coherer, we progressed to winding our own coils and made a much more up-to-date crystal set that worked well. This in turn led to a one-vacuum-tube radio, which I incorporated into my gas mask case instead of the gas mask that all British children were required to carry in the early days of World War II. Our best radio was a super-heterodyne of an advanced design and had four tubes. It worked as a “bread board”, but disappointingly not when rebuilt as a more finished product.When I was about 16, one of my father’s friends gave me the engine from a motorcycle. Harry and I made it run, and became interested in owning a complete motorcycle. My first was a 1926 Rudge Whitworth which was notable for having rim brakes that did not work when it rained. Harry helped me exchange the front wheel for one with a safer internal expansion brake, and I used the Rudge regularly to travel to and from college. I also tried, but to no avail, to make it run on a gasoline-water mixture to eke out the very limited gasoline ration. Subsequently, by judicious trading, I managed to acquire motorcycles of increasing power, but always old, and they were an enjoyable and adventurous part of my life for several years. The cars that succeeded the motorcycles were equally old, and kept up my skills as a mechanic. Modern cars and laboratory equipment are unfortunately now only repairable by replacing subassemblies, so the current generation has lost this strong incentive to learn how to use simple tools.Heath Grammar School was an Elizabethan free school founded in 1597. When we attended the school, it had a superb staff of dedicated and highly-educated teachers. History was taught by C. O. Mackley who tried, in vain, to persuade me to study history with him in the sixth form. Chemistry was the task of A.D. Phoenix – who kept order with the flick of the rubber hose from a Bunsen burner. H. Birchall, the games master, tried kindly to bring me up to speed in athletics, but it was a hopeless task with a boy beginning to play games at age 14. My first year in the sixth form, at age 16, was spent with a few other pupils in supervised study of physics, chemistry and mathematics at a more advanced level. The first term of my second year in the sixth was spent in unsupervised study in preparation for the Oxford University scholarship exams. I concentrated on physics (I was thinking of studying the subject at the university, although in the end I chose medical school), and was fortunate in being awarded a Brackenbury Scholarship at Balliol College. Consequently, the remaining two terms in the sixth form were a blast in more ways than one. I was allowed to do whatever I wanted to, which was messing around (alone) in the laboratory. I synthesized many substances that caught my fancy, including phenyl isothiocyanate, which my textbook said was one of the worst smelling substances known to mankind. I made nitrocellulose (a constituent of Nobel’s smokeless powder), and mercury fulminate (the detonator for his dynamite). Perhaps from some innate cautiousness I did not try to make them explode. Quite the opposite was inadvertently true of the nitrogen tri-iodide that I prepared. I had spilled traces of it which exploded when Mr. Phoenix wiped the bench (he was heard to say in an exasperated and loud voice “Smithies!”) My father had a similar reaction when some that I had put on the top shelf of our living room sideboard exploded with a puff of purple smoke as he walked by; it was extremely sensitive when dry.I had three remedies for the homesickness that I felt on first going to Oxford. One was to look out of my college room window in the direction of my home in the north of England. Unfortunately I was actually looking south. I never did get the geography of Oxford right because of this error. The second remedy was to read all the Brontë novels again. The three sisters lived in Haworth, only a few miles from Halifax, and their novels were filled with descriptions of the Yorkshire moors that were such a part of my youth. The third remedy was to go down to the porter’s lodge and look for a letter from home. Thereby hangs another tale. Balliol College at that time was heated only by open fireplaces in individual rooms. I lived in a room on the second floor reached by a spiral stone staircase. In the cold damp weather typical of autumn in Oxford, water would condense on the walls and trickle down the staircase. My room was narrow with ill-fitting windows at either end, and with stones covering half of its floor. It was heated (somewhat) with a small fireplace in which I could burn my weekly ration of coal – it was war time. On one occasion when I returned from my homesick visit to the porter’s lodge, the corridor was full of smoke and my fire was gone. I followed the trail of smoke and found two second year medical students enjoying *my* fire in *their* grate. We immediately became friends. C. G. A. (Geoffrey) Thomas was one of them – which is how I remember the base-pairing rules of DNA – C with G and A with T.A. G. “Sandy” Ogston, who had interviewed me during my scholarship exam, was the normal tutor for Balliol college’s medical students, but his wartime duties prevented him from being my first tutor. David Whitteridge served in his place. Whitteridge was a brilliant scientist but a hard nosed tutor. I remember him saying to the Master of Balliol (A. D. Lindsay) during our end-of-term meeting that “Smithies can’t spell”. Lindsay’s response “Oh, all interesting people can’t spell,” was encouraging. Whitteridge’s comments “Diffuse, undisciplined, and at times inaccurate” written across my term paper were typically scathing, but deserved. His verbal comment to another student who had copied part of his weekly essay from a source that Whitteridge could recognize was equally to the point – “These scissors and paste jobs will do you no good.” Oxford tutors could be ferocious, but that is what made their lessons unforgettable.I studied anatomy and physiology with a little organic chemistry for two years as a medical student. I surprised the “real” anatomists and myself by winning the anatomy prize, I think because of my answer to one of the exam topics set by Professor Le Gros Clark, who was a pioneer in what we now call cell biology (he was also famous for uncovering the Piltdown-man fraud, and for helping Leakey with his pre-human fossils). I almost walked out of the room on reading the question: “Compare the regenerative powers of muscle, bone and nerve.” But I suddenly thought of a principle that I thought made their similarities and differences understandable, and so I stayed. Perhaps Le Gros Clark enjoyed reading my answer as much as I enjoyed writing it.My third year at Oxford was spent in studying for an honors degree in animal physiology (which included biochemistry). By then Sandy Ogston was back from his wartime duties and had resumed teaching and giving lectures on the application of physical chemistry to biological problems. He was best known for his three-point attachment explanation of how an optically active product can be generated from a symmetric precursor. My weekly tutorials with him were always stimulating and led to many memorable incidents. One occurred during the reading needed to prepare for a tutorial essay on carbohydrate metabolism. After learning something about metabolic pathways, I had been struggling to understand the biological “need” to carry out the complex series of reactions that the body uses to extract energy from carbohydrates. I found the answer in volume 1 of *Advances in Enzymology* in a long article written in 1941 by Fritz Lipmann. In this article Lipmann describes the difference between energy-rich and low-energy phosphate bonds, a difference that makes sense out of the complex series of reactions used to metabolize carbohydrate. I read his article in my Balliol college room with a level of excitement that I still remember. I even recollect the look of the glossy paper, the look of the pages, and the color of the cloth binding of the volume – a very similar feeling to that when I was introduced to decimals by my father.This introduction to the importance of energy-rich phosphate was the cause of my later coming to Sandy’s weekly tutorial with a way to generate an energy-rich phosphate bond from a low energy phosphoester bond by a cyclical oxidation and reduction scheme. Because my scheme could produce energy for nothing, I knew that it was wrong – like the Spitfire slowing down 150 mph – but I didn’t know why. Together, Sandy and I – but mainly Sandy – realized that the standard free energy of a reaction (at that time used to classify the energy resulting from a reaction) was not a valid way of calculating how much energy the reaction would produce within a cell. One needed to know the actual concentrations of reactants and products in order to calculate this. My first scientific paper (Ogston & Smithies, 1948) was the outcome of this endeavor. Looking back at the paper, I can see Ogston’s analytical mind at work – the paper hints at what is now known to be correct – the need to keep the reactants within a large molecular complex if realistic rates of reaction are to be achieved. This paper was the first of about half a dozen hypothesis papers that I have attempted over my scientific life.My college “fire-stealing” friends were masters of how to study with the minimum of effort. We learned histology together by playing a show-and-tell game on Sundays that taught us to recognize the tissue on a microscope slide after only a second’s glance – just as one recognizes a face. Once identified in this brief time, one could then carefully describe from memory what should be there. If the slide was of liver, for example, we would say “I can see the stellate cells of von Kupfer etc. etc.” We never did see them, but this technique, passed on to subsequent generations, meant that Balliol students always came first in the histology examinations. Organic chemistry was equally conquerable if one used all one’s senses, as illustrated by Geoffrey Thomas’ finding that all the compounds which we were likely to be given could be identified by three tests: “taste, smell and appearance”. I put his principle to good use in the final practical examination in Biochemistry. On being presented with a clear colorless, slightly viscous liquid that smelled of caramel and tasted acidic, I thought it might be lactic acid. A confirmatory test was positive, and I finished the exam in less than 10 minutes.Sandy Ogston’s fascination with the relevance of physical chemistry to biological systems was infectious, and I decided to drop out of medical school and do research in this field. The fourth and fifth years of my Oxford period were consequently spent in acquiring a sound background in chemistry. Since I already had a first class honours degree in physiology I did not have to worry about how well I would do in the exams. I could therefore pick and choose among the topics that I would study. I had a grand time. My organic chemistry was confined to biological compounds, my inorganic chemistry could emphasize the simple inorganic materials of biological relevance, Na+, K+, F–, Cl–, etc., rather than rare earths and the like. And I could emphasize those parts of physical chemistry that I enjoyed or were particularly relevant to biological systems. I remember well studying for and writing what I thought was an outstanding twelve-page essay on “The [Pauli](https://www.nobelprize.org/nobel_prizes/physics/laureates/1945/) exclusion principle and the periodic table”, which Ronnie Bell, my first tutor in chemistry, had assigned for one of my early tutorials. I only got half way down its first page when Ronnie spotted a weak link in my argument. The rest of the hour’s tutorial was spent in teaching me that “You never, ever, write down anything that you do not understand, or cannot justify.”After completing the undergraduate part of the chemistry degree, and now in my sixth year at Oxford, I joined Sandy’s lab in the department of biochemistry as a graduate student. It was a happy place. The oldest of us was Rupert Cecil (a veteran bomber pilot and a wing commander in the Royal Air Force). Rupert, in addition to his own research, managed the complex equipment of the laboratory with complete confidence. One of his responsibilities was a [Svedberg](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1926/) ultracentrifuge – a large machine built on a concrete pillar and equipped with a powerful electric oil compressor in a pit below the floor. I never cared for the beast, and studiously avoided being sucked into its tentacles. Nevertheless, my thesis topic centered on an artifactual problem that the ultracentrifuge had generated – “the apparent conversion of the globulin fraction of plasma proteins into the albumin fraction.” I was to look for some type of disassociation–reassociation reaction by studying the osmotic pressures of mixtures of proteins. I never did get to that part of my problem, but I had a thoroughly enjoyable two years trying. The outcome was a thesis, half of which was devoted to what are now (to me) un-understandable thermodynamic equations. On later re-writing this part of my thesis for publication I discovered a fatal flaw, so my equations never saw the light of day. The other half was devoted to my development of an extremely precise osmometer. The data it produced were so tight that the line through the experimental points had to be interrupted for them to show. This work was published (Smithies 1953), although the resulting paper has the dubious distinction of never being cited by me or by anyone else. Nevertheless, this thesis work re-enforced my natural inclination to pursue experiments to a conclusion with little regard for the time required to reach this end.The osmometer required a home made water bath with its temperature controlled to within 0.001°C. This I achieved by using a submerged electric light bulb as a controlled heater. Sandy’s next graduate student, [Barry Blumberg](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1976/) (Nobel laureate in 1976), inherited my bench – and the water bath. He is said to have destroyed it in a fit of rage induced by the repetitious on-off cycle of its light bulb.When the time came for me to think about post-doctoral work, Sandy urged me to think about going to the USA. I was not enthusiastic – but was persuaded to overcome my prejudices by Sandy and Robert L. (“Buzz”) Baldwin. Buzz was a Rhodes scholar from Madison, Wisconsin, working towards his doctorate with Sandy, and he painted a fine picture of life in Wisconsin. So I applied for and was awarded a Commonwealth Fund fellowship to continue my education as a post-doctoral fellow under the guidance of J. W. (Jack) Williams, a learned physical chemist in the Department of Chemistry at the University of Wisconsin. There were other fine physical chemists in Jack’s group, including Bob Alberty, Bob Bock, Dick Golderg and Lou Gosting. My stay with them increased my knowledge of physical chemistry greatly, but the work I did was not particularly rewarding; it culminated in another article that rightly received virtually no attention (Smithies, 1954). In contrast, the reward from the kindness and collegiality of these colleagues and of the other friends that I made in Wisconsin was enormous. They completely removed my foolish preconceptions about “Americans”.My regard for Americans was further increased by my meeting and becoming engaged to Lois Kitze, a graduate student working in virology. But she was reluctant to cross the Atlantic, as I had earlier been in the reverse direction. So, because my acceptance of a Commonwealth Fund fellowship precluded my staying in the United States, I looked for work in Canada. I was fortunate in finding David A. Scott, who in 1954, offered me a job in Toronto. “Scottie” was an older man when I met him, and was winding down a distinguished career in science. He was the first person to crystallize insulin as a poorly soluble zinc salt, which is widely used in the commercial preparation of insulin and still forms the basis for a slow release form of the hormone. He was a Fellow of the Royal Society of Canada, and of the Royal Society of England. When I met him, he was working by himself in a small room in the Connaught Medical Research Laboratories, a part of the University of Toronto, and spent his mornings looking for a protein in plasma which he thought might bind insulin. In the afternoons, he played golf. He offered me the opportunity to work on anything I wished “as long as it is related to insulin”. After reading the available literature, I chose to look for a precursor to insulin. I never found it. But the difficulties I encountered in trying to find it, and a childhood memory that the starch which my mother used for my father’s shirts turned to a jelly when it cooled, led to my invention of starch gel electrophoresis. The high concentration of starch needed to make a strong gel introduced a new variable into electrophoresis – molecular sieving. Finding the best variety of starch and how to process it for making the gels became necessary when my supplier’s stock of processed starch was exhausted. Many hours were spent in testing all the raw starches that I could buy, and then in grocery stores finding potatoes from Holland Marsh, New Brunswick, Prince Edward Island and Idaho from which to make the raw starch. None gave as good gels as those made from my first batch. I eventually found out why: my original supplier had purchased starch processed by a second company that had used raw starch imported by a third company from Denmark because of an attack of potato blight in Canada!The starch gel method proved very effective. With it I discovered previously unknown differences in the plasma proteins of normal healthy persons, which Norma Ford Walker and I showed were inherited (Smithies and Walker, 1955, 1956). Many new opportunities were opened up, and my friends suggested that I would be helped by having a technician. Somewhat reluctantly I agreed, and was joined part time by Otto Hiller, a young immigrant from Germany. He proved to be an excellent choice. We worked together well and soon became friends. Otto had an excellent mechanical sense, and began to make the starch gel equipment that I and other scientists needed for our work. He came along to Wisconsin when I moved there in 1960, but not as my technician. Instead he set up a business to manufacture the plastic equipment and assemble Heathkit® power supplies which were suitable for the gel electrophoresis. He also arranged for a manufacturer in Denmark to produce a starch suitable for making the gels, and then distributed the starch to scientists all over the world.Otto and I spent many Saturday afternoons in his “shop” doing the same sorts of things that Harry and I had done in the loft. We assembled a Heathkit® digital alarm clock, and found out that it had a design flaw which caused it to lethally “electrocute” its own Intel CMOS integrated circuit. We worked out a remedy after several replacement chips, and had some enjoyable interactions with the Intel engineers who we found had drawn a Mickey Mouse on an unused part of the chip. This led us to try to make our own precision digital clock, and to attempt bread boarding a microcomputer using Intel chips. But our knowledge and bread boarding technique proved inadequate. So Otto bought a mail order kit for an Altair 8800 microcomputer, while my interest in *making* a computer was replaced by *using* a time sharing GE computer located in Milwaukee, 60 miles from Madison. Communication was by teletype, and the computer language was BASIC. The immediacy of a time-sharing computer suited me, and I subsequently enjoyed directing my student, Bob Goodfleish, while he wrote a group of programs to extract amino acid sequences from our Edman sequenator (Smithies *et al*., 1971). Nearly 10 years later I had the same enjoyment in directing John Devereux during the writing of a group of programs for analyzing nucleic acid sequences. The resulting paper (Devereux *et al*., 1984) is my most quoted, with > 6000 citations. More recently I have returned to devising new biological uses of computers, thanks to the existence of generic programs (such as Stella®) that a person can use for modeling complex biological systems without the help of a computer scientist (Smithies *et al*., 2000; Smithies, 2003). The greatest value of devising these computer models comes, I have found, from their forcing one to clarify which elements in a complex system are most critical, rather from their ability to replicate experimental data or make predictions.The discovery of inherited differences in plasma proteins shifted my interests towards genetics. This shift, and my wife Lois’ homesickness for the States, led me to return to Madison in 1960, to join the strong genetics group at the University of Wisconsin. But I continued to collaborate with my Toronto friends to decipher the molecular/genetic basis of the protein differences found in plasma. This work revealed how homologous recombination could affect protein structure (Smithies *et al*., 1962). It also led me to hypothesize that antibody variability might be achieved by recombination (Smithies, 1967). As a consequence, I had an enjoyable period devoted to protein sequencing with the automatic Edman sequenator.This protein sequencing period ended with the advent of DNA cloning, which encouraged me to spend a sabbatical year with Fred Blattner on a floor below mine in the Laboratory of Genetics. During this time I learned to handle bacteria, bacteriophages and DNA (and took flying lessons at a small nearby airfield). Fred was deeply involved in developing safe procedures for cloning DNA, which at that time was thought might be environmentally hazardous. One of the safety tests required volunteers, of which Fred and I were two, to drink milk spiked with a large number of bacteria and then determine how many survived passage through the gut. The little packages of fecal material that we had to bring back to the lab were the sources of much merriment. During this period, I was invited to apply for various chairmanships in genetics, biochemistry and immunology. Somewhat selfishly, considering the great contributions that chairpersons can make to the scientific welfare of their faculty and students, I chose to continue my life as a bench scientist. But without this decision I might not have had the time to start the experiments, begun at age 57, which led to my best gene targeting paper, published after I was 60 (Smithies *et al*., 1985).In 1978, Lois and I, by mutual and amicable consent, gave up on our less than ideal marriage. And several years later I followed my mother’s example by falling for my post-doctoral student, Nobuyo Maeda. However, we were unable to find a way to continue working together in Wisconsin. So, after more than 25 years, I left Madison to accompany Nobuyo to Chapel Hill, North Carolina, where she had been offered an appointment in the Department of Pathology at the University of North Carolina. Nearly 20 years have passed since that move. We have been happy together, and our science has flourished. The academic environment in Chapel Hill is agreeable and collegiate. The weather changes more gently than in Wisconsin (except for occasional hurricanes), and the winters are less harsh than in the Midwest. As a full time research professor at UNC I have been able to spend even more time at the bench; and all my experiments using gene targeting to generate animal models of human genetic diseases have been carried out in the nurturing environment of the University of North Carolina.Music has been a part of my non-scientific life, beginning quite early when, as children, Roger and I both sang in the choir at Copley church. We enjoyed the music and also the camaraderie of boys playing pencil games during the sermons. All three of us children were required by our parents to learn to play the piano from 7 until 11, at which time we could choose. Roger chose to learn to play the cello, and he continued playing it and the piano for the rest of his life. Nancy became a professional musician, and taught music in high schools. I stopped music lessons, but continued to sing in the church choir until my voice changed. Later at age 18 during my first year at Oxford I joined the Balliol college choir. In my second year, I auditioned for the Oxford Bach Choir with Sir Hugh Allen – a notoriously brusque conductor, famous for his sharp tongue. He began the audition with a comment and a question “You’re from Balliol, I see. This is not your first year, is it?” I agreed. His next question was “Do you know how I know?” I replied “Yes sir, my tie [a Balliol tie] has been washed.” The audition never flagged thereafter, even when he asked me to sing my lowest note, only to be interrupted by his secretary saying “Excuse me, Sir Hugh, but this gentleman is a tenor”. To which he responded with “Oh, in that case sing your highest note!” followed shortly thereafter with “Stop! Stop!! You’ll blow your head off!!!” I sang with his choir for the remainder of my time at Oxford. And I continued to sing tenor with great pleasure with the Symphony Chorus during both my times in Madison, and with the Mendelssohn Choir in Toronto. In Oxford, I learned to play the flute from an ex-army flute teacher. I was not good enough to play in an orchestra, but I happily played for many years with several small groups and with various accompanists.My interest in flying also began at an early age, before I was 11. I had read all the “Biggles” books by W. E. Johns – fictional accounts of a World War I fighter pilot. I had also been entranced by the movie serial “Tail Spin Tommy” which played at the Saturday morning “Tuppeny Rush” cinema in Sowerby Bridge, a half hour walk from my home (the admission charge was two pennies). And I had read enough about sailplanes and their instruments to dream of flying them. But World War II broke out when I was 14, and gliding as a sport stopped. It was not until I was 38 that I had my first real encounter with flying. This occurred in 1963, during a visit to Toronto which I had made in order to learn from Gordon Dixon how to sequence proteins. The required experiments did not suit my temperament – so instead I went down to the Toronto Island Airport and spent the next 10 days taking flying lessons. Over the course of the next month, now back in the States, I took enough additional lessons at Morey Airport in Middleton, Wisconsin, to be able to solo (fly by oneself). But I did not continue. Not until the late 1970s, when I was 52, was I able to try again, thanks in part to the stimulus to learn new things that is part of taking a sabbatical year. This time, I took glider lessons from “Jake” Miller and power plane lessons from Field Morey. Field, the son of a Lindberg-era pilot, was and still is a world class flight instructor, and we have had many hours together as student pilot and instructor. And many more as friends, including the time in 1980, when I accompanied him as copilot on a record-winning flight for a single engine aircraft across the Atlantic from Goose Bay, Labrador, to Rekjavik, Iceland, and then on to Prestwick, Scotland. We knew it would be difficult because we did not have special fuel tanks. So at the end of the runway at Goose Bay and after being cleared for take off we shut down the engine and topped off the tanks until, after adding several gallons of gasoline, they literally overflowed. After flying for 8½ hours, we landed at Rekjavik with only 3 gallons of fuel left, enough to fly for about another 10 minutes! But we beat the previous record – by 17 minutes. Our record held for nearly 20 years.I learned to fly by instruments with Field, and remember rejoicing with him when “Only one drop dripped” (of sweat from my face). One of my glider students – who, like me, would sweat profusely during instruction – came back from his first solo flight with a big grin on his face, with his hand on the back of his shirt, and with the comment “Look Oliver; it’s dry!” Learning to fly is learning to overcome fear with knowledge. This same lesson applies to trying new things in science, and to life in general. I am forever grateful to Field for helping me to learn it, and for giving me the joy of flying airplanes, which still continues after more than 4000 hours of piloting – in all sorts of weather.Approaches into airports on cloudy days are carried out with the help of two needles on a dial from which indirect evidence the pilot can infer the position of the aircraft; if the needles cross at right angles you can infer that you are on the beam. Our first assay for gene targeting was likewise indirect, being based on finding bacteriophages of a specific type; if we found the bacteriophages we could infer that targeting has occurred. The airplane instrument approach and the gene targeting experiment both have a moment of truth. When the aircraft comes out of the clouds, either the runway is there, or it is not. Likewise, when DNA from a cell colony identified by the indirect bacteriophage assay is tested directly (by a Southern blot), either the gene is altered or it is not. In 1985, at a Gordon Conference during which I first described our success in gene targeting, I told the audience how I was thinking of this airplane analogy while developing the critical Southern blot autoradiograph. On presenting the positive result to the audience I said “And there’s the runway!” All the rest of the speakers at that meeting accompanied their critical data slide with the comment “And there’s *my* runway!” |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0543= OS [Unknown] – Hello.  [Adam Smith] – Hello, may I speak to Oliver Smithies please?  [Unknown] – Yes, may I ask who is calling?  [AS] – Yes, this is Adam Smith from the Nobel Foundation’s website.  [Unknown] – Yes, just a second please.  [AS] – Thank you.  [Oliver Smithies] – Yes, good morning.  [AS] – Good morning, is that Professor Smithies?  [OS] – Yes, it is.  [AS] – Hello, my name’s Adam Smith. I’m calling from the Nobel Foundation’s official website, Nobelprize.org …  [OS] – Uh-huh.  [AS] – … and we have a tradition of recording very brief interviews with new Laureates and I wondered if you’d mind just answering a very few questions?  [OS] – No, I’d be happy to.  [AS] – Thank you very much indeed. Well, first of all, of course, many, many congratulations on the award.  [OS] – Well, thank you.  [AS] – It’s pretty early where you are, I imagine you were asleep when the call came?  [OS] – Yes, that’s correct. I was just about to shave and have a shower, now, and I would be sleeping still normally.  [AS] – And what was your first thought when the news came?  [OS] – Well, my first thought was to ask with whom it was, because I so much admire the work of Mario Capecchi and Martin Evans. So that’s a big delight to me, to share it with them.  [AS] – And indeed you shared the Lasker Prize with them in 2001.  [OS] – Yes, that’s right. We’ve shared several in the past and they’re both, well I would call them friends really now. I mean we met through science, but we’ve known each other for a long time, and Martin Evans, for example, brought the embryonic stem cells that we used in our work, he brought them himself, in his own pocket.  [AS] – When you collaborated?  [OS] – Well, I suppose you would call it collaboration. It wasn’t an official collaboration, he just brought the cells, at the time. You know, those were … did we actually ever collaborate with him Nobuyo, I don’t know that we ever published together, did we? No, we never actually published together (I’m just asking my wife).  [AS] – But a nice act of generosity.  [OS] – Yes, it was marvelous.  [AS] – And of course the three of you are renowned as the fathers of the knockout mouse, a very widely-used tool now for molecular biology and physiology.  [OS] – Yes.  [AS] – Are you surprised by the overwhelming number of transgenically-modified mice that are now around?  [OS] – Well I suppose I’m not really, it’s just grown, just gradually, and it’s been fairly obvious that they were very useful. I think probably Mario Capecchi’s changing the approach to do knockouts was the catalyst for most of the increase in numbers. My original work was to demonstrate that it was possible to do homologous recombination, and the mice we made, we were thinking about gene correction, we were thinking about correcting genes, and then he realized I think that the most useful thing was to do knockouts, to knockout a gene, if you have to do one specific thing. And that was the catalyst for the big increase, plus a good method of doing it more easily that Mario devised.  [AS] – Yes, because the success rate of transfection was very small.  [OS] – Yes.  [AS] – You’ve described yourself previously as an inventor, and …  [OS] – Yes, I still think of myself as that.  [AS] – What would you describe as the characteristics of a successful inventor such as yourself?  [OS] – Oh, to make things work with minimum stuff, as it were. You use whatever’s lying around, and you see something needs to be done and you try to do it. I think it’s just making things work, you know, somehow. I don’t know that it’s any great imagination, it’s just I need to do this and perhaps I can do it with this little piece of stuff. Or I picked that up the other day and I can use that. My grandfather used to pick up nails and straighten nails, and I still pick up wires and things that I find lying around. “Oh that’ll be useful for something.” And when I was a student they had an expression for me, because of this tendency, they had a rather coarse expression, “NBG BOKFO: No Bloody Good But OK For Oliver”, for things that were lying around, that might be useful.  [AS] – Well obviously you made good use of them in the end.  [OS] – Yes.  [AS] – What gives you the greatest pleasure then? Is it tinkering around, or is it in fact the realized invention once it’s done?  [OS] – No, I think it’s doing it, I don’t think it’s the … I mean I suppose it goes back to the same thing again, when I was a child, they used to say I always said “Ollie do”, before I could speak, I always wanted to do things. And it’s the actual doing of it; the daily experiments. I still work at the lab and still work at the bench, and my enjoyment is just doing the experiments. Of course one enjoys the results, but if you don’t enjoy the doing of it you won’t succeed in science because most of the time you don’t get results that you particularly want!  [AS] – Another word you’ve used to describe yourself is ‘Toolmaker’, and I imagine there’s a special pleasure in seeing the tools you make being so widely used.  [OS] – Oh, yes, that’s absolutely true. I mean I look at a journal and I open the pages and I see people use gel electrophoresis and I see they use gene targeting and you just get a little sort of shared enjoyment.  [AS] – And in your original work do you think there was a Eureka moment, one that you can point to, or was it just a set of …  [OS] – Oh no there’s a very definite Eureka time when I realized how I could make homologous recombination work, and it wasn’t really make it work, it was that I had an experiment that would allow me to find if it was possible, because one didn’t know that it would be possible really, and I have one page in my notebook where the whole scheme is written out in one page.  [AS] – Right.  [OS] – And that was as a result of teaching. I was teaching at the time, a graduate course, and having taught a paper that used a method that I realized would allow me, if I used the same principle as that method I could therefore detect what I thought would be a very rare event. I called it gene correction. So I wrote this page in my notebook and that’s a Eureka page, as it were. Perhaps not a moment, it’s a page. I’ve had a number of Eureka moments, but that was a Eureka page.  [AS] – And how long was it in time from that Eureka page to …  [OS] – Oh, it was more than three years.  [AS] – I don’t want to keep you on the phone long, it’s going to be a busy day for you, but I just wanted to ask; I know you’re a pilot …  [OS] – Yes, I was flying yesterday.  [AS] – So now will you plan a special flight, with loop the loops?  [OS] – Oh no, the aeroplane I fly now won’t … it’s not certified for aerobatics. But no, I flew yesterday, I’ll do my usual flying. I have a motor glider and I had a very good day yesterday. It was one of those days that I always enjoy, the three things: I did some science, I took my wife to lunch and I went flying.  [AS] – Well, it’s hard to better that day but perhaps this one is starting off quite well as well.  [OS] – Well, it’s started well, hasn’t it?  [AS] – Yes, indeed. OK, well I’ll let you get on with your preparations.  [OS] – OK, thank you.  [AS] – Lovely to speak to you.  [OS] – Nice to talk to you, bye, bye.  [AS] – Bye, bye. |
| Interview |  |
| ID | 0544 |
| Biographical | Andrew Zachary Fire was born on April 27, 1959 at Stanford University Hospital in Santa Clara County California. Spending most of his early years (until age 16) in nearby Sunnyvale, he attended the local public schools: Hollenbeck Elementary School (1964–1970), Mango Junior High School (1970–1972), and Fremont High School (1972–1975).Fire enrolled at University of California at Berkeley in the Fall of 1975, receiving an AB degree in Mathematics in 1978. Fire then entered the Ph.D program in Biology at Massachusetts Institute of Technology as a National Science Foudation Fellow in the Fall of 1978. Fire’s Ph.D. thesis, titled “In Vitro Transcription Studies of Adenovirus”, was submitted in 1983. From 1983 to 1986, Fire received training in the *Caenorhabditis elegans* group at the Medical Research Council Laboratory of Molecular Biology in Cambridge, England as a Helen Hay Whitney Foundation Fellow. During this time, Fire initiated research directed toward improvement of microinjection technology and development of assays for expression of foreign DNA in *C. elegans* worms.During his last year at the MRC lab, Fire applied for a research position at the Carnegie Institution of Washington’s Department of Embryology in Baltimore Maryland, also applying for an independent research grant “Gene Regulation during early development of *C. elegans*” from the US National Institutes of Health. Both applications were successful and Fire moved to Baltimore in November of 1986. From his arrival at the Carnegie until 1989, Fire held the title of Staff Associate, an independent research position that was designed to facilitate the development of novel research programs in the absence of additional academic responsibilities. In 1989, Fire was appointed as a regular staff member at the Carnegie, with his group continuing to develop DNA transformation technology and collaborating on a number of studies to understand the molecular basis of gene activation in muscle cells. Along with the appointment as a full staff member at Carnegie Institution, Fire also acquired an adjunct appointment as a faculty member in the Department of Biology at Johns Hopkins, where he was involved in both graduate and undergraduate teaching and mentoring.In 2003, Dr. Fire moved back to Santa Clara County, taking a position at the Stanford University School of Medicine, where he currently holds the title of Professor of Pathology and Genetics. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0544=AF [Andrew Fire] – Hello.  [Adam Smith] – Good morning, may I speak to Professor Fire please?  [AF] – This is he.  [AS] – Oh hello, my name is Adam Smith. I’m calling from the official website of the Nobel Foundation. First of all of course many, many congratulations on the award of the Prize. Where were you when you heard the news?  [AF] – Um, I was presumably in my kitchen, where the phone is. I went to get the phone at one something in the morning, our time.  [AS] – Yeah, that’s pretty early. You must be sleepy. What was your first thought on being told?  [AF] – Well, one’s elated, but science is a big thing. So, you immediately think of all the people that have helped make it happen and think about the fact that you’re still a pretty small cog in a pretty big wheel.  [AS] – Yes, indeed. You and Professor Mello have been winning quite a few prizes recently. Was this one expected at this time, do you think?  [AF] – I don’t think this is an expected thing for anybody anytime. You know, it’s obviously a great honour. We’ve treated all these things as wonderful gifts, essentially, but in terms of expecting anything we’ve already gotten tremendous amounts of credit out of it, so neither Craig nor I feel that we deserve anything more.  [AS] – The discovery has really inspired a very large number of people to enter the field. Do you think the award of the prize will further encourage people to move into the RNA field?  [AF] – I certainly hope it will. It has been tremendous to watch all the different waves of people from different expertise coming to the field. First a whole bunch of biochemists and then a bunch of chemists doing the character of the RNA, and people doing genetics of it. And then suddenly you get pharmacologists, people coming in and saying how could we change this into a drug and a treatment. And the high throughput people, experts, engineers. And so I think that will continue, and what one sees in the next five years I don’t know.  [AS] – What led you to move into the field? Was there one person or line of enquiry that led you to RNA interference?  [AF] – Well, we were led to it pretty much by our experimental noses. The people in the plant field had done tremendous work on gene silencing and so we, sort of, were following in their footsteps in trying to sort out what was responsible for this weird silencing phenomenon in the worm. The other groups that I think really led us was a whole bunch of people working on this little filamentous fungus called Neurospora, and they had discovered some interesting silencing mechanisms that turned out to be slightly different (at least the ones that had been characterized were much more complex) but were really sort of an impetus to keep going and study it. And I think the third thing is that before we had really put our toe into this field a lot of people, including Craig and Craig’s lab and a number of other labs – the first person being Sue Guo when she was a graduate student at Cornell – had been doing what they called antisense to knock genes out in the worm as a tool, and started to observe all these unusual features. I get drawn to unsolved questions that don’t make any sense, so, it certainly was a draw.  [AS] – Right, right. There are obviously very high hopes for the application of RNA interference now, in many fields. Which do you think will be the most immediate benefits of harnessing the natural mechanism you have discovered?  [AF] – The most immediate benefit is going to be doing experiments that teach us things. People have already done tremendous numbers of experiments. There’s a wonderful study that Rene Bernards’ group in Holland did where they used RNA interference to basically characterize a given tumour type and then once they figured it out they said, “You could treat this with aspirin.” And then they put aspirin on it. And so, that wasn’t using RNAi as a drug, it was just using it to learn about the [system]. I think that, for a while, that’s going to be the major … nothing may be quite that simple. And then eventually people may figure out exactly what it takes and what the risks and the benefits are of using it as a therapy. And there’s a great amount of wonderful work going on in that area; just the early stages, very early clinical trials, some animal model studies. It is going to be a little while I think. One thing I remember saying to a reporter once, on the occasion of RNAi getting thought about as a treatment for high cholesterol, was don’t celebrate with ice-cream, celebrate with frozen yoghurt. So, you know, I think the successes are going to be there but it’s also going to take a lot of stamina from the people doing the work. There may be things that don’t work quite so well, there may be setbacks, as for any new therapeutic.  [AS] – It’s a basic research tool at the moment?  [AF] – It’s a basic research tool with some eyes, with some windows into potential therapeutics. I’ll be as excited as everybody when it all pans out.  [AS] – Yes, of course, and talking of excitement, have you been able to give any thought yet to what you might do to celebrate today?  [AF] – I haven’t really thought about that. It’s obviously a special day for a lot of people.  [AS] – Yes, there are an awful lot of people to tell although I guess they’ll learn through various sources. But thanks very much for taking the time to speak to us now, and again, many, many congratulations.  [AF] – Thank you very much. |
| Interview |  |
| Q6 | Andrew Fire and Craig Mello, welcome to Stockholm. When we spoke a couple of months ago, just after you’d heard the news that you’d been awarded the Nobel Prize, you both sounded quite surprised that it had come as quickly as it has done. Has that surprise subsided at all? |
|  | Andrew Z. Fire: I’m still surprised by the whole thing. It’s obviously a really major honour to be honoured by one’s colleagues in such a way but at the same time, there are a lot of other scientific discoveries and other contributions to the field we’re in that are probably no less deserving and so it’s an interesting situation to be in.Craig Mello: I agree, every day I’m still not sure it’s really me that’s the recipient of this recognition. I really feel it’s more the prize is awarded for the science and in that respect we’re representing many researchers and it’s a great honour to be here to be spokespeople for the discovery and to bring some attention to the science and the fun of science. |
| Q6 | How have the last couple of months been, have they been whirlwinds? |
|  | Craig Mello: Very much so.Andrew Z. Fire: Yes, we each have our scientific day to day lives and intertwined with that has been a lot of interesting other things and also planning a trip to Sweden, so the combination of things has made for a busy couple of months for both of us, I think. |
| Q23 | I can imagine. The prize was awarded for a very concrete discovery, a single event if you like. Is there a moment you can recall when the penny dropped that RNA interference was what you were looking at and you understood how it worked? |
| Q26 | Craig Mello: Certainly not, because we still don’t understand how it works. I think it’s been very exciting and fun to be part of this field because of all of the interesting interrelationships between the RNA interference phenomenology and then the developmental mechanisms that are related to it. I think we have so much still to learn about the basic mechanism of gene regulation, even going beyond RNAi as playing a role in that process, but honestly I feel that it’s been exciting at many steps along the way, but I can’t think of a single point where we felt we understood the mechanism really. I still feel we don’t understand the mechanism fully, we have a much better idea about the underlying mechanism now but we have so much more to learn that it’s just still a lot of fun, it’s a very exciting field. |
|  | Andrew Z. Fire: That’s certainly a major part of it. The other major part of it was that the groundwork that had already been laid in the puzzle, primarily by other people. A major part of it was the people that worked with us that all had put very significant contributions to it. It was really a matter of being in the right place at the right time, particularly the work that had been done in plant systems and in fungal systems and some of the work that was done elsewhere in the worm system by /- – -/ and other people really set it up so that we could just inject RNA that we would make in the lab and then get a result in a couple of days or a day. That happened and that made a very sort of efficient system to begin to test hypotheses.Craig Mello: I think the understanding that there was an organismal response to the injected material was part of what was very exciting to me, even though I didn’t understand certainly what was happening. The observation that the silencing signal could spread from cell to cell and even be transmitted in the germ line were extremely exciting and yet we didn’t understand how the silencing was triggered. In fact, we were not focused on double stranded RNA, in my case we were thinking more in terms of double stranded RNA potentially as a replication intermediate or something that was produced during the amplification process that was necessary for the inheritance to occur. We thought more of double stranded RNA therefore as an intermediate in the silencing and Andy really deserves credit for thinking perhaps the double stranded RNA is an important trigger as well because in some organisms like ourselves, there’s clearly a double stranded RNA response that had been studied previously that’s involved in anti-viral mechanism.We were thinking more of it as an intermediate, which it really is as well, it’s interesting, double stranded RNA is a trigger but it’s not the only trigger for this type of silencing. I think that also was an element that added to the confusion in the literature on the earlier work done in plants, because it wasn’t clear when a virus or a transgene was introduced into an organism, what the trigger was. I think the reason some of that confusion exists is because there are more than one trigger for this. It’s an interesting twist really that we still don’t understand all the different ways that you can trigger the silencing but double stranded RNA is in fact an intermediate in many of these related silencing pathways, so that’s one of the elements we still are very much in need of understanding. |
| Q17 | You emphasised the basic science aspect of all this and that there’s a lot still to be understood. I suppose the world has really embraced RNAi as a technology and an application. Do you find that worrying that people leap on it in its partially understood form and want to use it? |
|  | Craig Mello: I don’t find it a worry, I think it’s natural for people to want to use, especially when you have a sick family member, this sincere desire for some sort of a treatment or cure and I think it’s important for the scientist to make sure that that doesn’t get blown out of proportion, that that hope doesn’t get overstated. I can totally understand the excitement. I think that if anything, we really need to focus on, it really is an exciting discovery and there are many applications that it can be put to and I think we need to get that message out. I don’t think there’s anything to fear except perhaps going too far and being too hyperbolic in promoting it, but I do think we need to get the message out because it’s very important as a research tool, certainly and potentially as a therapeutic, so I think it’s important.Andrew Z. Fire: It’s almost a humorous thing, but one of the things I found is that when I’ve gone to lecture in classical genetics which is many of the tools of which were pre-existed us by several decades and 100 years or whatever. One of the things I find is the students will suggest, why not do everything by RNAi? There’s still very much room for classical genetics, it’s really the basis for a lot of what we do and what we think about and other techniques of genetics that also have come up in the last few years. Targeted gene disruption, which is extremely valuable technology and useful and a number of other things. I think that students realise that when they get into the depths of research problems, that they really have to understand not only what’s been developed in the last few years but also things that were developed 100 years ago. |
| Q10 | Do you think the funding climate is as accepting of basic research as it used to be? |
|  | Craig Mello: I think that the funding climate is tight now, in part because of the tremendous wealth of information that we have about the human genome for example, the sequence of every gene. With that as background and the information technology that we have for searching that database I think it’s harder to get funding to do the kind of work that Andy and I did and quite often it’s a priority that has to be made whether to fund this or to fund that and both really should merit funding, but there just isn’t enough money. In a way I think we’re being strapped in part through the success of the scientific enterprise as a whole, creating more good science that can be done and I think that really can be looked at as an opportunity in the message that we have to get out to the people who make policy in terms of the politics and the funding decisions, that there is a great opportunity with the advances that have been made in medical research.The genome sequence and the information technology that gene profiling technology for looking at the expression of genes in cells and things like RNA interference that allow you to shut off genes to study their function. These provide opportunities that make it actually harder to get basic science funding because now you can do a lot of these experiments in human cells and that’s not always good. The fact is, if you’re taking away the money from the very basic science, that could lead to new technologies, new discoveries that would be very hard to get in a vertebrate cell system. I think, as in the pre-review process, we’ve seen this, I know that I have, where you have to make a decision and there are just, several grants that should be funded and they’re just not going to make it, no matter what, because there are all these others that need to be funded. These priorities just becomes an impossible situation and to fix that we just need to get the message to the public to support science more, so that we can continue to get the funding we need. |
| Q10 | Does your funding come mainly from basic research funding, from NIH or is there also an industrial component to what you do? |
|  | Andrew Z. Fire: Our funding comes from non-profit sources, both completely are. My lab is funded completely by NIH and …Craig Mello: I have funding also from the NIH and Howard Hughes Medical Institute. The work that was done really was funded privately, some private grants other than those mentioned as well, so philanthropic support for disease-oriented grants like the ACS, the March of Dimes funded some of my research and also the Pew Charitable Trust, so to mention I think all of them.Andrew Z. Fire: Those are all charitable organisations and they’re public organisations but they’re all toward the goal of improving healthcare in a general way. |
| Q26 | When you bring new people to work on the problem into the lab, I was interested to know what you look for in those students coming in? |
|  | Andrew Z. Fire: I learnt a lesson from a mentor of mine, a gentleman named Donald Brown. If someone walked up to the door and said, I want to learn, that was a major feature, even if the person might not come in with the most spectacular of previous mentorship or whatever, that was a really major thing. I think that’s something that one looks for, someone that really wants to learn.Craig Mello: It’s very hard I think, sometimes students who are very bright are not motivated enough. I think the major ingredient is motivation and a desire to follow through with an experiment. Those are qualities frankly that you cannot glean in an interview, so I think some of the best scientists have struggled sometimes getting into the lab because the interview process might weed them out, or they may not have the patience for it, in order to go through it. But I find, once you work with someone you really get to know what they’re like, so most laboratories have what we call a rotation process, so students will get an opportunity to work with you in the laboratory as they decide on which group they want to join during graduate work. I think that’s been for me the most important aspect, is having time to spend with the student in the laboratory, find out what they’re like.I suppose that recommendation must become a very important part, if you’re looking for somebody’s long-term commitment to problems, you need to know that they’ve done that before.Craig Mello: It can be but they’re so unreliable.Andrew Z. Fire: Right, it’s hard because the recommendation letters often say as much about the person writing the letter, so you have to factor two different components into the equation. It’s sometimes too difficult to parse out which is which.Craig Mello: Many letters from Asian laboratory heads are incredibly brief and it’s hard to read into the line what they really mean. I think it’s a stylistic choice that they make not to overstate anything and then sometimes in the US you get these letters that go on and on and on and you don’t know how much is genuine either, so I think there’s no perfect way, I really feel that it’s hard to tell in advance. |
| Q12 | You mentioned mentorship and obviously you’ve both been the recipients of great mentorship. What’s that taught you about your own practice of mentoring? |
|  | Craig Mello: I feel so fortunate to have had great mentors along the way and still colleagues that I’ve learnt so much from. It’s very, very important but I could spend hours talking about mentors but … |
| Q12 | Could you summarise just a couple of the things perhaps that you try and practice as a mentor for your students? |
|  | Andrew Z. Fire: It’s a hard question.Craig Mello: Do you want to take a crack at that?Andrew Z. Fire: I think that one tries to listen to what people are thinking because first of all that’s part of the mentorship process and second of all it’s part of the scientific process. No matter who it is, even somebody who’s just walked into the lab – we’ve had high school students working in the lab. The other thing is that you try and work with people as colleagues for each other and get them to ask each other questions because again, I don’t necessarily provide the best mentorship for people in the lab, the best advice and getting advice from each other has always been really critical and that’s one of the nice things about running a research lab in some cases. You can’t just sit back and let the ship run, but on the other hand there are a lot of cases where the really important, critical suggestions come because one person on one project suggests something to another person working on another project. It’s a really important aspect of it, to keep a collegial environment where people are comfortable talking to each other and suggesting things to each other. I’ve just been very fortunate in having had people in the lab who are both outstanding scientists and also outstanding mentors to each other and to me as well, in a lot of cases.Craig Mello: Yes, I think it’s so important, the conversation that you have in the laboratory with your students or with your adviser as I can recall in my own past. Those are so important as a way of learning and as a way of coming up with ideas. It’s interesting because the two people walk into the room and the idea is not there, it’s not always brought there by one individual. Usually the idea materialises in the room or in the discussion group and the one thing that I really fear is coming in with my own idea that’s wrong and pushing it too hard. When you’re mentoring, it’s important not to be too forceful about pushing your idea and to try to let people know that they should voice their ideas. Sometimes that for me has been the most difficult part, is getting the people in the lab to say what their ideas are. A lot of times their idea’s wrong and my idea’s wrong and the other person’s idea’s wrong, but you put them all together and all of a sudden there’s a new idea.Andrew Z. Fire: That might also be wrong, but it’s still a lot of fun.Craig Mello: At least maybe there’s an experiment you can do that will distinguish. That’s the fun, that is really a fun part of the process and one thing I fear and I’ve heard that once you have this kind of a prize, that your students are too respectful and they won’t question. You say something and they’ll actually believe it.Andrew Z. Fire: That’s scary.Craig Mello: Science is all about questioning things and if you don’t question it …Andrew Z. Fire: Doubt it.Craig Mello: … doubt it, yes. I think we need to reinforce that message to our students after we come back from this brief period of celebration. We need to go back and make sure that we get right back to the questioning. |
| Q12 | That neatly brings me onto the question of your youth, you’re both very young and this is going to bring considerably greater notoriety. How do you think it’s going to affect your future research paths and that question of distance from your students is certainly one aspect? |
|  | Craig Mello: I hope not too much in that respect. I feel that it’s like having a new job, an additional job, in addition to running the lab and trying to be a good adviser and leader for your group, to have this new responsibility to be a spokesperson for the science and to try to do the right thing in terms of promoting and the understanding of the science which … We just had a very interesting discussion in parliament in that I actually felt a little bit guilty during the discussion because scientists really haven’t done a very good job of educating the public about science and that’s partly because it’s nobody’s job. They don’t really make that your job, somehow it’s supposed to be part of your job but that’s not the part that you get paid for, you get paid for doing the research and publishing the papers, which are read by your peers not by your neighbours. I think it’s an important responsibility I feel, but I hope it doesn’t distract too much from the science. I’m very excited all the time by what’s going on in the lab, want to get back to it.Andrew Z. Fire: I really like my day-to-day life of teaching and research and family and that’s a pretty full life for both of us and so adding, as Craig says, an extra job to that, I’m not quite sure how it’s going to work but somehow we’ll probably manage. |
| Q15 | When you talk about educating people about science, is there a particular target group you think of, is there one group of people who you think need this more than any other? |
|  | Craig Mello: No, I think it’s a lifelong process to be educating yourself constantly because science is a fluid thing and it’s not just science, it’s all realms of knowledge really. There’re all kinds of interesting things to learn in this world and I think we need to make our children into lifelong learners somehow, don’t lose them along the way, to the interesting world that you can expose them to and it’s very difficult. There’s no easy solution, I think, to this question of how best to educate and that’s what we also were talking about earlier today. I’d be interested to know how the Swedish people have solved that problem. It’s interesting to learn about different cultures and how they approach learning, but it’s very important.Andrew Z. Fire: Yes indeed. |
| Q5 | What turned you on to being a lifelong learner? What was it that happened to you that made you? Was there a single event that made you want to learn? |
|  | Andrew Z. Fire: I hate to say it was a single event because it’s a lifelong thing. I think one thing, in terms of lifelong learning is that it’s surprising how little you need to change a description of a piece of science between talking to the Nobel Assembly of the Karolinska Institutet, which is one of the highest audiences in science and people that are extremely knowledgeable about everything you’re talking about, down to kindergarteners. If you just change some of the language, you can use almost the same discussion for both groups and have a significant fraction of them, probably, at least come away with some understanding of what you talked about, probably the same fraction in each case.Craig Mello: I think science as a process though, it naturally tends to make you want to be a lifelong learner. If you’re going to enter into an enterprise where there really are no right answers, that’s what science is all about, it’s testing ideas, it’s trying to disprove an idea. Once you have an idea, the first thing you do is try to test it to see if it’s right and the most fun thing is when it’s wrong and then you have to come up with a new idea, so it’s a constant process. If you ever thought that you would understand everything, certainly that would be very boring to be part of a science that is now a complete understanding of a process. Fortunately, I don’t think that’s going to be our problem for many, many, many years to come, so I think it’s a natural process once you’ve decided that you would like to be involved in science.The nice thing is, every day it’s an exploration, it’s a new discovery out there waiting to be made and just the process itself I think lends itself very well to the basic human nature of liking to explore and to understand and to see new things. That’s what science is all about, so I think we can do a lot better in terms of recruiting people into the sciences if we could somehow project that at an earlier level in education. Right now I think too much of our education is focussed on memorising facts and not enough on the exploratory process of science. What a real scientist does is so different from what you’re exposed to when you take science in high school or grade school. I feel that for me and my own understanding of what it would be like to be a scientist, I was fortunate to have a father who was a palaeontologist, so I was aware of science going on at this Smithsonian where he worked, the museum where he worked and going on field trips with him. Getting to see that real scientists don’t just read books, they actually do things, is so important. |
| Q3 | I’m interested in this idea of being able to explain the work to any audience. I think [Ernest Rutherford](https://www.nobelprize.org/prizes/chemistry/1908/rutherford/facts/) said that you shouldn’t be doing science if you couldn’t explain it to your tobacconist, which is a kind of antiquated concept nowadays perhaps, especially in the US. Your field doesn’t lend itself immediately to simple explanations, there’s a lot of jargon associated with it, so the fact that you feel that you can, with few alterations, explain it simply is a very encouraging message. |
|  | Andrew Z. Fire: I think it takes a little bit of time. One of the things that’s challenging is to explain things in a very short time. You need to be able to go back through some of what’s been learned, often with a group that’s not as aware of the history and go through that. I think with that it becomes more straightforward. What I think is a challenge and it’s often impossible is just when people say, can you tell us in a few words. The one that struck me in the few days after the announcement of the award was thinking about the scientists or the mathematicians who solved the Poincaré conjecture, which is a very important conjecture in mathematics and thinking about someone walking up to them and say, Well, in a few words can you explain to the general audience both the conjecture and the proof of it? Of course that certainly is doable in a little bit of time but it’s difficult in a short period and when I thought about that, I was a little bit more relaxed about my somewhat ineptitude in one occasion when I’m asked to explain things in a few words, at being able to do that totally clearly to everybody, it can be a challenge.Craig Mello: I think one of the real interesting things about talking to people about your work is, you’re right there’s a lot of jargon and a lot of times that’s just very distracting but I find that sometimes children even ask the better questions because they just don’t know what a word means for example and they say, Well, what is DNA? or What is RNA? What is a protein? You could then spend hours and hours discussing what it is and as long as the child or the adult continues to ask questions, you’ll find this wonderful conversation that can go on for quite a while. I agree with Andy, it just takes time and it takes the audience also being curious enough and not afraid of asking a question. I think most scientists are happy to spend some time discussing their work and quite often they wonder why no-one asks a question. They didn’t understand something very early in the talk and so they stopped listening and it’s important to raise your hand and say, But can you explain this one thing and quite often that’s a really good question. The hard part is losing people, and it’s a two-way thing. Conversations with a child can sometimes be even easier because you know how to track the conversation to keep them engaged. |
| Q23 | Terrifying, because they reveal the fact that one can’t explain it oneself but yes. One of the things we did this year for the first time was to invite some of the public to ask questions to you via the Internet and I’d like to, if I may, just pose a couple of those questions. First, a rather specific one from Kerry Austin in Texas who says, What application in genetics will offer the most effect use of RNA interference? |
|  | Andrew Z. Fire: I think there are probably lots. In the field of genetics there are probably many different applications, again combined with the tools of both classical data genetics and the sort of more modern set of technologies that don’t necessarily involve RNA gene disruption. I think altogether they give us a really good toolbox. Not something that in 20 years we’re going to say, You’re doing that? You know these were the crude tools we had in 2006 to do experiments and I think that they’ll also improve over time, so I’m not sure they’ll be one best application in research genetics, I think there’ll be many applications but they’ll be combined with all the other tools and we’ll always be wanting better tools.Craig Mello: Yes, certainly it is speeding, I think the use of vertebrate cells as genetic tools for studying the function of genes and there’s some really exciting technologies that have been developed that allow it to be applied fairly broadly in studying genes in cells in culture. I think that that’s helping a lot, but by itself it’s just the first step, so I think it’s being used primarily as an inexpensive but fairly rapid way of doing genetics and really needs to be backed up ultimately with other kinds of genetic tools such as real knockout cells and perhaps even animals to test these ideas before you really understand what’s happening. You have multiple lines of data or investigation that support your work, but RNA interference is an important tool I think for doing that first round of genetics where there are 20,000 genes and you want to know which ones are important in tumour or in some other disease. You have to sort through a lot and it’s a quick way of doing that, maybe a new way that would have been impossible earlier, so I think it’s providing an important function there. |
| Q23 | There was a time when people were talking a lot about the need for standards for such experiments. Is that time passed, are they now widely accepted for the publication of RNA interference? |
|  | Andrew Z. Fire: I think there’s still a need for standards. There are publications that have a very high standard for proving something and those cases you really are quite sure that what they’re reporting is indeed due to a decrease in a specific gene. There are some cases where, because of the system, in a few cases where it’s quite difficult to do the kinds of controls you want to do and for other reasons too, you come away not being as sure of the results. You’re certainly sure that the observations are correct, but whether the results are indeed due to a specific gene. I think there’s an interesting give and take amongst people writing and doing work in the field. |
| ID | 0545 |
| Biographical | I recall a sunny September morning in Virginia. I remember the sound of the school bus taking away the older kids, including my two siblings Jean and Frank. My mother, no doubt, was busy with my baby brother Roger. I was playing in the creek as I often did, turning over stones, looking for small animals. I remember a mourning dove cooing on the telephone wire, and the way the sunlight felt on my red sweatshirt and my rolled up hand-me-down blue jeans. I remember a sense of contentment with being alive, a feeling that infuses many of my early memories in a general, fuzzy, unfocused way. However, this memory is different. It was etched with stunning clarity in my mind by adrenalin and other sharper emotions.“I’m still turning over stones, hoping to find something new.That morning, a box turtle decided to choose this peaceful moment to make its way across the street adjacent to the field where I was playing. My attention was drawn to the road by the sound of an oncoming car, and I remember my excitement with seeing the turtle changing to shock as I watched the car swerve with clear intention toward the turtle. I remember a smirking teenage boy driving off, leaving the turtle, his shell broken, still struggling to move to the edge of the road. The turtle died before my eyes, etching this scene deeply into my mind. Even though this might seem a sad memory, the fact is that I’m grateful in a sense. That morning of my youth seems timeless now. I can see in my heart that the child playing in the creek is me, and that I haven’t changed much really in the intervening years. I’m still turning over stones, hoping to find something new. I’m still struggling to understand what drives us humans to cruelty and hoping that knowledge of our place in the world can help us to achieve a higher purpose.I was born in New Haven, Connecticut on October 18th 1960, the third child of a paleontologist father and artist mother (James and Sally Mello). In 1962 my father completed his doctorate in paleontology at Yale University, and my family moved to Falls Church in northern Virginia so that he could take a position with the US Geological Survey (USGS) in Washington, DC. My parents met while attending Brown University and were the first children in their respective families to attend college. My grandparents on both sides withdrew from school as teenagers to work for their families. My paternal grandfather, Frank Mello, was of Azorean descent although he was born in Warren, Rhode Island. He was an outstanding athlete nicknamed “Bullet” Mello for his speed. He played semi-pro baseball and football. He worked a variety of jobs including delivering grain for many years and operating trucks for the town. My grandmother, Elena (Primiano) Mello, was of Italian descent, but was also born in Warren, Rhode Island, she worked in local textile factories. They both worked for their families for close to ten years before they were able to marry and start their own household at the age of 24. On my mother’s side I have English and Scottish roots dating to colonial times and including a distant link to Lyman Hall who signed the declaration of independence. My maternal grandfather, William Cameron, ran a very successful plumbing business in Middletown, CT. My grandmother, Ida (Hall) Cameron, was a home- maker. I’m proud of my melting pot origins, and of the accomplishments of my grandparents. They worked hard, and sacrificed so that their children could go to college. They were wonderful, creative, thoughtful and extremely loving people who gave me a refreshing perspective on what’s important in life.After a brief stay in Falls Church, we moved to Fairfax, VA, when my father switched from the USGS to a position as assistant director at the Smithsonian Museum of Natural History. Among my fondest early memories are field trips with my father and the whole family to Colorado and Wyoming and more frequent trips to the Blue Ridge mountains in Virginia. I remember searching for fossils, hiking, exploring, and wonderful family discussions around the campfire.My family had a very strong tradition of discussions around the dinner table. This experience was extremely important to me. I learned to argue, to listen, and to admit it (sometimes grudgingly) when I was wrong about something. These were often lively discussions, and my parents did a great job of allowing each of us to be heard. At a time when I was not performing so well in school, these daily discussions helped to build my confidence and self esteem. I struggled during the first few years of grade school. I started first grade at the age of 5 in a local private school because I was too young to enter first grade in the public system. I don’t know if I was a slow learner, or just not interested, but I did not do well in school until the 7th grade. In second grade, I remember faking that I could read and the embarrassment of being called on in class. I much preferred playing outdoors, in the woods and creeks, to time spent in the classroom. Meanwhile, my older siblings were model students, raising the teacher’s expectations for me. If not for the family discussions, where I was respected and could hold my own in arguments, I might have been discouraged with my academic prospects.During these early years, I remember having no doubt that I would be a scientist when I grew up. I was amazed that so few adults (including my teachers) understood basic concepts such as deep (geologic) time, the vastness of the universe, and the common evolutionary origins of life. In first grade, the private school I attended had a Bible session each day, and I remember being shocked that the teacher presented the story of Noah and his ark as fact. Similarly, I was exposed to religious instruction in Sunday school. My father had agreed to raise us as Catholics. My mother was a Methodist by birth but did not practice her religion and did not attend Catholic services with the family. I remember learning the argument of intelligent design in Sunday school, as a counterargument to evolution. Given my own exposure to my dad’s museum, and our family discussions about evolution and the history of the earth, these exposures to religious dogma actually had the effect of intensifying my interest in science as a way of knowing about the world.QuoteThe world is a far more remarkable place than we can imagine. Its mysteries define the human condition; to exist without knowing why.By the time I was in middle school, I had decided to reject religious dogma altogether. The ‘absolute knowledge’ offered, was in my view, inadequate to explain the world around me. Furthermore, it seemed wrong to claim knowledge based on ones culture or upbringing. I saw the leap of faith involved in religion as smothering dialogue, closing the door on non-believers and walling them out of one’s society. In contrast, the scientific method with its focus on asking questions and admitting no absolutes, was and continues to be refreshing to me. Science is grounded on, and values, dialogue. It is a human enterprise that breaks down walls and challenges its practitioners to admit ignorance and to question all ideas. However, we must all arrive at and defend our moral choices of right and wrong. Science can’t touch these issues and shouldn’t try. I believe that there is no more spiritual and worthwhile undertaking than that of trying to understand the world around us, and our place in it. The world is a far more remarkable place than we can imagine. Its mysteries define the human condition; to exist without knowing why. My first exposure to academic science came in 7th grade, and during that year I can remember for the first time applying myself to my studies. I became an avid reader of science fiction, an amateur astronomer, and a serious student. I remember organizing my desk at home and doing homework, with music blasting, for at least a couple hours every night. I attended Fairfax High School, where I took all of the science courses offered except advanced physics. My earth science, chemistry and biology teachers were excellent. My biology teacher, Randy Scott, was also my wrestling, football and track coach. He was a wonderful man, who had a large role in fostering my interest in biology. I reconnected with him and was able to thank him after the news of October, but tragically, he has since lost his battle with cancer.In 1978, I learned about molecular biology from a newspaper article in the Washington Post. The article described the cloning of the human insulin gene in bacteria, and described how the bacterial cells were able to read the human genetic code and produce functional human insulin. I found this concept incredible and extremely exciting. Incredible because the bacterial cells were able to speak the same language as the human cells, reading out the genetic code to make functional, life-giving, human protein for diabetic patients. Prior to that time, diabetics used animal insulin. I found this extremely exciting because I could see the potential for understanding disease at the genetic level and for treating it with molecular medicines, like insulin, and with gene therapy.At Brown University, I pursued biochemistry and molecular biology as my major and had inspiring teachers, including Frank Rothman, Ken Miller, Susan Gerbi and Nelson Fausto. Brown provided a wonderful environment for learning, and had the added benefit of being close to my grandparents’ home in Warren, RI, and to my small sailboat on the Warren River, a tributary to the upper Narragansett Bay. Sailing continues to be an important part of my life. It gives me a sense of place that settles and refreshes my mind. I sail in a wide range of conditions, for hours and hours (if possible). I don’t prefer to race, but rather to explore. I gradually trained my parents and grandparents to accept the fact that if the wind died, then I might not get back until long after dark. Eventually, they even agreed to my taking camping gear and doing overnight trips ranging along the coast from Martha’s Vineyard to half way up Long Island Sound.After Brown, I went to Colorado for graduate school, where I enjoyed the mountains again and a really fantastic and inspiring course in molecular, cellular and developmental biology. The course consisted of a small group of 15 or so students with outstanding instructors, including Drs. Dick McIntosh, Mike Yarus, Larry Gold, Bill Wood and others. At Boulder, I was introduced to *C. elegans* in the laboratory of Dr. David Hirsh. David’s lab was fantastic – filled with people who would prove to be really important in my future training. These included Dan Stinchcomb, who introduced me to the practice of molecular biology; Mike Krause, Jim Kramer, and Ken Kemphues, with whom I collaborated; and Jim Priess with whom I did my postdoctoral work. When I joined David’s lab in 1982, no one had succeeded in introducing DNA back into *C. elegans* (a method referred to as “DNA transformation”). Work in yeast had identified functional DNA elements that direct the replication and partitioning of chromosomes (replication origins and centromeres, respectively). Working with Dan Stinchcomb, my project was to identify such elements from the worm, with the goals of 1) understanding these essential functional chromosomal elements, and 2) of using them to produce stable artificial chromosomes for worm molecular genetics. During my first year in Boulder, David Hirsh decided to take a position in industry, and so I chose to move to Harvard University where I could continue my research with Dan Stinchcomb, who was starting up an independent lab there.I thoroughly enjoyed Harvard! Dan set up his lab at the Biolabs in Cambridge next to [Victor Ambros](https://www.nobelprize.org/prizes/medicine/2024/ambros/facts/), another brand new, junior faculty member at Harward working on *C. elegans*. Dan and Victor integrated their labs to make a single “wormlab”, and both served as advisors to me during my studies. I loved my project and worked long hours in the lab, never going home until I had a gel running or something incubating, so as to use the overnight hours. I took advantage of opportunities to attend lectures on a wide range of subjects. I obtained permission to use the large refracting telescope located atop the Science center, which was, surprisingly, available for individual use. I got to meet and teach with Stephen J. Gould, who’s essays on natural history and the philosophy of science had inspired me over the years. Gould’s, “*The Freezing of Noah*,” is one of my favorites as it captures the essence of good science; admitting when your theory is wrong and developing a new theory.I learned an important lesson in graduate school; that it’s not enough to be persistent and to work hard, it’s also important to attack the question you wish to address from every conceivable angle. By focusing on identifying worm centromere activities using yeast as a model system, I ended up learning about the yeast centromere, not the worm centromere. While this project was fulfilling and interesting to me, it was flawed. To study the yeast centromere, I should have been working with the yeast sequences directly. To study the worm centromere, I should have been injecting DNA into the worm. Only after I began to experiment directly with the worm did my project really take off.Technology is what drives science, and yet, developing new technology is often a thankless task. Getting something to work that has never been done before can be exceedingly frustrating because you may never know how close you were to success, and failures quite often teach you nothing. Partly because of this, those working on technology development often tend to band together and share ideas more than would otherwise be common among scientists. This was certainly the case for Andrew Fire and me. We were both working on developing techniques for DNA transformation in worms. Andy had some early success and developed a number of clever methods. I followed up with some improvements. And together we made DNA transformation a routine procedure for the worm. In the course of these studies, we became frequent correspondents, spending hours on the phone (before email was invented). We developed the mutual trust and respect that ultimately led to our collaboration on RNAi.After graduating from Harvard, I joined the lab of Jim Priess at the Fred Hutchinson Cancer Research Center in Seattle Washington. Jim is one of those rare scientists who has “a feeling for the organism” as E.F. Keller put it when describing [Barbara McClintock](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1983/index.html). Jim put me in touch with my own feelings for the worm. Through Jim, I was able to learn genetics, without which our later work on RNAi would have remained entirely descriptive. In Jim’s lab, we identified genes that act as regulators of early development in *C. elegans*. It turns out that some of these genes are connected to RNAi-related mechanisms in ways that we are still trying to understand.In Seattle, my daughter Melissa was born in 1992. I wish she could remember those first two years of her life in Seattle. We hiked and biked together regularly and had a wonderful time. However, her mother and I struggled to find enough time together as a family. Melissa’s mother, Margaret Hunter, worked mornings and weekends as a chef at a Café in Seattle. Because my schedule often demanded late nights and weekends, we handed Melissa off from one to the other and rarely had enough time to be together as a family. Shortly after we moved to Massachusetts in 1994, we separated and divorced. Fortunately, we remain respectful and friendly to this day. I focused on my work and continued to have Melissa with me half of each week.Shortly before I started my lab in 1994, I learned from Ken Kemphues and his student Sue Guo about an “antisense” RNAinjection technique that surprisingly well in *C. elegans* silenced target genes. I began using this method to study the genes we had identified during my genetic studies with Jim Priess. The genome-sequencing project for *C. elegans* had begun in earnest and had revealed dozens of genes in the sequence data base that were similar in DNA sequence to those that I had discovered in Jim’s lab. These related genes (or homologs, as we call them) could have important developmental functions, and so I began using the RNA injection method described by Guo and Kemphues to silence them in order to identify those functions.This was truly amazing and prompted further studies …At that time, RNA injection was performed according to the same procedure that Andy and I had developed for DNA injection. A fine, sharp, glass needle was inserted with care through the cuticle of the worm and positioned inside the large shared cytoplasm of a gonad that contains hundreds of germline nuclei. After positioning the needle and injecting, the procedure was then carried out a second time on the other gonad arm, two injections per worm. The power of this gene-silencing approach accelerated our studies and we began to make rapid progress in understanding the developmental mechanisms that specify cell fate in the early embryo. However, we also became interested in the silencing phenomenon itself. The first observation that truly galvanized my interest occurred when, having injected RNA targeting *apx-1*, a gene essential for embryogenesis, I observed by chance that some embryos hatched and matured to adulthood only to produce 100% *apx-1* dead embryos. The silencing phenomenon had skipped a generation and had been passed on *via* the germline to the next generation! This was truly amazing and prompted further studies that demonstrated the transmission of silencing for multiple generations *via* both the sperm and the egg.The first graduate student to work on RNAi in my lab, Sam Driver, discovered, in part by accident while learning to inject, that the RNA need not be delivered directly to the germline. Injection anywhere in the body was sufficient to induce interference that spread into the germline and was transmitted to progeny. These findings, along with the inheritance properties, and the lack of strand specificity (first noted by Guo and Kemphues), prompted us to recognize the silencing phenomenon as an active response in the organism to the RNA. To distinguish this mechanism from the earlier “antisense” methodology, we decided to give it the simple name RNAi (for RNA interference). We envisioned a mechanism where either strand could template the production of the other strand and could somehow build up silencing RNA levels. The specificity of the silencing indicated that ultimately, after amplification, the antisense strand must unwind from its complement to find its target RNA and induce silencing.Throughout this period, Andy and I continued to correspond and collaborate. It was Andy’s suggestion that dsRNA contaminating our preparations could be the actual trigger molecule underlying RNAi. At the time, I was still thinking of dsRNA as an amplification intermediate, rather than trigger. It was not until after Andy sent me purified double stranded RNA to test in my own hands that I became a believer in this molecule as a potent trigger for gene silencing. We now know that dsRNA is both a trigger and intermediate in RNAi. The concept of dsRNA as a trigger for sequence-specific gene silencing only makes sense if one recognizes that the organism is actively responding by unwinding the RNA strands both for amplification and to generate single strands capable of base pairing with targets. This concept of an active response in the animal prompted Hiroaki Tabara in my lab to undertake his exciting genetic studies that identified cellular gene products that mediate silencing. As discussed in my [lecture](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2006/mello-lecture.html), dsRNA is not the only trigger for this silencing mechanism. However, importantly, dsRNA turned out to be a highly conserved trigger that rapidly led to the application of RNAi in diverse species including humans.1998 was a truly outstanding year. In January of that year, Andy and I published our paper on RNAi. In August, I married Edit Kiss and became the stepfather of two wonderful kids, David and Sarah Apotheker. In the year 2000 our daughter Victoria was born. In an unfortunate twist of fate, Victoria developed type-one diabetes in the fall of 2001. Suddenly, I had to learn how to inject into a human, my own daughter, for the first time. Ironically, human insulin, the same bacterially synthesized molecule that inspired me to pursue molecular biology, is now giving Victoria her very life. This experience has given me a new perspective on the importance of medical research. Edit, who is a wonderful nurse, is now taking care of Victoria, and serving as a diabetes counselor for newly diagnosed families.With RNAi and the completion of the genome sequences for humans and numerous other organisms, we now have unprecedented opportunities to develop new, life saving therapies and to advance the basic understanding of our biology. We humans have a potentially very bright future. The biological mechanisms at work inside our cells are truly ancient and remarkably stable, more stable even than the positions of continents and oceans on the face of the Earth. However, in my view, our thriving global economy has engendered serious problems. Climate change and other forces beyond our control could easily disrupt our economies causing widespread human suffering at unprecedented levels. We are fishing out oceans, depleting our topsoils, and exhausting our sources of fossil fuel and fresh water. Scientists and policy makers must begin to work together to foster the development of technologies that are sustainable and resilient. As humans, we must work with common purpose around the world to prepare for the challenges and opportunities ahead. I hope that I can further that cause. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0545=CM [Unidentified] – Hello?  [Adam Smith] – Hello, may I speak to Professor Mello please?  [Unidentified] – Hold on for one second.  [AS] – Thank you.  [Craig Mello] – Hello.  [AS] – Hello, Professor Mello, my name is Adam Smith and I’m calling from the official website of the Nobel Foundation.  [CM] – Yes, hi.  [AS] – Well first of all many, many congratulations on being awarded the prize.  [CM] – Thank you so much.  [AS] – Where were you when you heard the news?  [CM] – I was checking my daughter’s blood sugar. She has type 1 diabetes so I was actually up, one of the few, I guess, in the North Americas who was awake.  [AS] – Yes, I imagine so.  [CM] – We check her frequently and I just happened to be up, checking her blood sugar. And she had a good sugar actually, 95, which is normal.  [AS] – That’s good news, yes.  [CM] – I was on my way back to bed and the phone rang.  [AS] – So two good pieces of news at once! I imagine you were thinking of other things but what was your first thought on being told?  [CM] – Well, you know, gee, that’s a really hard question! You know first it’s disbelief, and I don’t think it sinks in quickly. I felt I was sort of too young to get it this soon and thought, if it happened, it would be a few years from now. So I wasn’t ready at all.  [AS] – It has been quite a short gap, a relatively short gap, between the discovery and the prize.  [CM] – Yes, it has. Is it unusually short for Physiology and Medicine?  [AS] – I don’t know about unusually, but certainly than some years recently, yes.  [CM] – But of course I was, you know, now it’s starting to sink in, I don’t think I still really appreciate how this might change everything, in terms of … we’ll see later today how it goes! But no, I was actually … now what was your question?  [AS] – It was just what your first thought was, but …  [CM] – There were lots of thoughts going through my head and it was a big surprise.  [AS] – Indeed. The prize has been awarded specifically for the phenomenon of gene silencing by RNA interference that you and Andrew Fire published. Was there a single Eureka moment you can recall when you realized what was going on?  [CM] – There really wasn’t for me until we got to understanding of the gene, the first gene we cloned, and for me that was very much like a Eureka moment because the phenomenology was exciting and interesting – the fact that this silencing was occurring and the fact that it could be transmitted from one generation to the next and spread from tissue to tissue – all of those things were amazing and exciting and of course inspired us to work hard at understanding the mechanism. But not until we cloned the first gene, which we had called *rde1* for RNAi decision gene number one, did we realize that the gene had homologues in essentially every organism including humans and plants and even fungi. And that, to me, was extremely exciting, especially because it was a novel gene and yet highly conserved, with extensive sequence conservations.  [AS] – Yes, yet more evidence that RNA cannot possibly be viewed as just the passive messenger of DNA.  [CM] – Exactly. And I think there’s more coming, I think this is just the beginning. I’m very excited now in thinking in terms of the role of this type of silencing in evolutionary change, rather than simply as something involved in regulating gene expression. Actually I think it has an impact, or a potential impact, on evolution on a broader scale as a source of inheritance and variation. And that’s something that I’m thinking about writing right now, a paper, essentially a hypothesis, that this may play a very important role in evolutionary change.  [AS] – Right. So your interest really remains very much on the basic science side.  [CM] – Yes. It has and it still is, although there are many applications for RNAi, to me there’s still a lot we don’t understand about the mechanism. And it’s then just really, really exciting how many different fields, seemingly unrelated, have just merged together with the understanding of the mechanism. As the understanding grows we just seem to be bringing together these very distant looking – sort of unrelated looking stories just keep coming together and unfolding in beautiful ways. So, there have been so many contributions from people all around the world, scientists who have been working on phenomena that we didn’t know were related to the one that we discovered. And all of their work has really helped to make this something that has been so widely recognized as a fundamental discovery, because lots of work was already being done. So I think that’s one reason it happened so quickly. It just was the last, but a very important piece in a puzzle that quickly fell together.  [AS] – Yes, because there really has been an explosion of interest in it. But what a lovely, unexpected consequence that it brought all these fields together.  [CM] – It is wonderful, and they’re great people and I just really loved meeting all the other scientists working on RNAi. They’re just a tremendous group of people, and I think the Nobel Committee should, at some point in the future, recognize the small RNA discovery itself, which is a different story. I don’t know if that’s something that could be taken up by Chemistry or Physiology and Medicine, but small RNAs, microRNAs (I’m sure you’ve heard of the little RNAs that are developmentally regulating gene expression) are one of the major discoveries that was made shortly after ours and was very exciting.  [AS] – That opens a whole new chapter. And we talk at greater length with the Laureates when they visit Stockholm in December, so hopefully that’s something we’ll have a chance to talk about then. One, just last question; any ideas how you’re intending to celebrate today?  [CM] – Uh, I haven’t gotten that far, but I’ll call my family and we’ll take it from there.  [AS] – Well, once again, many, many congratulations and thank you very much indeed for talking to us.  [CM] – Thank you. |
| Interview |  |
| Q6 | Andrew Fire and Craig Mello, welcome to Stockholm. When we spoke a couple of months ago, just after you’d heard the news that you’d been awarded the Nobel Prize, you both sounded quite surprised that it had come as quickly as it has done. Has that surprise subsided at all? |
|  | Andrew Z. Fire: I’m still surprised by the whole thing. It’s obviously a really major honour to be honoured by one’s colleagues in such a way but at the same time, there are a lot of other scientific discoveries and other contributions to the field we’re in that are probably no less deserving and so it’s an interesting situation to be in.Craig Mello: I agree, every day I’m still not sure it’s really me that’s the recipient of this recognition. I really feel it’s more the prize is awarded for the science and in that respect we’re representing many researchers and it’s a great honour to be here to be spokespeople for the discovery and to bring some attention to the science and the fun of science. |
| Q6 | How have the last couple of months been, have they been whirlwinds? |
|  | Craig Mello: Very much so.Andrew Z. Fire: Yes, we each have our scientific day to day lives and intertwined with that has been a lot of interesting other things and also planning a trip to Sweden, so the combination of things has made for a busy couple of months for both of us, I think. |
| Q23 | I can imagine. The prize was awarded for a very concrete discovery, a single event if you like. Is there a moment you can recall when the penny dropped that RNA interference was what you were looking at and you understood how it worked? |
| Q26 | Craig Mello: Certainly not, because we still don’t understand how it works. I think it’s been very exciting and fun to be part of this field because of all of the interesting interrelationships between the RNA interference phenomenology and then the developmental mechanisms that are related to it. I think we have so much still to learn about the basic mechanism of gene regulation, even going beyond RNAi as playing a role in that process, but honestly I feel that it’s been exciting at many steps along the way, but I can’t think of a single point where we felt we understood the mechanism really. I still feel we don’t understand the mechanism fully, we have a much better idea about the underlying mechanism now but we have so much more to learn that it’s just still a lot of fun, it’s a very exciting field. |
|  | Andrew Z. Fire: That’s certainly a major part of it. The other major part of it was that the groundwork that had already been laid in the puzzle, primarily by other people. A major part of it was the people that worked with us that all had put very significant contributions to it. It was really a matter of being in the right place at the right time, particularly the work that had been done in plant systems and in fungal systems and some of the work that was done elsewhere in the worm system by /- – -/ and other people really set it up so that we could just inject RNA that we would make in the lab and then get a result in a couple of days or a day. That happened and that made a very sort of efficient system to begin to test hypotheses.Craig Mello: I think the understanding that there was an organismal response to the injected material was part of what was very exciting to me, even though I didn’t understand certainly what was happening. The observation that the silencing signal could spread from cell to cell and even be transmitted in the germ line were extremely exciting and yet we didn’t understand how the silencing was triggered. In fact, we were not focused on double stranded RNA, in my case we were thinking more in terms of double stranded RNA potentially as a replication intermediate or something that was produced during the amplification process that was necessary for the inheritance to occur. We thought more of double stranded RNA therefore as an intermediate in the silencing and Andy really deserves credit for thinking perhaps the double stranded RNA is an important trigger as well because in some organisms like ourselves, there’s clearly a double stranded RNA response that had been studied previously that’s involved in anti-viral mechanism.We were thinking more of it as an intermediate, which it really is as well, it’s interesting, double stranded RNA is a trigger but it’s not the only trigger for this type of silencing. I think that also was an element that added to the confusion in the literature on the earlier work done in plants, because it wasn’t clear when a virus or a transgene was introduced into an organism, what the trigger was. I think the reason some of that confusion exists is because there are more than one trigger for this. It’s an interesting twist really that we still don’t understand all the different ways that you can trigger the silencing but double stranded RNA is in fact an intermediate in many of these related silencing pathways, so that’s one of the elements we still are very much in need of understanding. |
| Q17 | You emphasised the basic science aspect of all this and that there’s a lot still to be understood. I suppose the world has really embraced RNAi as a technology and an application. Do you find that worrying that people leap on it in its partially understood form and want to use it? |
|  | Craig Mello: I don’t find it a worry, I think it’s natural for people to want to use, especially when you have a sick family member, this sincere desire for some sort of a treatment or cure and I think it’s important for the scientist to make sure that that doesn’t get blown out of proportion, that that hope doesn’t get overstated. I can totally understand the excitement. I think that if anything, we really need to focus on, it really is an exciting discovery and there are many applications that it can be put to and I think we need to get that message out. I don’t think there’s anything to fear except perhaps going too far and being too hyperbolic in promoting it, but I do think we need to get the message out because it’s very important as a research tool, certainly and potentially as a therapeutic, so I think it’s important.Andrew Z. Fire: It’s almost a humorous thing, but one of the things I found is that when I’ve gone to lecture in classical genetics which is many of the tools of which were pre-existed us by several decades and 100 years or whatever. One of the things I find is the students will suggest, why not do everything by RNAi? There’s still very much room for classical genetics, it’s really the basis for a lot of what we do and what we think about and other techniques of genetics that also have come up in the last few years. Targeted gene disruption, which is extremely valuable technology and useful and a number of other things. I think that students realise that when they get into the depths of research problems, that they really have to understand not only what’s been developed in the last few years but also things that were developed 100 years ago. |
| Q10 | Do you think the funding climate is as accepting of basic research as it used to be? |
|  | Craig Mello: I think that the funding climate is tight now, in part because of the tremendous wealth of information that we have about the human genome for example, the sequence of every gene. With that as background and the information technology that we have for searching that database I think it’s harder to get funding to do the kind of work that Andy and I did and quite often it’s a priority that has to be made whether to fund this or to fund that and both really should merit funding, but there just isn’t enough money. In a way I think we’re being strapped in part through the success of the scientific enterprise as a whole, creating more good science that can be done and I think that really can be looked at as an opportunity in the message that we have to get out to the people who make policy in terms of the politics and the funding decisions, that there is a great opportunity with the advances that have been made in medical research.The genome sequence and the information technology that gene profiling technology for looking at the expression of genes in cells and things like RNA interference that allow you to shut off genes to study their function. These provide opportunities that make it actually harder to get basic science funding because now you can do a lot of these experiments in human cells and that’s not always good. The fact is, if you’re taking away the money from the very basic science, that could lead to new technologies, new discoveries that would be very hard to get in a vertebrate cell system. I think, as in the pre-review process, we’ve seen this, I know that I have, where you have to make a decision and there are just, several grants that should be funded and they’re just not going to make it, no matter what, because there are all these others that need to be funded. These priorities just becomes an impossible situation and to fix that we just need to get the message to the public to support science more, so that we can continue to get the funding we need. |
| Q10 | Does your funding come mainly from basic research funding, from NIH or is there also an industrial component to what you do? |
|  | Andrew Z. Fire: Our funding comes from non-profit sources, both completely are. My lab is funded completely by NIH and …Craig Mello: I have funding also from the NIH and Howard Hughes Medical Institute. The work that was done really was funded privately, some private grants other than those mentioned as well, so philanthropic support for disease-oriented grants like the ACS, the March of Dimes funded some of my research and also the Pew Charitable Trust, so to mention I think all of them.Andrew Z. Fire: Those are all charitable organisations and they’re public organisations but they’re all toward the goal of improving healthcare in a general way. |
| Q26 | When you bring new people to work on the problem into the lab, I was interested to know what you look for in those students coming in? |
|  | Andrew Z. Fire: I learnt a lesson from a mentor of mine, a gentleman named Donald Brown. If someone walked up to the door and said, I want to learn, that was a major feature, even if the person might not come in with the most spectacular of previous mentorship or whatever, that was a really major thing. I think that’s something that one looks for, someone that really wants to learn.Craig Mello: It’s very hard I think, sometimes students who are very bright are not motivated enough. I think the major ingredient is motivation and a desire to follow through with an experiment. Those are qualities frankly that you cannot glean in an interview, so I think some of the best scientists have struggled sometimes getting into the lab because the interview process might weed them out, or they may not have the patience for it, in order to go through it. But I find, once you work with someone you really get to know what they’re like, so most laboratories have what we call a rotation process, so students will get an opportunity to work with you in the laboratory as they decide on which group they want to join during graduate work. I think that’s been for me the most important aspect, is having time to spend with the student in the laboratory, find out what they’re like.I suppose that recommendation must become a very important part, if you’re looking for somebody’s long-term commitment to problems, you need to know that they’ve done that before.Craig Mello: It can be but they’re so unreliable.Andrew Z. Fire: Right, it’s hard because the recommendation letters often say as much about the person writing the letter, so you have to factor two different components into the equation. It’s sometimes too difficult to parse out which is which.Craig Mello: Many letters from Asian laboratory heads are incredibly brief and it’s hard to read into the line what they really mean. I think it’s a stylistic choice that they make not to overstate anything and then sometimes in the US you get these letters that go on and on and on and you don’t know how much is genuine either, so I think there’s no perfect way, I really feel that it’s hard to tell in advance. |
| Q12 | You mentioned mentorship and obviously you’ve both been the recipients of great mentorship. What’s that taught you about your own practice of mentoring? |
|  | Craig Mello: I feel so fortunate to have had great mentors along the way and still colleagues that I’ve learnt so much from. It’s very, very important but I could spend hours talking about mentors but … |
| Q12 | Could you summarise just a couple of the things perhaps that you try and practice as a mentor for your students? |
|  | Andrew Z. Fire: It’s a hard question.Craig Mello: Do you want to take a crack at that?Andrew Z. Fire: I think that one tries to listen to what people are thinking because first of all that’s part of the mentorship process and second of all it’s part of the scientific process. No matter who it is, even somebody who’s just walked into the lab – we’ve had high school students working in the lab. The other thing is that you try and work with people as colleagues for each other and get them to ask each other questions because again, I don’t necessarily provide the best mentorship for people in the lab, the best advice and getting advice from each other has always been really critical and that’s one of the nice things about running a research lab in some cases. You can’t just sit back and let the ship run, but on the other hand there are a lot of cases where the really important, critical suggestions come because one person on one project suggests something to another person working on another project. It’s a really important aspect of it, to keep a collegial environment where people are comfortable talking to each other and suggesting things to each other. I’ve just been very fortunate in having had people in the lab who are both outstanding scientists and also outstanding mentors to each other and to me as well, in a lot of cases.Craig Mello: Yes, I think it’s so important, the conversation that you have in the laboratory with your students or with your adviser as I can recall in my own past. Those are so important as a way of learning and as a way of coming up with ideas. It’s interesting because the two people walk into the room and the idea is not there, it’s not always brought there by one individual. Usually the idea materialises in the room or in the discussion group and the one thing that I really fear is coming in with my own idea that’s wrong and pushing it too hard. When you’re mentoring, it’s important not to be too forceful about pushing your idea and to try to let people know that they should voice their ideas. Sometimes that for me has been the most difficult part, is getting the people in the lab to say what their ideas are. A lot of times their idea’s wrong and my idea’s wrong and the other person’s idea’s wrong, but you put them all together and all of a sudden there’s a new idea.Andrew Z. Fire: That might also be wrong, but it’s still a lot of fun.Craig Mello: At least maybe there’s an experiment you can do that will distinguish. That’s the fun, that is really a fun part of the process and one thing I fear and I’ve heard that once you have this kind of a prize, that your students are too respectful and they won’t question. You say something and they’ll actually believe it.Andrew Z. Fire: That’s scary.Craig Mello: Science is all about questioning things and if you don’t question it …Andrew Z. Fire: Doubt it.Craig Mello: … doubt it, yes. I think we need to reinforce that message to our students after we come back from this brief period of celebration. We need to go back and make sure that we get right back to the questioning. |
| Q12 | That neatly brings me onto the question of your youth, you’re both very young and this is going to bring considerably greater notoriety. How do you think it’s going to affect your future research paths and that question of distance from your students is certainly one aspect? |
|  | Craig Mello: I hope not too much in that respect. I feel that it’s like having a new job, an additional job, in addition to running the lab and trying to be a good adviser and leader for your group, to have this new responsibility to be a spokesperson for the science and to try to do the right thing in terms of promoting and the understanding of the science which … We just had a very interesting discussion in parliament in that I actually felt a little bit guilty during the discussion because scientists really haven’t done a very good job of educating the public about science and that’s partly because it’s nobody’s job. They don’t really make that your job, somehow it’s supposed to be part of your job but that’s not the part that you get paid for, you get paid for doing the research and publishing the papers, which are read by your peers not by your neighbours. I think it’s an important responsibility I feel, but I hope it doesn’t distract too much from the science. I’m very excited all the time by what’s going on in the lab, want to get back to it.Andrew Z. Fire: I really like my day-to-day life of teaching and research and family and that’s a pretty full life for both of us and so adding, as Craig says, an extra job to that, I’m not quite sure how it’s going to work but somehow we’ll probably manage. |
| Q15 | When you talk about educating people about science, is there a particular target group you think of, is there one group of people who you think need this more than any other? |
|  | Craig Mello: No, I think it’s a lifelong process to be educating yourself constantly because science is a fluid thing and it’s not just science, it’s all realms of knowledge really. There’re all kinds of interesting things to learn in this world and I think we need to make our children into lifelong learners somehow, don’t lose them along the way, to the interesting world that you can expose them to and it’s very difficult. There’s no easy solution, I think, to this question of how best to educate and that’s what we also were talking about earlier today. I’d be interested to know how the Swedish people have solved that problem. It’s interesting to learn about different cultures and how they approach learning, but it’s very important.Andrew Z. Fire: Yes indeed. |
| Q5 | What turned you on to being a lifelong learner? What was it that happened to you that made you? Was there a single event that made you want to learn? |
|  | Andrew Z. Fire: I hate to say it was a single event because it’s a lifelong thing. I think one thing, in terms of lifelong learning is that it’s surprising how little you need to change a description of a piece of science between talking to the Nobel Assembly of the Karolinska Institutet, which is one of the highest audiences in science and people that are extremely knowledgeable about everything you’re talking about, down to kindergarteners. If you just change some of the language, you can use almost the same discussion for both groups and have a significant fraction of them, probably, at least come away with some understanding of what you talked about, probably the same fraction in each case.Craig Mello: I think science as a process though, it naturally tends to make you want to be a lifelong learner. If you’re going to enter into an enterprise where there really are no right answers, that’s what science is all about, it’s testing ideas, it’s trying to disprove an idea. Once you have an idea, the first thing you do is try to test it to see if it’s right and the most fun thing is when it’s wrong and then you have to come up with a new idea, so it’s a constant process. If you ever thought that you would understand everything, certainly that would be very boring to be part of a science that is now a complete understanding of a process. Fortunately, I don’t think that’s going to be our problem for many, many, many years to come, so I think it’s a natural process once you’ve decided that you would like to be involved in science.The nice thing is, every day it’s an exploration, it’s a new discovery out there waiting to be made and just the process itself I think lends itself very well to the basic human nature of liking to explore and to understand and to see new things. That’s what science is all about, so I think we can do a lot better in terms of recruiting people into the sciences if we could somehow project that at an earlier level in education. Right now I think too much of our education is focussed on memorising facts and not enough on the exploratory process of science. What a real scientist does is so different from what you’re exposed to when you take science in high school or grade school. I feel that for me and my own understanding of what it would be like to be a scientist, I was fortunate to have a father who was a palaeontologist, so I was aware of science going on at this Smithsonian where he worked, the museum where he worked and going on field trips with him. Getting to see that real scientists don’t just read books, they actually do things, is so important. |
| Q3 | I’m interested in this idea of being able to explain the work to any audience. I think [Ernest Rutherford](https://www.nobelprize.org/prizes/chemistry/1908/rutherford/facts/) said that you shouldn’t be doing science if you couldn’t explain it to your tobacconist, which is a kind of antiquated concept nowadays perhaps, especially in the US. Your field doesn’t lend itself immediately to simple explanations, there’s a lot of jargon associated with it, so the fact that you feel that you can, with few alterations, explain it simply is a very encouraging message. |
|  | Andrew Z. Fire: I think it takes a little bit of time. One of the things that’s challenging is to explain things in a very short time. You need to be able to go back through some of what’s been learned, often with a group that’s not as aware of the history and go through that. I think with that it becomes more straightforward. What I think is a challenge and it’s often impossible is just when people say, can you tell us in a few words. The one that struck me in the few days after the announcement of the award was thinking about the scientists or the mathematicians who solved the Poincaré conjecture, which is a very important conjecture in mathematics and thinking about someone walking up to them and say, Well, in a few words can you explain to the general audience both the conjecture and the proof of it? Of course that certainly is doable in a little bit of time but it’s difficult in a short period and when I thought about that, I was a little bit more relaxed about my somewhat ineptitude in one occasion when I’m asked to explain things in a few words, at being able to do that totally clearly to everybody, it can be a challenge.Craig Mello: I think one of the real interesting things about talking to people about your work is, you’re right there’s a lot of jargon and a lot of times that’s just very distracting but I find that sometimes children even ask the better questions because they just don’t know what a word means for example and they say, Well, what is DNA? or What is RNA? What is a protein? You could then spend hours and hours discussing what it is and as long as the child or the adult continues to ask questions, you’ll find this wonderful conversation that can go on for quite a while. I agree with Andy, it just takes time and it takes the audience also being curious enough and not afraid of asking a question. I think most scientists are happy to spend some time discussing their work and quite often they wonder why no-one asks a question. They didn’t understand something very early in the talk and so they stopped listening and it’s important to raise your hand and say, But can you explain this one thing and quite often that’s a really good question. The hard part is losing people, and it’s a two-way thing. Conversations with a child can sometimes be even easier because you know how to track the conversation to keep them engaged. |
| Q23 | Terrifying, because they reveal the fact that one can’t explain it oneself but yes. One of the things we did this year for the first time was to invite some of the public to ask questions to you via the Internet and I’d like to, if I may, just pose a couple of those questions. First, a rather specific one from Kerry Austin in Texas who says, What application in genetics will offer the most effect use of RNA interference? |
|  | Andrew Z. Fire: I think there are probably lots. In the field of genetics there are probably many different applications, again combined with the tools of both classical data genetics and the sort of more modern set of technologies that don’t necessarily involve RNA gene disruption. I think altogether they give us a really good toolbox. Not something that in 20 years we’re going to say, You’re doing that? You know these were the crude tools we had in 2006 to do experiments and I think that they’ll also improve over time, so I’m not sure they’ll be one best application in research genetics, I think there’ll be many applications but they’ll be combined with all the other tools and we’ll always be wanting better tools.Craig Mello: Yes, certainly it is speeding, I think the use of vertebrate cells as genetic tools for studying the function of genes and there’s some really exciting technologies that have been developed that allow it to be applied fairly broadly in studying genes in cells in culture. I think that that’s helping a lot, but by itself it’s just the first step, so I think it’s being used primarily as an inexpensive but fairly rapid way of doing genetics and really needs to be backed up ultimately with other kinds of genetic tools such as real knockout cells and perhaps even animals to test these ideas before you really understand what’s happening. You have multiple lines of data or investigation that support your work, but RNA interference is an important tool I think for doing that first round of genetics where there are 20,000 genes and you want to know which ones are important in tumour or in some other disease. You have to sort through a lot and it’s a quick way of doing that, maybe a new way that would have been impossible earlier, so I think it’s providing an important function there. |
| Q23 | There was a time when people were talking a lot about the need for standards for such experiments. Is that time passed, are they now widely accepted for the publication of RNA interference? |
|  | Andrew Z. Fire: I think there’s still a need for standards. There are publications that have a very high standard for proving something and those cases you really are quite sure that what they’re reporting is indeed due to a decrease in a specific gene. There are some cases where, because of the system, in a few cases where it’s quite difficult to do the kinds of controls you want to do and for other reasons too, you come away not being as sure of the results. You’re certainly sure that the observations are correct, but whether the results are indeed due to a specific gene. I think there’s an interesting give and take amongst people writing and doing work in the field. |
| ID | 0546 |
| Biographical | I was born in 1951 in Kalgoorlie, a prosperous mining town 370 miles east of Perth, Western Australia. Kalgoorlie was a gold rush town which sprang up in the desert after the Irishman Paddy Hannan struck gold there in 1892.At the time I was born my father was 19 years old and in the final year of his apprenticeship as a fitter and turner. My mother quit her nursing training to have me at the age of eighteen years.We moved quite a bit through my early childhood. After my father finished his apprenticeship, my parents decided to go and work in the new Uranium mine in Rum Jungle in the Northern Territory. They drove their Model A Ford up Australia’s west coast about 1000 miles but stopped at Carnarvon when the car broke down. The whaling station at Carnarvon was also offering excellent wages for good tradesmen and my father was one of the best. We lived near the whaling station while I grew from two to four years and my brother William was born there.My first memories are of life in Carnarvon. I recall a boat trip back to Perth on one occasion and a DC3 aeroplane flight to Perth on another. Our house was on Babbage Island about 100 yards from the beach. We had electricity, an outhouse toilet, dirt floors in parts of the house, a telephone, refrigerator, a car, a cat and a dog. Nearby was a derelictsteam engine on a railway siding. We had neighbours close by and other kids to play with.By then, my grandparents had the license on the Tower Hotel in Kalgoorlie and periodically we would return there to live. In Kalgoorlie I remember doing all kinds of things as a six and seven year old including making bows and arrows, slingshots and lighting crackers after school.After a period back in Kalgoorlie, my mother decided to move the family to Perth where my second brother, Andrew, was born in 1958. I was seven years old at the time. I suppose my mother could see the young boys in Kalgoorlie leaving school at 16 and going down the mines to work. It was an attractive proposition for them. They earned high salaries and had a wild social life drinking and partying on their off days. She wanted more for her children and hoped we would study and enter a profession. Moving to the city was the first step. We are lucky she made that decision. My two brothers and sister all went through University and have highly successful careers and happy lives.In school I sporadically hit the top of the class but mostly did not work hard enough to stay up there. At home I had plenty of interesting reading material. Dad always explained the car engine when he repaired it and he had many technical books so I was making electromagnets by age eight as well as reading my mother’s medical and nursing books. I suspect I was born with a boundless curiosity and this was encouraged through my childhood.Being the eldest of four children, I was expected to be the responsible one and often found myself controlling two younger brothers who shared my exuberant and inquisitive nature. I still feel guilty about the time I advised my younger brother to jump out of a tree and he broke his arm.My first exposure to fame came at age twelve when I was left in charge of the younger siblings while my mother attended to the grocery shopping. I had a history of responsible baby-sitting by this time so nothing should have gone wrong. During the morning my 18 month-old sister found a milk bottle half full of kerosene and drank some, perhaps also aspirating a little so that my brothers and I found her choking but did not know why. I called the emergency services and an ambulance arrived about fifteen minutes later. During the wait, as I had learned some basic CPR at the Royal Lifesaving Society Swimming training, I tried to perform mouth to mouth resuscitation on my little sister. I know now that it was pointless because she was actually still breathing. However, my close mouth contact enabled me to smell the kerosene and make the diagnosis of poisoning. I featured in the newspaper a few days later, with my fully recovered little sister on my lap. It was a good story about how to call the emergency number, and why you should not put poison into drink containers. Very kindly my mother did not leak to the press the fact that it was I who had left the kerosene within reach of young Marie!In our dad’s shed, my brothers and I had access to all the tools needed to build or dismantle anything. I frequently got into trouble doing both. My favourite book as a child was an old Newne’s Children’s Encyclopaedia which my grandfather had bought just before World War II and donated to our family after seeing how interested we were in it. Each volume had special chapters called “Things Boys can Do”. My brothers and I would pick out interesting projects. As the years went by, and I grew up, I recall building a slingshot, a crystal set, a Morse-code set, various guns, a hydrogen generator for balloons, electric devices and minor explosives. In those days fireworks had been banned, but chemicals were easily available from pharmacies and chemical suppliers so, in the tradition of Alfred Nobel, we would create various explosive mixtures and make firecrackers and bombs. This started rather benignly with simple gunpowder but graduated to more dangerous oxidising agents after a few years. Many times we were in trouble after disturbing the neighbours, but were fortunate never to cause serious injury. I often found myself in trouble with my parents when someone was hurt, but despite the minor punishments, I know my parents were quite proud of my ingenuity.Occasionally my father, Bob, was on the receiving end of my “brilliant” work. Observing a fraying cord on his electric drill, I repaired it but accidentally swapped the neutral and earth wire. He jumped rather high when he tried to use it a few days later while standing on wet grass. On another occasion my brothers decided to fly lighter-than-air balloons for our team at the school sports carnival. Since helium was not available, we built a device which pressurised domestic house gas and filled the balloons. Our technology was rather primitive however and these balloons contained quite a bit of air as well, but they did float satisfactorily. My father recognised this and warned us that they might be a little dangerous if they came in contact with an open flame. As an example, he demonstrated the risk by touching a lighted cigarette to one of the balloons as it floated under the back patio. He was enveloped in a ball of flame and his eyebrows were singed off. This did not worry us very much because we had seen him in this state before as he often seemed to be washing engine parts in gasoline and then testing the spark plugs of engines nearby.After high school, at Newman College, although interested in science and mathematics, I felt that my mathematical ability was not strong enough to do electrical engineering, so I chose medical school as an alternative which was at least as interesting, and which did not require daily exposure to calculus! In addition the opportunity to study biological sciences was an attraction, particularly biochemistry which was not available in high school.I met my wife Adrienne, a psychology student, at the University of Western Australia and we married in 1972 while I was doing my fifth year in medicine. I graduated from the University MBBS (Bachelor of Medicine, Bachelor of Surgery) in 1975 and thereafter performed internship and residencies in internal medicine at the Queen Elizabeth II Medical Centre (Sir Charles Gairdner Hospital). In those days I had no definite goals in medicine, but was interested in all aspects of clinical medicine including geriatrics, oncology and rheumatology. I was more interested in an academic career combining research with clinical medicine in a university hospital environment. I began my training as a specialist physician in 1978. In 1979 I moved to Royal Perth Hospital in order to become more experienced with cardiology and open heart surgery, which was only performed at that hospital in Perth.Although we didn’t appreciate it at the time, my wife Adrienne and I must have been very busy during those years. We had four children, Luke, born in 1973, Bronwyn in 1975, Caroline in 1978 and Jessica in 1981. Adrienne was finishing the honours year of her psychology degree as Luke was being born. She was working in-between babies as a counsellor with the Education Department. My non-medical time was spent delivering children to various child-minding facilities, renovating our house, and indulging in my hobby of computers and electronics.In the second half of 1981, my rotation took me to the gastroenterology division. It was there that I met Robin Warren. As part of my training I was encouraged to perform a clinical research project each year. I was already totally engrossed in a study of heat stroke in “fun runners” and might have progressed to sports or environmental medicine from there. However, I asked my boss, Dr Tom Waters, if there was a gastroenterology project I could start. He told me that Robin Warren had given him a list of patients with curved bacteria present on their stomach biopsies and needed someone to follow-up the patients to see what clinical diseases they had. I was especially interested because one of the people on Robin’s list was a woman I had seen in my ward, who had severe stomach pain but no diagnosis. In desperation we had referred her to a psychiatrist and commenced antidepressant medication for want of a better treatment. The only abnormal finding had some redness in the stomach and Robin’s bacteria on the stomach biopsy.So I called Robin in the basement area of Royal Perth Hospital where the Pathology Department resided. It was to be the first of many afternoon visits in the next year. In those days, Robin used to drink strong black coffee and smoke small cigars, “cigarillos” I believe they were called. I too used to indulge occasionally, and would try out one of Robin’s cigars from time to time during our meetings. In our first meeting, Robin showed me slides of the curved bacteria he had seen, and explained the histopathology of the gastric mucosa to me.I am often asked what made me listen to Robin and take up the research with him. Clearly this was an interesting thing to study, previously undescribed bacteria living in the acid-filled stomach. But I may have had other advantages compared with colleagues Robin had approached over the previous two years.I was undifferentiated in that I wasn’t coming from a background in gastroenterology so that my knowledge and ideas were founded in general medical basic science rather than the dogma one was required to learn in specialist medicine. As a trainee general physician with broader training, I was comfortable with the notion of infectious disease and antibiotic therapies. I am told by others that I have a lateral thinking broad approach to problems, sometimes to my detriment. In school my grades always suffered because I was continually mucking about with irrelevant side issues which I often found to be more interesting.At around that time also, I was aware of publications in the literature describing *Campylobacter jejuni* as a newly discovered common cause of food-borne gastroenteritis and colitis. Thus, I had seen pictures of campylobacters and could identify that Robin’s organisms appeared to be quite similar. In retrospect, one advantage of doing this research in Perth was that, as a modern Western society, H. Pylori was already in decline by 1981, so that rather than 80% of persons having the *CLO*, bacteria were only present in 30–50%. Thus, in any biopsy collection taken that year, Robin could see both infected specimens with inflammation (gastritis) and uninfected specimens which hardly ever had gastritis i.e. a “control group”. A further advantage I did have in 1981 was the new connection we had from the medical library to the National Library of Medicine at the NIH (*Medline*). Perhaps because of my interest in computer programming, this resource appealed to me and enabled me to enlist the librarians at Royal Perth Hospital to extensively search the past and current literature on gastric bacteria.By the end of that first afternoon with Robin I was very interested. Over the next six months I followed the literature from book chapters, to their references, to deeper references, to material in library archives. I found that spiral gastric bacteria had been reported again and again but passed over. I could see an interesting paper being produced, perhaps in an obscure microbiological journal, but had no idea at the time of what we were really about to discover.At the end of 1981, my gastroenterology term had almost finished and my term allocations for 1982 had been chosen. In the midst of all this time consuming and interesting research work I was still a physician in training. I was fitting in the research around education and patient commitments. In the first 6 months of 1982, I was to be a haematology registrar looking after the bone marrow transplant patients. In the second 6 months I was to be the physician at Port Hedland Hospital, a rotation to a point 2,000 kilometres north of Perth which attracted “hardship bonus”, i.e. $5,000 extra over 6 months. By then, I was very excited about the spiral bacteria. I had developed a degree of confidence in our methodology, and believed that we could safely carry out a study on 100 or so patients. I was able to keep the work going, continuing the research by fitting it around my other duties.In November 1981, Adrienne had delivered our fourth child, Jessica. I was beginning a project which would occupy every minute of my spare time for the next 6 months. Adrienne was on maternity leave and was full time at home. It meant I could leave much of the parenting to her. We never did find the time to complete our home renovations and at the last minute in 1986 took out an extra home loan to pay someone to finish it for us. We had to have it in a rentable condition while we were in the USA.I was fortunate to have a partner who was as enthusiastic about the work as I was. She also enjoys a challenge and shares my sense of adventure. Adrienne’s background in Psychology and experimental research was invaluable and she was always around to discuss the design of studies and the results of various other research works I had found. Over the years we took lots of chances. I took jobs on inadequate pay for many years. As my contemporaries were making their careers and achieving success I seemed to be falling further behind. I always had Adrienne’s full support. When she urged caution or vetoed some of my excesses, I knew it was time to really listen and re-evaluate. As time went on she became by my unofficial editor. All my early papers were edited by her and she helped with much of the discussion. Her liberal arts background means she is a more fluent writer than I. Over the past 25 years she has also helped to write and edit most of my books and speeches. All of the talks and speeches given in Stockholm were written with her substantial help.My hobby of electronics was also an important aid in my research. In the evenings during 1981, I continued with my hobby of computing and electronics, so that by the end of that year I had completed the construction of a home computer capable of word processing. I was able to type grant proposals, consent forms and protocols. I was always on the leading edge of technology and my communication with overseas researchers was efficient because of that. It also meant I was able to access information not readily available. By 1981 I could function better as a single unfunded scientist than many units with multiple support staff.The family moved to Port Hedland in July 1982 and I took all my references and textbooks with me. It was an important period. I had time to do an extensive literature search by correspondence and also had time to digest the results of our study and write it up for presentation. It was a great time for the family too. Winter in Port Hedland was beautiful, every day sunny with a temperature in the 80’s. We had a bit of extra money and we spent many weekends travelling in remote communities and camping with the kids under the stars.In October 1982, I presented the preliminary findings from our study to the local College of Physicians meeting, where it received a mixed response. I found that my contract at Royal Perth would not be renewed the following year. I had successfully completed my training as a physician and now wanted to work in gastroenterology or microbiology to continue the work. These jobs at Royal Perth were not available.Fortune stepped in when I was approached by Drs. Norm Marinovich and Ian Hislop at Fremantle Hospital who suggested they would find me a senior registrar position and fund me to continue. Fremantle is the third and smallest of the teaching hospitals in Perth and has a tradition of openness and experimentation. In the next two years at Fremantle I had an enthusiastic group of people working with me. Dr Ian Hislop, Norm Marinovich, Harvey Turner, David McGechie, Ross Glancy, Neil Noakes, Graeme Francis, Peter Rogers, Neil Stingemore, as well as great support from the Medical Superintendent, Peter Smith. The only downside of the appointment was that I was forced to halt my collaboration with Robin Warren. Robin did not have an appointment at Fremantle so the pathologist there, Ross Glancy, joined the team.They were happy and very productive years. I was able to confirm very quickly that our observations of the bacteria at Royal Perth Hospital also applied in other parts of the city, the majority of peptic ulcer patients having the organism. I was still officially unfunded. The hospital was picking up all the costs of my work. It was at Fremantle in those two years that the first effective treatments were devised. I solved the conundrum of why bismuth has been such an effective stomach treatment for the past 200 years. I did my famous self experimentation and the early urease tests were developed.A great piece of luck in early 1983 was finding Dr Martin Skirrow in the UK. I got his phone number from David McGechie. Skirrow arranged for the first presentation at the European Campylobacter Meeting in September 1983. Harvey Turner arranged a travel grant to take me to Brussels and the Gist Brocades Company, helped so that I could extend the trip, visit Martin in the UK and Guido Tytgat’s group in Amsterdam.In September 1983, I visited Martin Skirrow in Worcester England, and attended an endoscopy session at the Worcester Infirmary. Martin’s registrar, Cliodna McNulty, was able to successfully isolate the organism 3 days later, showing that the spiral bug was not merely an Australian phenomenon but was present in ulcer patients in the UK as well. Martin Skirrow in Britain and Adrian Lee in Sydney were enormously encouraging, helping me with the microbiology in those early years.In 1984 therefore, there were several groups around the world obtaining results which paralleled those of our group in Perth. In Australia, Adrian Lee in Sydney with Stuart Hazel and Hazel Mitchell also Nick Talley, John Lambert and Tom Borody were early researchers who made significant advances in the H. Pylori work. After the Brussels meeting, a core of researchers in Europe immediately picked up the research and much of the most important work on HP has been done by that group: my old friends, Mario Quina in Portugal, Tony Axon and Ashley Price in the UK, Francis Megraud in France, Peter Malfertheiner in Germany, Manuel Lopez Brea and Jose Pajares Garcia in Spain, Penti Sipponen in Finland, Dino Vaira and Giovanni Gasparini in Italy, Colm O’Morain in Ireland, Leif Andersen in Denmark, Alexander Hirschl in Austria, Guido Tytgat, Ernst Kuipers and Erik Rauws in The Netherlands, Michel Deltenre in Belgium, Pierre Michetti in Switzerland, Torkel Wadstrom and Lars Engstrand in Sweden. We became a closely knit group. The European group grew out of the campylobacter group I had met in Brussels in 1983 and today I count the members of that group amongst my closest friends. We have shared a remarkable story together.In the USA David Graham, Pete Peterson and Martin Blazer began as critics. They set out to disprove the hypothesis but quickly became leaders in the field of HP research in the USA. With Tadetaka (Tachi) Yamada, although he was not directly involved in the HP research, they played an important role in moving various bodies such as the NIH towards action and acceptance of HP as an ulcer cause. In Asia, Takashi Shimoyama, Ken Kimura, Susumu Okabe, Yoshihiro Fukuda, Toshio Fujioka, Bow Ho, and K.L. Goh, were doctors who I was in contact with through the 1980s. They were developing their own HP research and supporting mine. In Asia, the H. Pylori research was taken up very quickly and I made my first visit to Japan in 1985 to present my work. There are too many others to list here. Needless to say, reports that I was alone in the promotion of HP as a pathogen are somewhat exaggerated.But 1984 was a difficult year. I was unsuccessfully attempting to infect an animal model. There was interest and support from a few but most of my work was rejected for publication and even accepted papers were significantly delayed. I was met with constant criticism that my conclusions were premature and not well supported. When the work was presented, my results were disputed and disbelieved, not on the basis of science but because they simply could not be true. It was often said that no one was able to replicate my results. This was untrue but became part of the folklore of the period. I was told that the bacteria were either contaminants or harmless commensals.At the same time I was successfully experimentally treating patients who had suffered with life threatening ulcer disease for years. Some of my patients had postponed surgery which became unnecessary after a simple 2 week course of antibiotics and bismuth. I had developed my hypothesis that these bacteria were the cause of peptic ulcers and a significant risk for stomach cancer. If I was right, then treatment for ulcer disease would be revolutionized. It would be simple, cheap and it would be a cure. It seemed to me that for the sake of patients this research had to be fast tracked. The sense of urgency and frustration with the medical community was partly due to my disposition and age. However, the primary reason was a practical one. I was driven to get this theory proven quickly to provide curative treatment for the millions of people suffering with ulcers around the world.Becoming increasingly frustrated with the negative response to my work I realized I had to have an animal model and decided to use myself. Much has been written about the episode and I certainly had no idea it would become as important as it has. I didn’t actually expect to become as ill as I did. I didn’t discuss it with the ethics committee at the hospital. More significantly, I didn’t discuss it in detail with Adrienne. She was already convinced about the risk of these bacteria and I knew I would never get her approval. This was one of those occasions when it would be easier to get forgiveness than permission. I was taken by surprise by the severity of the infection. When I came home with my biopsy results showing colonization and classic histological damage to my stomach, Adrienne suggested it was time to treat myself. I had a successful infection, I had proved my point.At the end of 1984 I was funded by the Australian Medical Research Council to conduct a prospective double blind trial to see if antibiotics could cure duodenal ulcers. It was conditional on getting a large number of patients into the study so I decided to move back to Royal Perth Hospital where the patient load is far higher. It meant I would be leaving my Fremantle colleagues and it was with some reluctance that I moved. When I returned to Australia in 1996, I was asked to be Patron of the Fremantle Hospital Research Foundation and I take great pride in having that position. At Royal Perth I was again working with Robin, John Armstrong, Len Matz, John Pearman, Stewart Goodwin, Doug Annear and Helen Royce.Even though I was not officially collaborating with Robin when I was working at Fremantle Hospital in 1983–84, we still met to discuss the papers we were writing for the Lancet and would meet for dinner with our wives. We had one of these dinners only a few weeks after my self experimentation experiment. I was enthusiastic about the results and the severity of my illness. It was also the first confirmation of infection with documented results. I was eager to share the news with Rob and he was equally excited about it. Early the next morning he had a call from a journalist in the USA at 5 am who had his timing totally off. No one is ever able to figure out what time it is in Perth. When asked the usual question about “How do you know it’s a pathogen and not a harmless commensal?” Rob blabbed the results of my still unreleased work with “I know because Barry Marshall has just infected himself and damn near died”; a slight exaggeration, but it made for good copy. What he didn’t know was that the journalist he was speaking to was from the “Star” newspaper, a tabloid that often features with stories about alien babies being adopted by Nancy Reagan. This was right up their alley. The next day the story appeared, “Guinea-pig doctor discovers new cure for ulcers … and the cause.”This became one of the serendipitous, life changing events in my life and I have Rob’s temper to thank for it. Firstly, I was contacted by a continuous line of patients in the USA who read the story and were desperate for treatment. I was able to help. I was treating patients by proxy in the USA as early as 1984.Ten years later this became important in a dispute with another doctor who claimed to be the first. I still had the records from some of these patients and was able to get in touch with them to prove my claim to be first.The second result was that it was read by Mike Manhart, a microbiologist working for Proctor and Gamble in the USA. He tracked down my published letters and realized the economic potential for P & G who made a bismuth drug and set up a business relationship. P & G later patented much of my work and also helped me with patents on my diagnostics. There was little money in any of this for the first 10 years but after 1995 it became a significant income for us. P & G funded a fellowship for me in the USA to replicate and push the research there. We departed Australia, believing that it shouldn’t take more than 2–3 years to convince the world that antibiotics would cure most gastric diseases.It also brought Bruce and Claudette McCarty into my life. Bruce was head of Health and Personal Care products at P & G and became an important mentor. He arranged support funding to set up a lab at University of Virginia. Bruce became a good friend and a keen advocate for H. Pylori research in the USA. He taught me a lot about how business works best in a trusting and responsible way to benefit everyone. It also seemed to me that he and Claudette spent lots of time in their life just having fun with family and friends. Tragically, Bruce died in 2004. It was a great sadness for me and Adrienne that he and Claudette were not there in Sweden to see me receive the Prize. He always believed in me and his faith in the work and great enthusiasm never failed.The ten years spent at University of Virginia, were a chance to extend my research, particularly in the area of treatment and diagnostics. I became an advocate for treatment though many called me a zealot. They were often hard years for the family particularly the first few years when we were on a financial shoestring. They were rewarding as well. I had continuous stream of letters from patients who had been treated and freed from a lifetime of pain and disruption. I worked with a great team at UVA. Richard McCallum was head of Gastroenterology and Dick Guerrant in Infectious Diseases. McCallum gave me free rein and sponsored my academic rise in the USA. I also did great collaborative work with Dick over the years. David Peura, a long-time H. Pylori enthusiast from the US Army, moved to UVA in 1992. My team included nurse Susie Hoffman, nuclear technician Michael Plankey, post-doc Matthew Coombs, data manager Linda Mosen, programmer Sherry Boyd, assistant Nancy Noblette and many others. We were regarded as being outside the mainstream but were a great enthusiastic group and became life­long friends.I also met Bill and Sandy Fry in 1987. Bill owned a company Tri-Med along with Phil Patterson and Kevin Dye. Bill Fry bankrolled a USA study for my CLOtest diagnostic and launched it in the USA. Later he was to also pick up the C14-Urea Breath Test and shepherded it through the FDA at a cost of several million dollars. I count Bill amongst my closest friends, a brilliant salesman and an example of a team leader. No matter how black things looked, Bill could always find a silver lining for us even though I am certain he was secretly concerned about our chances of success. Bill’s credo which he lives by is that “Good things happen to good people”. We have done a lot of good stuff together and had many great times.Patients often wanted to make a donation to the work so I set up a foundation to use the money for patient and doctor education about the research. On one occasion there had been a story about the cure in the Sunday papers across the USA. In the following weeks we received 30,000 letters all with donations of a dollar or two to pay for postage and photocopying of information. We had to hire in students to handle it all.Over the years the journalists who covered the story helped significantly in educating the public to ask for and later demand the new treatments from unwilling doctors. Suzanne Chazin in the Readers Digest, Terry Monmany in the New Yorker, Mark Ragg in the Bulletin and Larry Altman in the New York Times all wrote detailed reviews of the work that became important sources of information. The BBC show Ulcer Wars produced by Michael Mosley is still shown around the world.The tide of acceptance began to turn in the early 1990s and by 1992 I could go to meetings and receive as much praise as criticism. 1994 was a watershed year for us. In February 1994 the NIH held a consensus meeting in Washington DC which ended after 2 days with the statement to the effect that the key to treatment of duodenal and gastric ulcer was detection and eradication of Helicobacter pylori.I had been waiting for ten years for this day and I felt a combination of relief and satisfaction that I had achieved what I set out to do. Years before, I had developed the hypothesis, tested it, proved it and now it had reached official acceptance.The next year proved to be harder. I began to receive awards and recognition. At the hospital, I was still carrying a full load of patient care and research. However, I was increasingly dissatisfied. Much of my time was being spent attending meetings and travelling. I think the pressure of the previous 10 years was beginning to show. Because I had been so involved in the exponential rise of Helicobacter, I had been unable to update my training in new areas of molecular biology which by then were coming to represent a large proportion of the Helicobacter publications.In typical fashion Adrienne took over the decision-making and at the end of 1994, I took a year of leave from the university. We cashed in my superannuation and decided to live on that for a year to figure out what would be next in our lives. In that year I still travelled and lectured but my primary work was with Tri-Med, getting the breath test through the FDA regulatory process. I am proud of my diagnostics tests, the CLOtest and PYtest. They are often my forgotten children, eclipsed by my work on treatment. Although less glamorous than high impact papers, reliable cheap and available diagnostics are just as important in medicine as treatments. They don’t always get the same recognition. After 1994 my business interests became more important. The diagnostics were starting to earn an income. In Australia, close friend Rod Blechynden took on the role of managing it for me. Rod and Adrienne take care of the business aspects of my work. Their work frees me to focus on my research.Once I had completed that project, Adrienne decided it was time for us all to go home. I was still unsure but it has turned out to be the best decision for me and the family. We moved back to Perth in 1996. I was awarded the McFarlane Burnet Fellowship which funded my lab at the University of WA for a 5 year period. In 1998, Tri-Med USA bought the manufacturing rights to CLOtest. I was keen to keep the manufacturing in Western Australia. It has been a long term ambition of mine to develop industry here in Perth. I set up a new manufacturing facility here but, sadly, it didn’t last. Tri-Med in the US was later sold and the new owners moved all the manufacturing back to the USA. Tri-Med in Perth continues in a small way doing R&D and selling medical products.Before finishing I want to acknowledge all those scientists who failed to recognize HP. Without them I would have had a very different career. Some of their stories are described in my book “Helicobacter Pioneers”. I also want to thank Irvin Modlin for the foreword he wrote for it. He is a great guy and was able to say things about the joy of scientific research that I never could.One of the truly great things about winning the Nobel Prize in 2005 was that I was living and working back home. I got to share it and celebrate with those who had been involved in the initial work at Royal Perth and Fremantle Hospital.I continue to live in Perth Western Australia. I have an appointment at The University of Western Australia and still see patients at the gastroenterology department at Sir Charles Gairdner Hospital. My other interests continue. I take an active role in Tri-Med and in 2005 began a new project with vaccine company Ondek.There were many occasions when luck played a role in my life; meeting with Robin, the first culture of the bacteria and chance meetings with many people who helped me and collaborated with me. I look back and am grateful to the many friends and family who helped me along the way, most importantly, my wife Adrienne, and my children, their partners and my grandchildren. |
| Autobiographical |  |
| Podcast | **”I wasn’t interested in learning stuff. I was just interested in understanding, because I could see what a fabulous shortcut it always was”**Meet 2005 medicine laureate Barry Marshall in a dynamic talk with the Nobel Prize’s Adam Smith. Marshall tells us about his blog (something very few laureates had in 2005!), his time as a yo-yo expert and his research that paved the way to a Nobel Prize.Self-experimentation is another topic that is up for discussion. Marshall takes us back to the moment he drank a bacterial culture of Helicobacter pylori to prove that gastric ulcers were caused by bacterial infections – it’s a story you don’t want to miss!Listen as we take you back to this conversation with Marshall, recorded in February 2014 as part of the series ‘Nobel Prize talks’. The host of this podcast is nobelprize.org’s Adam Smith, joined by Clare Brilliant.Below you find a transcript of the podcast interview. The transcript was created using speech recognition software. While it has been reviewed by human transcribers, it may contain errors.Clare Brilliant: Welcome to Nobel Prize Conversations and this encore presentation of our February 2014 talk with physiology or medicine laureate Barry Marshall. I’m Clare Brilliant and I’m here with our host Adam Smith. Hi Adam.Adam Smith: Hi Claire, here we are again. What a lot of funny things we end up doing together over the years. And it has been many years hasn’t it? It seems to be forever, it’s in a good way.Brilliant: It’s hard to believe because looking back on these conversations which were around 10 years ago, we’ve worked together for more than double that time, Adam. Although we weren’t at Nobel then, we were working together back in 2005 when Barry Marshall was awarded his Nobel Prize.Smith: Indeed and that prize for the discovery of the link between helicobacter pylori and gastric ulcers was one I remember well because it really captured the public imagination.Brilliant: Yeah and that doesn’t sound so dangerous but his methods were quite unusual is that right?Smith: Yes, he gained a daredevil reputation for experimenting on himself. He became frustrated because people just didn’t believe that there was a link between the bacterium which wasn’t supposed to be able to live in the stomach and stomach ulcers. So he just drank a concoction of the bacterium from a conical flask himself, gave himself gastric disease and then had to cure himself with antibiotics so it proved the point in a rather dramatic way.Brilliant: Yeah and I think we get some insight as to perhaps why Barry Marshall was so fearless. He talks about this in relation to his childhood but I think that comes through in his attitude to experimentation in science later in life.Smith: Yes, he’s not much interested in received wisdom, he’s just interested in finding things out for himself and that sense of inquiry seems to know few boundaries.Brilliant: It was really interesting to hear him talk about the internet at the time was such a new thing in terms of what it gave him.Smith: It’s funny that isn’t it? It does seem like a slightly different world where he talks about the fact that he’s one of the first laureates to use a blog and the power of the internet to make the world smaller. Things that we kind of take for granted now you assume it’s always like it’s been today but actually it changes things radically and it’s really interesting to get this snapshot of how we thought about the internet and blogging 10 years ago.Brilliant: Exactly. I think it’s a good point now to listen to Barry in his own words.Smith: Yes, now it’s time let’s listen to this second episode in our encore presentation of Nobel Prize conversations with Barry Marshall.Barry Marshall: Hello, Barry Marshall here.Adam Smith: I’m really pleased to have the possibility of talking.Marshall: We’re coming up to we’ll talk about it later, but we’re coming up to the anniversary of it, which is Easter, of course.Smith: Yes, exactly. What was the actual date of the experiment?Marshall: Well, probably 7 April. I’d have to look on my blog. The 7th of April.Smith: It’s interesting you do blog because not many laureates do. What started you off on that?Marshall: There were things that rumour built and things that people find out about me get blown out of proportion, then reported in the press, and then they turn up on different websites which is, and so often to set the record straight is worthwhile having a blog to get in there and actually say exactly what happened. The other place you can do that is Wikipedia, which you have to get in and edit every now and again, so one of the famous rumours about me was that I was the Australian yo-yo champion several years in a row. The actual truth was I won the heats in my age group in Perth but was knocked out in the finals. I did win about 24 bottles of Coca-Cola, which was delivered to my house in the street. All the local kits had a bottle of Coke that afternoon, on a hot day. I was pretty famous locally, within a hundred yard radius to my house. I can still play yo-yo.Smith: You can.Marshall: A bit anyway.Smith: Can you do tricks with them?Marshall: I could do a couple of tricks, yes.Smith: Oh, that was that.Marshall: I wouldn’t put any money on me in a competition.Smith: Is there a YouTube video out there somewhere of Barry Marshall doing yo-yo tricks?Marshall: There’s probably one in Japan somewhere because they did get one off me for the science museum in Tokyo. I did some yo-yo tricks there for one of the reporters for their website.Smith: At least in the child population of London I’d say it’s a declining art, but maybe it’s growing in Japan.Marshall: It’s quite interesting. I’ve got half people actually present me with yo-yo sometimes when I turn up and ask me to do a trick. But I have probably half a dozen different ones. They are fabulous yo-yos you can get these days. They often have automatic LEDs in them and automatic clutch, so they’ll spin nicely. The technology’s really moved on quite a lot and probably it’s something that’s going to come back.Smith: All these things have their cycle. Do you still play for relaxation or just when you’re asked to give a demonstration?Marshall: I have to say that every month or so I might get one out and have a go at it. I’m looking around on the left and I can see three of them on my shelf with my collection of different junkie, different items and things. Any kind of interesting junk that I’ve collected during my life, I tend to stick up on the shelves next to my work area because I work at home about a third of the time often I’m just communicating with somebody. Today I was working on Skype, booked for several hours with somebody finishing a paper. As you get more into research, a lot of the time these days is actually spent on the web and communicating with colleagues.Smith: The fact that you are an Australian laureate and living in Australia makes you part of quite a small community although Australia’s produced a good number. What’s it like doing science in Australia these days?Marshall: It’s a lot easier than it was. I always felt that Australia was about three years behind the rest of the world. That was in the eighties. Now I think we’re just like any other western country, and we’re within a few months, say three to six months of anything happening in the UK or US or Europe. It’s pretty well known about in Australia. Obviously that’s partly due to publications, the internet and various news feeds that you might keep up to date with collaborating, talking to your colleagues. I do think that the Australians need to go to an international meeting each year, because quite often the abstracts and posters and the new ideas and speaking to investigators on new technologies is done at the poster sessions rather than the formal sessions in the conferences.Smith: You mentioned earlier that a lot of a scientist’s life is spent on the internet, so you can keep up with pretty much everything that’s going on, but it was that physical isolation that was interesting. Is there though an advantage in place where Australia is? In Europe there are lots of meetings going on and it’s easy to get around, but at the same time, we are very far away from Asian science, for instance, physically. Whereas you are placed quite close to that.Marshall: You make a strong point there. The growing area in a lot of sciences and technologies is Asia, particularly led by China. Even though China is having a bit of a quiet year, they’re still growing at 7%. They’re still funding far more scientists and far more new technologies than most other countries. It’s actually pretty active here in Asia. If I have several choices I can quite often choose to go to a meeting in Japan, Korea, China, Malaysia, Singapore, or Indonesia, and sort of get the same opportunities that I might get if I go to Europe often less sophisticated. There is a lot of research going on, particularly in helicobacter stomach diseases with new observations being made.Smith: How important do you think it is that there is a good international mix of people working on any one area, any one problem? Does it matter what the nationalities are?Marshall: Not so much the nationalities, but of course people have a different slant on it in different countries. I think that we’ll be able to tease out some of the helicobacter theory built by having people study helicobacter in different countries. I think that probably we’ll find their dietary components overlaying any kind of gastric diseases. Obviously if you have a totally different diet, something that would just sits on the surface of your stomach is going to be quite different in one country versus another. I’m interested in that and I think that sort of thing will be teased out in Asian studies. The other thing is that Chinese studies are very useful for testing hypothesis in humans. You might say, I think that this kind of helicobacter and this gene on the tox, this toxin gene is the key thing for stomach cancer. That’s a great idea. You take it out of the genomics lab in London or somewhere, and you go and study 5,000 people in Beijing. It takes you about a year with a good Chinese group. You come back and say it’s totally irrelevant or it’s looking interesting. That’s the sort of thing. In fact there’s a lot of good theories that have actually gone down the drain after being tested in China and not being seen to be particularly important.*MUSIC* Smith: I wanted to talk about you and what made you into the person you are. What kind of childhood did you have?Marshall: I was an interesting, fairly smart kid and I did have all kinds of stimulations because my father was a mechanic, an engineer. He worked on a whaling station as a fitter or diesel mechanic. He worked on whaling boats. He worked on cray fishing boats, but he was also doing weekend work on different things. He then became a refrigeration engineer. All these different technologies were actually continually laid out for me as he was credentialed over the first probably 10 or 12 years of my life before we settled down into his main career.Smith: What was his main career in the end?Marshall: Ultimately he ran a chicken processing factory, and he built that factory in the late sixties. In the sixties, somewhere Kentucky Fried became globalised. All of a sudden in Perth, Western Australia, maybe 1964 or 1965, Kentucky Fried Chicken came to Perth. The consumption of chicken in Australia went from special food that you had on special days, like once a month for Sunday dinner, to something that you could have two or three times a week if you wanted it. It was frozen chicken everywhere. His being in the refrigeration business and the meat processing business, his company really started producing massive amounts of chicken until they were supplying 40,000 chickens a day. There was a very big operation. It ended up being quite sophisticated. I think my father had a bit of an inferiority complex that he didn’t have a tertiary education, but not many people did in 1950. But he did have a good tradesman’s ticket. He was probably one of the smarter tradesmen. He actually built on that with various other training courses. For instance, he had certification ultimately on Caterpillar, Marine diesels, and then he had refrigeration. There was always a lot of technology and quite interesting books around that I could read on thermodynamics. So maybe what it did for me was just make me fearless about technology. I could look at medicine or electronics or engineering and or even look at a trade. Carpentry seems like a lot of fun, but I could look at all those things and say, well, I could do any one of those. I don’t see that there’s any difficulty with them.Smith: That is very important, isn’t it? Because the lack of fear, the feeling that you could build it yourself and you don’t have to rely on somebody else’s knowledge and therefore, for instance, that piece of equipment, you don’t just have to trust it’s giving you the answer it should. You can find out why it’s giving you that answer.Marshall: True. Whenever I came across something that was very difficult to understand or seemed very difficult or technical, it seemed to me, I just had to find the right person who knew about it, and then they would transfer the knowledge or the understanding. I wasn’t interested in learning stuff. I was just interested in understanding, because I could see what a fabulous shortcut it always was. I think my father was quite a good teacher in anything that he knew he could teach me in five minutes. Some of my teachers at school were like that. But I had a great chemistry teacher. I had a great physics teacher. I recently met one of the Christian brothers, one of the brothers actually gave us, at the boys school, the sex education lectures. That was excellent as well. Quite surprising, really.Smith: Somehow he had understanding.Marshall: Yes, he was a bit of a character. So it might’ve had an interesting background.Smith: Was it by chance that you fell into doing medicine or was it a passion that was growing within you as a teenager?Marshall: My mother was a nurse, so as well as my dad’s technical books, there wouldn’t have been much reading material in my house. There were some people, dad’s trades books and engine books. Maybe 10 of those. There would’ve been my mother’s nursing books, because she did nursing. There was anatomy and physiology based in about the 1952 vintage post World War II vintage. I don’t know how good the physiology, anatomy, biochemistry and that in there was probably fairly superficial. But there was a pretty good understanding of disease processes and the anatomy, which I was very interested in and looking through. I probably read those books cover to cover at different times when I was home with the chicken pox or the measles. We only had a radio until I was about 12 years old, then we got TV. So there was really nothing to do if you were at home by yourself, except find books to read.Smith: It’s interesting, the differentiation between learning and understanding. It’s obvious, but at the same time, I don’t know whether our school systems these days realise the difference. What do you think?Marshall: You do have to have a basic level of knowledge to actually be able to pick out the important new thing. Even in medicine I felt that medicine, I think it takes a while for you to make a discovery, because you have to understand the current paradigm, the problems that exist, what’s rare and what’s common. Then you can see the opportunity or the new observation, or develop a new idea for treating. I do think it takes you maybe at least five years in clinical practice seeing a lot of patients before you know that what you’re seeing is an unusual thing or you’ve got a new idea or a relevant observation. It just so happened that when I met Robin Warren, he showed me these bacteria. I wasn’t interested in ulcers in those days, looking down the microscope and saying, ‘yes, I agree with you, Robin. There’s absolutely no doubt these things are growing in the stomach. And the stomach should be sterile. So that’s great. Let’s figure out how they live there.’ If I hadn’t have a bit of general knowledge of gastroenterology and internal medicine microbiology, I wouldn’t have been able to see the importance of Robin’s observation. Then I might’ve gone off doing something else. There were lots of other interesting projects I could’ve done, but I chose that one. Luckily.Smith: Yes. But then, this is a very good point at which it’s the difference between learning and understanding. Again, because you need to learn enough to recognise the importance of the phenomenon, but not learn so much that you are totally committed to the paradigm, the existing paradigm. Therefore say ‘things can’t grow in the stomach. This is just impossible.’Marshall: That’s true. If you have to just be extremely sceptical of anything. The people have taught this now in school. I think this is something that’s happened in the last 10 years in most educational programs. Let’s teach the kids how to be sceptical, how to evaluate new data and reject the stuff that’s not proven and accept things that are proven or look for the evidence and then move on with a solid base rather than having all these very fuzzy bits of foundation knowledge, which have never actually been checked out. It is very sad that your grandchildren are questioning everything you want to tell them. You have to accept that they’re probably smarter than you are. Kids these days are totally fearless about technology which is nice. You can put them in front of any kind of a computer, and the next minute they’ll be on the web, they’ll find their favourite game they’ll be doing. There’s a game they’re all playing, which is where you construct these walls all over the place.Smith: Minecraft.Marshall: Yes, Minecraft.Smith: Yes. I’m suffering with that too.Marshall: I don’t know what my grandson’s plan is, but he probably wants to be like the world best Minecraft player at age nine or something like that. He’s good. There’s a chance he could do it, I think.Smith: Oh, goodness. Right. I better not introduce him to my eight year old because it sounds like my eight year old would be a bit phased by your grandson’s abilities.Marshall: It’s a careful balance though, because when I was a kid, because we had brothers and sisters and everybody was pretty busy just staying alive. If you look at what your mother used to do in those days of the washing, the cooking, getting the groceries and taking the kids here and there and walking up to the vaccine clinic, taking everything, taking half a day to do. You can see why kids in the fifties and sixties weren’t very well supervised compared with today. Nowadays every mother knows where her kid is within 10 meters at any second. They’ve got tracking devices probably. We used to get up to some mischief and do a lot of dangerous experiments. Luckily my brothers and I and my sister all got through in one piece. I think there were a lot of risky activities that went on when I was a kid that you probably wouldn’t let your kids do these days.*MUSIC* Smith: So that takes us straight into you and your personal risk. When you decide to drink a bacterial culture, you are the poster child for self-experimentation and kind of ignoring the risks.Marshall: Yes. Not many of us, maybe the others all died.Smith: How worried by the risk were you when you drank that culture?Marshall: I was worried. What had happened was that I had some animal studies planned where we were trying to infect animals, pigs, rats, etc, in the animal research area at Royal Hospital with the helicobacter. We had these plans. I had submitted an application for these experiments. In the application I said, ‘well, at the end, if it didn’t work in animals, we really have to move on and do a human experiment to see if the bacteria could infect humans because they seem to be human pathogens.’ That was like a throwaway line at the end of the research application that I hand in. That was done a year before I’d actually did the self-experiment. Obviously I’d had that in the back of my mind for at least a year and had discussed it with people, even my wife. But not actually recently when I did the experiment so it was done, finally, I decided I have to find out the result of this experiment. I have to get this information. Can this bug, which everyone said was probably a commensal and irrelevant, could it infect a healthy person and lead to all this gastric inflammation, which seemed to be, which could potentially be the underlying problem in people with ulcers? It was an important question. By the time that 18 months had gone by, we’d exhausted all other avenues of research. We didn’t really have cell cultures that we could experiment with very much. I said, ‘Okay, well, I have to do it on somebody, I should do it on myself, because nobody really could assess the risk apart from me. No one knows enough about it.’ All our work was still unpublished. I discussed it with Robin at some point. Then my boss in microbiology, I kind of threw away a few hypothetical lines to him at one day at morning tea, I think. Then I went ahead with planning the experiment, which was initially to get some endoscopy biopsies from myself to show there was no gastritis. I did not have helicobacter at the baseline. Then I chose a bacterium, which was susceptible to antibiotics. So I said, ‘well, it’s a good chance I could get rid of it.’ The third thing was that myself and a couple of groups in England had done some serum epidemiology, like serum surveys of blood donors. It could show that 30-40% of blood donors, apparently healthy people had helicobacter. They couldn’t even remember when they caught it. As far as I was concerned, there was a very good chance that it was going to be asymptomatic. Then we’ll see what happened. Would I get an ulcer eventually? So that when you think of all those, put all those facts in, as I think about it carefully the obvious thing would be to do human experiment. Then the next question was, if it’s such an important question, should I ask an ethics committee to make a decision on whether or not I can do it?Smith: Mhm.Marshall: Well, if they said no, I still would’ve done it.Smith: Yes. I mean, can they regulate? What could I do? Can they regulate self-experimentation? Are there regulations on it?Marshall: I have to say that they usually bail out. I haven’t, I’m not going to tell you what my current plans are, by the way.Smith: <Laugh>Marshall: But they usually bail out and let you do it right. Nowadays, I think they say we don’t know as much about it, but it’s just a risk you would take.Smith: Did you ask permission when you drank your culture, or did you just do it?Marshall: I just did it. My lab tech knew about it. I said, ‘Next Tuesday we’re going to, I’m going to drink helicobacter. Can you grow me up some plates of helicobacter?’ I turned up that I’d already had the endoscopy, of course. My boss had said to me, so at the beginning of my endoscopy list, which was starting at eight o’clock in the morning, so it’s 7:15. At 7:45 I asked my boss to pass the scope on me and take a few biopsies. He said to me, ‘Barry, I don’t know why I’m doing this, and I don’t want you to tell me.’ He went ahead and did it. But then straight away I had the endoscopy without any anesthesia and straight away did my endoscopy list. A few weeks later, I was then ready to drink the bacteria, which I cultured from a patient. I think it was a Tuesday morning, and I think it was about the 10th of July. I think it was 10th of July 1984 and I drank it.Smith: Yes.Marshall: And felt fine.Smith: But do you remember, was there a sudden moment of contemplation of backing out as the vial came to your lips?Marshall: I can tell you exactly what it was like. Can you imagine being in the army and they give you a bit of training on how to jump off a little wooden thing with your parachute strapped to your back. You get a feel for it a few times, and then the next minute you’re up in a plane and the doors open and they say, right hook on and jump. It was like that. It had been well planned, and statistically you were going to survive, should be fine, but it was completely jumping out into the unknown. I had no idea where it was going to go at that point. Obviously, if I became infected and developed gastritis, which is what happened, then I was going to follow that research lineup. If nothing happened, then that meant the whole question was a lot harder than I thought. I could be wrong. That would’ve meant if I continued in research, I would’ve had to put my head down for a few years and work harder on animal models, try to figure out what was going on. It wasn’t just going to be straightforward but because we had the result of gastritis bacteria were cultured and everything then it really did put a fire under the boiler, if you like, of my research. This does seem to be the way to go. Let’s follow it up, but let’s try out different antibiotics, et cetera. It was pretty exciting. But what came out of that study was the information about the acute h pylori infection. I know an awful lot about this now, but then nobody had described it. No one knew anything about acute h pylori infection. It didn’t really exist. When I was writing up that paper, I wrote a first draft. It was really just a prescription of the biopsy, the appearance with histology. I was rather short and I was putting it together. I showed it to my colleague John Armstrong, who was the electron microscopist. He said, ‘Barry, you’ve left a lot, a lot out of this’. I said, ‘well, what, what do you mean?’ He said, ‘Well, that week you took the bacteria, you looked terrible, and you had halatosis. You had such a bad breath.’ I said, ‘Well, hang on. My mother said I had a bad breath. My wife said I did as well.’ So I went back to the lab and asked the work colleagues, and they said, yes, but we were too polite, we didn’t like to tell you. I had a very lonely week when I did that experiment because I was doing other work, but everyone had moved out my lab into the next lab and was just leaving me there by myself. I was working late, and I would be sitting there in the lab all by myself, preparing samples at eight o’clock at night thinking, oh God, I can’t keep this up. It’s not much of a lie. The h pori was in there brewing, and then I started having vomiting attacks and everything, and I’m wondering, ‘well, this is a bit weird. I don’t usually do this. I wonder if it’s the bacteria’. So then I had the biopsies. I was a bit nervous about putting anything clinical into that paper because it’s very subjective. You’re just talking about yourself and saying, well obviously you would say that. There was a bit of that in it. That’s why the paper was written in the third person, that person did that. It wasn’t until about four years later that I owned up to the fact that it was me.Smith: That’s interesting. Four years, gosh. Was there any lasting damage to your stomach from the experiment?Marshall: I don’t think there was, but I did have vomiting attacks for a few days.Smith: Those long years of being disbelieved by the community at large. But on the other hand, being believed by quite a lot of patients who came to you for treatment. It must have been confusing in a way to be popular and unpopular.Marshall: Yes. It was a little bit frustrating because usually what would happen if you discovered a new treatment, if you discovered the cause of something that there was absolutely no treatment for, everyone would say, it’s a miracle. We’ll take this, we need something. But to discover the cause of ulcers and have a new treatment, treatment was rather complicated. On a background of, everybody thought they already had the answer anyway, was the acid blocking drugs and every year there was a new one. We had Zantac coming out, getting rolled out all through the eighties. At the end of the eighties, we had omeprazole coming out which was even stronger. That was going to be even better. It’s not like people were waiting around for helicobacter to be discovered. It was a bit frustrating for me that I’d really discovered the cause of ulcers for 10 years too late. If we’d done it in the seventies, well then it would’ve really been a miracle to be able to take amoxicillin or something. It’s a bit harder to get it accepted when there was no longer a super need for it. There was actually a need from the patients because they knew they were not better. But as far as the medical community was concerned, the wonder drugs had made such a difference that they stopped being concerned about ulcers.Smith: They’d ameliorated symptoms but couldn’t remove the underlying cause.Marshall: That’s right. The fact that patients had to keep taking these $3 a day medicines didn’t really affect the medical profession very much. In Australia, of course, the government paid for them. In America most people probably had them on their insurance or had to pay for them. I ended up in America at that stage, and there were people in America who didn’t have insurance, who were paying a thousand dollars a year for their drugs. I noticed a difference in the United States. People would come from miles to possibly find something that would cure them and get them off these expensive medications. There were a number of things like that that happened in the States because it was not socialised medicine. Whereas in Australia, and probably in the UK, it was all a bit muted because everybody could actually get something for free if they had an ulcer. In the United States, we used to have all kinds of people coming from different places. One of the interesting ones that turned up one day was a fellow who was a US Air pilot. Because he was a pilot, he’s not allowed to take any psychotropic drugs. One of these drugs was potentially metronidazole because in the fine prevented said, some people get neuropathy or hallucinations or something. He could not actually take a h pylori antibiotic treatment without stopping flying. He used to come down and have his ulcer checkup and his medication prescribed when he was on his Christmas holidays. I think he worked from out of Chicago or somewhere, but he used to secretly fly down to Charlottesville, Virginia, see me, get on the treatment, and then take it for two weeks. Then when Abeer was gone, he would then start working again at the end of his holiday. Interesting people like that just to turn up.Smith: Would you say that the impact of HP treatment on people was held back by that time? By if you like, vested interest in the other treatments?Marshall: I think it was, and there’s two ways it could happen. Obviously they could oppose it and say, we don’t believe it, but if as soon as they do that, they give it some oxygen, if you like, the credibility in that they are opposing it. The better strategy was what most companies adopted, they just would not comment on it. There were a few experts who would stick their neck out and say they didn’t believe it. Then they would get on the lecture circuit with opposed to me, and we would have debates at UCLA and different places about it. There was a lot of mileage in that. The best thing to do was just to continue on as if helicobacter never existed because there was so much money going into H two blocker research that the H two blocker and acid suppression information would swamp anything we could muster from helicobacter treatment studies. We would actually get a lot of publicity from small studies and from research meetings, far out of proportion to the millions of dollars that were being spent on the H two blockers and omeprazole in the eighties. But they probably did delay the rollout of Helicobacter treatment by five years, just by doing what they were already doing and ignoring it.*MUSIC* Smith: One slightly unusual aspect of this sort of global group of patients who came to you is that you were able to start this Helicobacter Pylori Foundation from donations you received from them.Marshall: I’d never thought of anything like that, but in the early nineties, as I was seeing some high flyers at the University of Virginia. One of the patients who said to me, ‘Oh, Dr. Marshall, can I make a donation to your research?’ And I said, ‘Sure, thank you very much’. I was thinking $50 or something, and he wrote out a check straight away for $3,000, which was fairly significant donation as far as I was concerned. I said, ‘thanks very much’. Then I had to spend weeks trying to figure out how to launder this money into my university research account without the dean taking 20% off the top. I then spoke to some colleagues. One of them was Dr. Steve, he’s now Chief Medicine University of Maryland. Steve said, ‘Barry should start a foundation, and then the money can go in there and you can spend it on whenever you want’. So I did that, and at the same time, the internet was invented. I was interested in that because of my electronics interests and computing. I contracted somebody, actually out of my own pocket, to start up a website. Then I had the Helicobacter Pylori Foundation registered as a tax exempt entity in the United States. Before people were really conscious of the value of the internet. I had an internet site in Virginia, which was the Helicobacter Pylori Foundation, putting out information about helicobacter. It was quite interesting that it really did have quite a take up. Pretty soon there was millions of people on America online who could access it. The reason I did it, because a lot of people were getting interested in helicobacter, and they would say, ‘Oh, Dr. Marshall, can you send us a couple of pictures of helicobacter? We want to do a story’. It became very repetitive then. I would say, ‘Just go to this website and this directory, and you get some pictures. There’s a picture of me, there’s a picture of Dr. Warren, the helicobacter etc’. Having it already meant that we actually were able to roll out lots of publicity about he back to Pylori on five minutes notice. Then we had some news stories, ABC news, CNN. Then someone did a foldout. There was a magazine in the Sunday newspaper called Parade that was distributed to 40 million homes. We did a helicobacter article there and put a link to a website on the bottom of it, had contact Dr. Marshall for small, for more information, send $10 and in a stamped addressed envelope, and we’ll send you some information about it and take your doctor. Then we had 40,000 letters. We only had a tiny little mailbox so if we didn’t pick up the mail for three days, the whole post office would be filled up with the cardboard boxes, mail for us. I suddenly realised the power of the internet. We probably got about 60 or $70,000 just from that one article, and funded a research fellow from Korea for a couple of years in my lab in Virginia. Since then, I’ve always kept that foundation going. That’s helico.com, and we have a quite an active forum there. Anybody can get on and post their symptoms, questions about antibiotics, et cetera. If they have a question that’s a bit technical, someone in my lab will try to answer it. If it’s a really a new thing or very tricky we’ll have a bit of a little meeting about the difficult questions on the site, and I’ve got about a hundred posts on that website, I think. It’s fairly up to date.Smith: A lot of people would be quite scared about opening themselves up to that kind of worldwide questioning, going to be deluged by stuff, never deal with it, but obviously you just take it in your stride.Marshall: It’s something that is a big responsibility. If someone asks a question about the side effects for an antibiotic, and if you look on the website, you can find things like this and whether they should take it with this or that drug, then you might see about a hundred words of a reply from me, whether bit of a reference at the end of it. You say, ‘Well, Dr. Marshall just knows that stuff’. But in fact, I probably spent four hours doing research on Sunday morning reading the articles. Might’ve called somebody. Last time I did it, I called somebody in Michigan at eight o’clock at night asking him about this paper he’d written. That it’s not something I’d do lightly. We try to give the right answers. The advantage to us is that we are receiving input from all around the world as to what’s going on in the particular country regarding Helicobacter. Obviously by looking at where we get hits from, on our website reports, we can see where people are searching for Helicobacter from. You can see that people in Florida have a lot more Helicobacter than people in Minnesota. If there’s anything new someone might be telling us about it, we learned that there’s a lot of hocus pocus and holistic naturopathy and stuff like that that goes on around the world. We are forever telling people that ‘No, garlic does not cure Helicobacter’. Questions like that.Smith: Thank you very much indeed. It’s been absolutely marvelous this conversation. I can’t leave though, without just referring to one famous incident, which is the fact that when you received your phone call telling you that you’d been awarded the Nobel Prize, you and [Robin Warren](https://www.nobelprize.org/prizes/medicine/2005/warren/facts/) were sitting together having a beer by the river. Maybe there’s somebody out there who can correct us, but I think it’s probably unique that the laureates had been sitting together. You did go for a beer together traditionally, or a dinner together traditionally on the day of the medicine announcement each year.Marshall: That’s true. People had been saying to us for about 10 years that we should win the Nobel Prize. It’s very important. I would say, don’t ever say that in public. It’s bad luck. I was concerned one way of never winning the Nobel Prize would be to talk about it. But we did know that it was an important discovery and it would be a candidate. Around year 2002, Helicobacter seemed to be getting lots of publicity. There was lots of interest in it from dairy, various international groups. Robin and I had won several big international prizes by then. Some Swedish person, I suppose said, ‘you know, Barry, I heard a rumour that your discoveries on the short list’. I said, ‘oh, that’s very nice. Let’s not talk about it. Change the subject’. At about 2002, I think we had a little conference on Helicobacter and Robin and I said, ‘Well, when they on announcement night, let’s go down the pub just together’, because we weren’t working together anymore. He was retired. I used to pick him up about four o’clock in the afternoon and take him down to the brewery pub on the Swan River, and we would have fish and chips and have a cup of big beers and then look on our phone or somewhere and listen to the radio, try and see if we could find out who won the Nobel Prize. That information would come out about five 30. It was just the right time, middle of the fish and chips. We’d stay there for about another hour, then I’d take him home and go home. We’d done that for about three years in a row. It seemed to me that the Helicobacter thing had totally peaked by then. It was about the fourth year that we had done it. That was 2005. We were sitting there just getting our fish and chips, and he had a pint of Guinness. I had my pint of Swan lager, I think, and actually the one I used to use drink is Emu export. Then his phone rang. Hans Jörnvall said to Dr. Warren, ‘I’m calling just to tell you that you’ve won the Nobel Prize, but there’s a big problem we can’t find Dr. Marshall. We’ve been calling his home. We’ve called his office. He’s nowhere to be found. What are we going to do? We have to announce it soon.’ Robin Warren said, ‘Oh, he’s here with me at the pub, we’re having a beer together’. He handed the phone over, and then they were able to tell me that I share the Nobel Prize with Robin. But Hans Jörnvall years later said that the committee was actually quite concerned about the fact that we were already celebrating before they’d told us.Smith: Yes, they must have thought there was a leak.Marshall: Yes. They thought we must’ve had the conference room bugged or something. They’re a little bit concerned about that, but I said ‘No. We always have a beer like that on Nobel Day’.Marshall: We still try to do it. We haven’t exceeded a couple of times because we’ve had a pretty heavy travel commitment and sometimes one of us is at a different meeting or different country. But it’s a fun tradition. We always enjoy each other’s company and we don’t take anybody else with us, usually just go by ourselves.Smith: Nice story. It’s been extremely kind of you to talk to me. I’m sorry it’s late evening there now. It’s been a joy. Thank you.Marshall: Okay. So if people have car accidents from going to sleep during the podcast, I’d disclaim any responsibility. It hopefully won’t happen.Smith: I sincerely doubt it. Anyway we talked about risk earlier. There’s always a risk, but I don’t think so. I don’t think so in this case.Marshall: Okay. Alright. Thanks very much, Adam.Brilliant: This podcast was presented by Nobel Prize Conversations. If you’d like to know more about Barry Marshall, you can go to nobelprize.org. Where you’ll find a wealth of information about the prizes and the people behind the discoveries.Nobel Prize Conversations is a podcast series with Adam Smith, a co-production of FILT and Nobel Prize Outreach. The producer for Nobel Prize Talks was Magnus Gylje. The editorial team for this encore production includes Andrew Hart, Olivia Lundqvist and me, Clare Brilliant. Music by Epidemic Sound. You can find previous seasons and conversations on Acast or wherever you listen to podcasts. Thanks for listening. |
| Telephone  interview | 0546=BM – Hello. Barry Marshall here.  – Hello, Barry. This is Joanna Rose from the Nobel Foundation. I’m making a recording for our Web pages.  – Oh, great!  – Congratulations to the Prize.  – Thank you.  – Did you expect it?  – I think … Well, Robin and I often have a beer …  – Yes?  – …down by the riverside at this time of year. But it’s more of a joke, and I think… Of course, it’s funny how things like this are such a surprise, but … I mean, of course, we would always dream about winning the Nobel, but we never really thought we’d … A thing like this, we could say it was an important discovery, but there are so many important things in medicine these days that … I could say that, if we never had won it, it wouldn’t necessarily be a disappointment. It’s just that there are so many other good discoveries out there, and hard workers.  – What does it mean for your work, do you think, now – from now on?  – I think my work’ll be a little bit disrupted. [laughter] But I think there some very exciting projects that I’m doing at the moment, and I think that I have to continue on with those, because that’s where the future of my … That’s where my interest is at the moment; I love doing this work. So it will just create some extra activities for me! So, I’m not sure what’ll happen. I think I’ll just have to float in the breeze, I guess … and see what happens.  – Your colleague, Robin Warren, he mentioned to me that nobody really believed you in this at the beginning.  – Well, it’s so entrenched that ulcers are caused by stress; and so, even now in the movies in Hollywood you still see people developing ulcers from stress. But I think most … Well, I suppose people that are educated haven’t heard about these bacteria that cause ulcers. But … it’s not as exciting as it was a few years ago, because so many people now are being cured and you don’t know people with ulcers any more. It’s becoming a rare disease in modern countries, Western countries. But, of course, in a lot of countries it’s still very common.  – When did you realise that you’d been awarded the Prize?  – Well, when we received a call from Sweden about an hour ago.  – So now you’re celebrating?  – Well, we’re not … We’re being very careful – we’re just having one glass of beer at the moment. And I don’t want to appear on television, intoxicated. Dr Warren and I, we’re very moderate in our activities and, usually, one beer is enough to keep us cheerful.  – For how many years did you make the jokes about the Prize?  – Oh … Well, the first time we … We first had a publication in *the Lancet* in 1984 …’83 or … it might have been ’83, and we made a joke then: we thought we’d probably win the Prize in 1986. [laughter]  – So it’s just 19 years later – it’s lost it’s kick!  – 19 years later! [more laughter] So we still enjoy it very much, and I visited Sweden a couple of years ago and I’m just looking forward to visiting again so much and showing my wife all the wonderful things we saw there.  – Well, you are so much welcome here. Hope to see you here in December. Thank you very much.  – Oh, yes. Thank you.  – Bye-bye. |
| Interview |  |
|  |  |
| ID | 0547 |
| Biographical | I was born on the 11th of June 1937, in North Adelaide, South Australia, the first child of middle-class parents. I am a fifth generation South Australian. South Australia is a charming state, a little overfull of the fact that, along with Victoria, it was settled by free settlers from England, who took part in a land investment program. There were no convicts. Elsewhere in Australia, the major cities began as prisons for Britain’s unwanted, when America became closed to them after the War of Independence. The original settlers arrived in 1836–7 and the beautiful city of Adelaide was chosen as the main settlement. It was imaginatively designed, with the main city square mile crossed by broad streets and surrounded by parkland. Adelaide rapidly expanded during the Victorian era, and by the end of the 19th century it was a bustling city of about 100,000 people.The Warrens migrated from Aberdeen in 1840. Their eldest son, my great grandfather John Campbell Warren, was a member of the local government, Captain of the Light Cavalry, and patriarch of a family of 16 children. He owned a large estate in the Adelaide Hills. At the turn of the century, he sent his sons to outback South Australia (Anna Creek) and Western Australia (Katanning) to open up huge areas for cattle and wheat. My father, Roger Warren, studied viticulture and became one of Australia’s leading winemakers.My mother’s ancestors migrated from England to Adelaide with the first settlers in 1836–7. My grandfather, Sydney Verco, belonged to a dynasty of doctors. The Verco family still make up many of Adelaide’s doctors. He died young, leaving my grandmother, Alice, with no income and four children to feed and educate. Somehow with the help of the extended family, she managed to send all the children to private schools. She scratched and saved to get enough money to send her son, Luke, through medical school. My mother, Helen, had desperately wanted to be a doctor, but could not be similarly financially supported. She eventually trained as a nurse instead. I cannot remember my mother ever pressuring me to study medicine, but somehow this always seemed to be my aim. We were all very proud of my uncle Luke Verco, who was a captain in the Army Medical Corps during the Second World War. I still have clear memories of him in his uniform. After the war, he became a country general practitioner, and my favourite uncle.My parents married during the depression. Life was not easy. When I was born, we lived at the seaside suburb of Brighton, which I only remember from photographs taken by my father. In 1939, we moved to my grandmother’s old home in the southern suburb of Unley. My earliest memories were of riding my little tricycle to a local private school, which would have roughly coincided with Japan’s entry into World War II. For me, the war was rather unreal. We knew it was something to do with the Japanese up north, who were bombing Northern Australia. I recall attending an exhibition of Japanese submarines caught in Sydney Harbour. There were books about our brave soldiers fighting Germans in North Africa. For children in quiet little Adelaide these were all faraway events, almost an adventure story.Other things that we saw, without really understanding them, were the almost total absence of cars, and the impossibility of getting electrical goods for the home. One car on our street used a ‘gas producer’, which burnt coke and produced carbon monoxide to fuel the motor. We used to watch these cars, with rusty black burners attached to the back, in some wonderment. A car near our home had a gas bag on top of the roof, as big as the car itself, filled with coal gas. Petrol was almost unavailable, but this had little effect on me. Food and clothing were rationed, but my mother seemed to be able to keep the family well fed and clothed, even if our idea of luxury was ‘bread and dripping’, made with fat and meat juices from the roasting dish, smeared on bread. When the war ended, we were able to buy a refrigerator. Previously, food was kept cool in an ice chest.During and after the war, I attended the local public primary school, Westbourne Park School. Education in those days was much more by rote than today, particularly learning how to spell columns of words and memorize multiplication tables. I suspect the balance now has tilted too far the other way. With the onset of calculators and then computers, arithmetic was no longer done in the head, although I never regret the ability. Rote learning was actually only a small part of our education – certainly not all of it, as the media often seems to suggest today. My children seemed to be expected to pick up spelling as they went along, reading and studying literature, but with the onset of increasing home entertainment they seem to read less than we did. We used to listen to the radio, and I made myself a crystal radio set, which enabled me to hear the radio in bed. My mother made sure that I could get any books I wanted, and I was an avid reader of all the usual boy’s adventure stories, both new and classic. I also used to read books about science.As I grew older, I obtained my first bicycle, which I used to ride to school and visit my friends. In those days, the Adelaide suburbs were remarkably safe. You hardly needed to lock the house to go out (although mother always did). There seemed to be no worry about children being attacked. There were still very few cars on the roads, and the idea that it was unsafe for children to ride alone was a generation away. I also used to amuse myself riding in the Adelaide foothills, sometimes picking wild blackberries (which my mother made into beautiful jam) or catching occasional ‘yabbies’ (the local wild freshwater lobsters). I watched my father take family photographs with his old Voitlander camera, and I finally persuaded him to buy me a Kodak box camera for my 10th birthday. I soon obtained developing dishes and printing paper, and my lifelong hobby of photography was definitely started.I was never good at sports at school, although I enjoyed a game of cricket (played at a pretty low level), but I did become more adventurous with my bicycle and camera, touring around the Adelaide Hills and taking landscape photographs. I was a bit of a loner, riding on my own and doing whatever I wanted, not having to worry about how fast or slow companions were. This did somewhat hinder my social skills, but no doubt made my eventual profession in pathology much easier.As I entered my teenage years, I began my secondary education. This was at the oldest school in Adelaide, St Peter’s College, the same school Lord Florey attended. At least two previous generations of Warrens went there. I found my father’s name carved into a desk and dated 1917. Life there was quite different from the local primary school. It was much more competitive. The best students were in the top level, with four levels in each grade (year). They had an arrangement similar to English league football, with the bottom students in each term exams being relegated to the class below. This happened to me once, to my extreme annoyance, and I vowed to return to level one and stay there. Most students who later attended university were in the top class. The curriculum there included English literature, two foreign languages (usually Latin and French), mathematics (my favourite subject), physics and chemistry. All were required for matriculation to the science oriented university schools such as medicine or engineering.Sport was an important part of the school curriculum. Unfortunately, I was never much good at it, and did not really enjoy it. However, I continued my weekend cycling and photography. I attended the school’s army cadet unit, where I learned army skills and, presumably, instant obedience. I particularly enjoyed the rifle shooting. Target shooting, which I learnt in the school cadets, became the primary sporting activity of my adult life.I matriculated from the school in 1954, gaining a Commonwealth scholarship. These scholarships were the initial attempt by the Commonwealth government to provide free tertiary education for the masses. I still think it was an excellent idea. There were just about enough scholarships to cover anyone who wanted to enter the major University schools, such as medicine or engineering, so most people attending the University were provided with free education. The situation is much more complex now, with the government paying the fees, but requiring them to be repaid by the students when they start earning money. About this time I had my first experience of girls. I only had brothers, and somehow my mother did not count. Girls had always been very distant and strange people, especially the snooty-looking ones who walked past our front gate on the way to the local catholic convent school. (I married a catholic girl from a different catholic school, who thoroughly agreed with my description above!) Just before matriculation, the students were expected to attend dancing classes and then invite girls to the annual school ball. At first this seemed a strange affair, trying to learn ballroom dancing with a lot of girls who seemed just as shy as me. However, we soon got the idea, and we began to have a lot of pleasure, with groups of boys and girls developing personal relationships. There was none of the ‘going steady’ culture, which seems to dominate that period in America, and certainly a generation later with my children. For us, it was all very easygoing and pleasant, nothing serious.  Also, during my matriculation year, an event occurred that was to mark most of my life. One morning, my mother found me unconscious on the back lawn. I recovered without apparent ill-effect, but some time later it recurred. I was soon diagnosed as suffering grand mal epilepsy. I was placed on phenobarbital, and then a variety of other drugs to try and control the seizures, but control remained imperfect. I was unable to obtain a driving licence, a major event for young people at that age. There were apparently numerous comments to my mother at the time from people, both professional, friends and relatives, who should have known better. Many apparently suggested keeping me at home, no university, definitely no medical school, and so on. Thank goodness, none of this filtered through to me at the time; it made life difficult and embarrassing enough as it was at that rather sensitive teenage period. Mother had enough sense to give me a free rein to do what I liked, and none of this was ever mentioned. It was only years later that I came to appreciate just how much my mother had gone through to support my independence and personal maturation. My cycling in the hills continued, never interrupted by epileptic attacks or by admonitions that it was ‘too dangerous.’ Apparently, mother was worried sick, but she never said a word about it.  I obtained entry to the medical school of the Adelaide University in 1955, and the next stage of my life began. The first year was a wonderful entry to the university environment. Much of the work was a repetition of the final year at school. There was far more freedom. For the first time, we learnt about responsibility; we could work or not, as we liked. The only difference was that at the end of the year, a pass or fail was on the student’s own shoulders. Help was always there, if we wanted it, but some of my colleagues revelled in the ability to do nothing. Luckily for me, I was enjoying the work too much to miss it. I particularly enjoyed botany and zoology, new subjects for me. I remember dissecting a frog and setting up its skeleton – my specimen showing a marked absence of any imagination, just bones glued to a piece of cardboard!  Both before and after starting university, I always read widely, including numerous scientific books and medical history books. Astronomy was a particular interest of mine at the time. I remember reading Fred Hoyle’s books about the universe. I read the Oxford Junior Encyclopaedia, all 12 volumes. I probably should have spent as much time reading textbooks! Unfortunately, while I found textbooks fascinating to read as my curiosity and interest dictated, when I had to learn them for exams, they tended to lose their charm.  Medicine began in earnest with the preclinical years two and three. I was at the medical school almost full-time. The medical school was set apart from the main university buildings and the direct association with the university during first year was largely lost. Most of our time was spent in the anatomy department dissecting a cadaver or learning bone and joint structure and attachments, then the inner organs and the brain. I have never regretted the chance to learn anatomy (and, in later years, pathology) in such detail, which today’s students do not have time for. While I do not remember all the anatomy, it soon comes back with a glance at Gray’s textbook.  We also learned physiology, biochemistry, pharmacology, embryology and histology. I illustrated my notes for the latter two subjects with full colour sketches from the practical classes, using purple and pink pencils for haematoxylin and eosin. In those days there was only a very simple range of available drugs and, though we did not realise at the time, pharmacy and pharmacology were very simple in comparison to what the students need to know today.  The next adventure began with the clinical years four, five and six. In those days, the Royal Adelaide Hospital was the only general teaching hospital in South Australia. In both its scattered buildings and in its function, it was like a living museum. Some of the best wards were “temporary” buildings erected for World War I. One was named Verco Ward, after one of my mother’s uncles. Some of the more Victorian wards were like an old English moving picture; a huge barn-like structure, with beds along each wall and Sister at the high table at one end. Nobody argued with Sister, especially not the students, who were assigned patients to study and follow-up and were treated as the bottom of the social ladder (by everyone but the nurses – who wanted future doctors to marry – and the patients, who generally seemed to appreciate our attention). This three-year term of surgery, medicine and obstetrics and gynaecology, passed very quickly. There always seemed to be something new and interesting around the corner.  After medical school, life became very busy. We were called ‘Junior Resident Medical Officers’ – the equivalent of today’s interns. We actually were residents, living at the hospital residents’ quarters. A second government hospital opened, and I obtained a position there. At that stage in life, I was still very much an innocent, with very little it exposure to the outside world of finance and employment. All graduating medical students were given Junior Resident positions. These entailed about 100 to 120 hours per week working, with very little payment (I received £17–10 per week). Nevertheless, I was young and fit, and the constant work was actually very enjoyable. I bought a Leica M3 camera, and started to turn my hobby to professional subjects, photographing interesting clinical lesions. I do not think I have ever worked in a branch of medicine that I did not enjoy.  This period changed my life around again. The new hospital also provided a second obstetrics facility for the medical school. The obstetrics students lived in the resident’s quarters. Some of the students were young women. Their dormitory was near mine. We soon became good friends, and then I found myself very attached to one Winifred Williams. In fact, before we knew what had happened, I was spending all my spare time at her home. I remember one magic day, we wandered through the Botanic Gardens together, and it started to rain. Next thing we were arm in arm in the glasshouse, but we did not notice the flowers. Soon we were engaged and, a year later, married. For me, that was the biggest and best decision of my life, and so easy to do at the time.  I remained a little innocent about the big bad world outside. I did not realise how easy it was for us, with automatic positions provided – even if it was almost slave labour. Law students for instance, had to find clerking positions with private firms to complete their Articles of Clerkship, before they could practice at all. Other students had to find employment for themselves. I learned a valuable lesson at the end of my resident year. I assumed it was good manners to only apply for the second year position that I wanted, registrar in psychiatry. I did not get the post and found myself, to my surprise, unemployed. Luckily there were still a few positions available, and the one which appealed to me most was Registrar in Clinical Pathology at the Institute of Medical and Veterinary Science, attached to the Royal Adelaide Hospital.  In practice, ‘Clinical Pathology’ meant mainly laboratory haematology, which I thoroughly enjoyed. We had a good deal of freedom and responsibility. Although the usual work entailed reporting on blood smears and bone marrow, we had a wide range of other tasks, including examining faeces for parasites, examining urine and testing skin and nails for fungus. I put my drawing skills to work again, with detailed sketches of the various ova, amoebae and other organisms we saw. It really was an excellent all-round position to give one an overall feeling for pathology.  By the end of that year, Win graduated MB BS, and we had our first baby on the way. My pay was just about double what I earned in the intern year and, in pathology, my time of work was largely during the day. Life was settling into an enjoyable routine, if less adventurous. I had learnt about employment by them, and I applied for every position advertised at the end of the year. My first choice was Temporary Lecturer in Pathology at the Adelaide University, and I obtained the position. The work there consisted largely of morbid anatomy and histopathology, under the guidance of Professor Jim Robertson, which completed my overview of pathology and convinced me to go for membership of the (then) new College of Pathologists of Australia. Our baby boy, John, was born and we thought he was so wonderful, we had to start another. Of course, the baby soon started to crawl around, still wonderful, but a constant handful. By the time we realised our mistake, it was too late and our second baby was on the way. Win was still trying to fit in her intern year (it took her four years in bits and pieces to finish).  Melbourne Again I applied for every position possible, both in Australia and overseas. As it turned out, I was offered the position of Clinical Pathology Registrar at the Royal Melbourne Hospital. We moved to Melbourne, for one of the happiest periods of our lives. The pathology community in Melbourne was much bigger and more active than in Adelaide, and Sydney was only a short distance up the coast. Everything seemed to be at our fingertips. The work was similar to that at the Medical and Veterinary Institute two years before. A couple of years of clinical pathology under the tutelage of Dr David Cowling and Dr Bertha Ungar enabled me to pass the college exams in haematology and microbiology.  After this, I became Registrar in Pathology, for training in morbid anatomy and histopathology. All hospital deaths received a post-mortem examination, for which we were responsible each morning. After morning tea, we examined the day’s biopsy slides and presented them in a Grand Round, using a primitive old slide projector that was lit with two arcing rods of carbon. It really was quite an entertaining and educational show, with most of the surgeons present. Dr Doug Hicks, the head of department, would bark out questions to the resident and comments or answers to other questions. We had to work hard and fast, but Dr Hicks was an excellent teacher, and everybody learned from the show.  After four years in Melbourne, I finished my College membership and was a fully-fledged pathologist. Our second son, David, was born during our first year in Melbourne. Win somehow managed to fit in her intern year between babies. This was complicated by the unexpected arrival of twin sons, Patrick and Andrew, two years later. We had four sons under 31/2 years old! After this we decided that the Catholic Church methods of contraception needed assistance! Win was now able to practice, if only part time. This was very difficult, in an era when “women stayed home”. Part-time positions required a lot of talking, with promises to leave if she was not suitable (she was never asked to leave).  I was trying to obtain a position as pathologist at Port Moresby in Papua New Guinea, which was then in the process of obtaining independence from Australia. I thought I could obtain experience with some of the more exotic and unusual diseases. However, this had to be done through the Department of Foreign Affairs, and government red tape was extraordinarily slow. I was working in my room one afternoon, when a thickset man with a strong Germanic accent walked in and said, “You are working with me next year.” and walked out. There was no chance for explanation or argument. I discovered he was Professor Rolf ten Seldam, the Professor of Pathology at the University of Western Australia and the Royal Perth Hospital. He was apparently a man no one argued with, or at least not twice. So I gave the Department of Foreign Affairs one day to settle the position in Papua and when they failed to reply, I accepted the position in Perth, Western Australia.  Perth We arrived in Perth in January 1968. In Melbourne, we had no trouble renting a flat for the family. In Perth, there was nothing to rent, especially with four children. We had little money and no experience of buying property. Luckily, our first real estate agent was a good choice. He found us a good house to buy and a rental property in the interim. What I had not realised was that he told the owners that I was ‘the new doctor at the Royal Perth’ – quite true, but the owner thought he meant the new medical superintendent, who had received a good deal of newspaper publicity, and not just the junior pathologist! Life quickly settled down.  Pathology at the Royal Perth Hospital was totally different from Melbourne. We went along at a much more leisurely pace, but with a much more flexible timetable. We did less work, but it seemed to take longer to do it. Perth was a small and isolated community. It has doubled in size over the last 30 years, with a population now of over one million. These days, most pathology training in Australia is in a single specialty. In Perth, this had always been the case, perhaps because of a lack of positions for training, other than haematology or morbid anatomy. Trainees were encouraged to keep the same position. In contrast, the eastern states, with most of Australia’s population in one quarter of the continent, provided numerous training positions in all branches of pathology. General training was considered to be the norm, to give a broad base in all branches of pathology, before specialising in one area, as I did. I think this helped me later when dealing with *Helicobacter*, but it made me something of an oddity to my colleagues in Perth, who had all specialised in their particular branch of pathology from the start, giving them an in-depth knowledge on a narrow base.  In 1970, our last child, Rebecca, was born, our first daughter. Since Win only had sisters and I only had brothers, our knowledge of the difference between boys and girls was strangely superficial. Somewhat to our surprise, with no pushing from us, our daughter was quite different from the boys. Where they enjoyed running around in the dirt and pulling things to pieces, she would sit inside playing with dolls. After this, Win managed to get more work, and became quite an experienced general practitioner. She decided to specialise in psychiatry, and was accepted into the college training scheme, which took most of her time into the early 1980s.  Helicobacter During the 1970s, I wrote up a few interesting cases and developed an interest in the new gastric biopsies that were becoming frequent. I also attempted to develop improved bacterial stains for use with histological sections, as I describe more completely in my Nobel lecture. Then, in 1979, on my 42nd birthday, I noticed bacteria growing on the surface of a gastric biopsy. From then on, my spare time was largely centred on the study of these bacteria. Over the next two years, I collected numerous examples and showed that they were usually related to chronic gastritis, usually with the active change described by Richard Whitehead in 1972. I attempted, with some difficulty, to obtain a negative control series, by collecting cases reported as normal gastric biopsies. This was more difficult than I expected, because all gastric biopsies were coded the same, wherever they came from in the stomach. Almost all so-called normal biopsies were from the corpus. Normal biopsies from the gastric antrum were very rare, but I eventually found 20 examples, and none showed the bacteria. With this material available, I began to prepare a paper for publication.  In 1981, I met Barry Marshall, and we agreed to undertake a more complete clinico-pathological study. He could cover the clinical aspects and provide improved biopsies, specimens for culture, clinical history and endoscopy findings. This resulted in our papers of 1983 and 1984, linking the infection to duodenal ulcer and culturing a new organism. My letter to the Lancet in 1983 was a summary of the paper that I was preparing when I first met Barry Marshall. After this Barry and I continued our association, but he moved to the Fremantle Hospital. I was involved with the pathology related to several studies: Professor Goodwin, improving the accuracy of culture to diagnose the infection; Dr Ivor Surveyor, producing the breath test for diagnosis; and doctors Marshall and Morris, attempting to fulfil Koch’s postulates to demonstrate that the bacteria was a pathogen.  Winifred, who was much more literate than me, used to read our papers. She was able to point out clichés or excessive jargon, and suggest ways of making the work more widely readable. Before I met Barry, Win was the only person to accept my work and encourage me. Considering that much of this work was done after hours or at home, thereby stealing her husband, she had every right to be annoyed. Particularly as she was a doctor, and knew the standard teaching that nothing grows in the stomach, and therefore that I was trying to prove the ‘impossible.’ As a psychiatrist, she could have suggested I was mad. But she stood beside me and helped me when no one else would.  My last major work was the pathology for a large study by Barry Marshall *et al.* to show the effect of eradicating the bacteria on the relapse rate of duodenal ulcer. The study extended over seven years. It clearly showed that, after successful treatment of the infection, recurrence of peptic ulcer was rare; otherwise, it was usual. For me, the study provided a wealth of material to study the associated pathology. It soon became clear that active gastritis was very closely related to the infection. Treatment of the infection produced a very rapid and complete resolution of the active changes in the surface epithelium. Other changes, including lymphoid infiltration of the stroma and some epithelial changes, disappeared more slowly or not at all. The active changes varied considerably. The classic severe changes described by Whitehead were present in about 10 to 20% of cases. At the other end of the spectrum, some biopsies showed only occasional single intraepithelial polymorphs. These epithelial changes were almost absolutely related to the infection. With experience, I found the same features in the mucosa from the corpus, usually much more mild, superficial and focal than the antrum. Finally, the duodenal ulcers seemed to be distal pyloric ulcers rather than true duodenal ulcers. They appeared to arise in the distal pyloric mucosa, or perhaps the gastroduodenal junction.  By 1990, our findings began to be recognised by the medical community. We started to receive increasing numbers of honours and requests for attendances at meetings and lectures. It had been an interesting decade. After our initial publications in 1983–84, a wealth of further studies appeared, most of them apparently just repeating our work, with similar results. No one proved we were wrong. Yet in spite of this, no one but patients and local general practitioners appeared to believe our findings. Many patients demanded treatment, and some GPs were very keen to treat them. Otherwise, it seemed that only our wives stood beside us.  In 1996, I was invited to Japan for a lecture tour. The following year, a three-month tour of Germany and adjacent countries was arranged by Manfred Stolte and Hansjörg Meyer. This provided us with some real recognition for our work, and it seemed the fighting was over. The tour was a wonderful working holiday for Win and me. However, soon after our return, Win experienced difficulty eating, and investigation showed duodenal obstruction due to an inoperable pancreatic carcinoma. Win gradually deteriorated and died four months later. After spending this time caring for her, I decided the time had come to retire.  At first, I spent most of my time trying to return to my hobby, photography. I intended to print my own pictures, using today’s improved digital technology. The early results were interesting, although more complicated than I had expected. Digital pictures only provide a narrow band of information. Only 256 tones are available for each colour. Outside this range is either total black or total white, with no information. This is quite unlike photographic film, which shows a flattening of the curve at each end of the tonal range, with an almost continuous variation still present in light and dark areas. I had to put this project aside to try and digitise all my old publications, microphotographs and other works, since I was receiving many requests for them. Now I have to put that aside, because the Nobel Prize has brought a stream of requests for my presence at meetings and presentations. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0547 – Hello?  – Hello. Is this Robin Warren?  – Speaking.  – Hello. My name is Joanna Rose. I’m calling from the Nobel Foundation in Stockholm. And we have web information about Nobel Prizes. Have you seen it?  – I haven’t seen it. But I got a phone call about an hour ago, from Stockholm, about it.  – My congratulations to the Prize …  – It’s only just starting to sink in, so …  – Do you think it’ll have any consequences for the future, for you?  – Well I don’t know about the future. [laughter] I think the future … It just depends what happens – I don’t know.  – Well, I hope you will come to Sweden.  – We’d love to come to Sweden.  – I was thinking about … Do you think it means any special responsibilities or any change in the direction of medicine?  – That’s what we did actually … I mean nobody believed that there were bacteria in the stomach until I saw them there. And then it took a long time to convince everybody that they were there. It took about fifteen years before it started appearing in the textbooks.  – I understand. How did that feel – that nobody believed you?  – You know, I didn’t really mind all that much; it was a bit annoying. But I kept on with my work because I knew I was right, because I’d seen them there, you see? The trouble was, I could see them, but other people – unless I showed them to them – they couldn’t see them, you see.  – How could you present your research?  – It’s easy enough to see when you … The thing is that medical … Medicine, before I saw them, was, going by the standard methods of teaching: nothing grew in the stomach – when you swallowed bacteria it was sterilised in the stomach, so it didn’t get through the intestines. Nothing grew in the stomach. And that was something that has been taught to the students for a hundred years.  – And how did you realise that it wasn’t true?  – Well, I saw the bacteria there. That’s all. And once I’d seen them, they were easy to find.  – Did you swallow them?  – No. I didn’t do that – Barry did. Barry swallowed them.  – Barry did it?  – Yes. I was sort of infected so I couldn’t do it. But Barry, he swallowed them to see what happened, and got very bad gastritis.  – So, he was the study object?  – Well actually, he was one out of the team then, so he did it. And now he’s still working. I’m retired now.  – I think … Is he with you there?  – He’s right here. Just a second. If you want to …  – It would be nice to meet you here in Stockholm in December.  – All right. I’ll pass you over in a minute; he’s on the phone now.  – Hello?  – Hello. Barry Marshall here … |
| Interview |  |
|  |  |
| ID | 0548 |
| Biographical | New York City is my world. I was born in Brooklyn, the first child of immigrant parents whose education was disrupted by the Nazi invasion of Poland. Although not themselves learned, my parents shared a deep respect for learning. I grew up in a home rich in warmth, but empty of books, art or music. My early life and education were centered on the streets of Brooklyn. Stickball, baseball with a pink ball and broom handle, and schoolyard basketball were my culture. In stickball, a ball hit the distance to one manhole cover was a single, and four manhole covers, a home run, a Nobel Prize. My father was a tailor. My mother, although quick and incisive, did not direct her mind to intellectual pursuits and I had not even the remotest thought of a career in academia. I was happy on the courts. In those days, we worked at a relatively young age. At eleven, I was a messenger, delivering false teeth to dentists. At twelve, I was laying carpets, and at thirteen, I was serving corned beef and pastrami in a local delicatessen. Vladimir, the Russian chef, was the first to expose me to Shakespeare which he recited as we sliced cabbage heads for coleslaw.My local high school had the best basketball team in Brooklyn but the Principal of my grade school had a vision different from my own and insisted that I attend Stuyvesant High School, far away in Manhattan. Stuyvesant High advertised itself as a school for intellectually gifted boys but had the worst basketball team in the city. I was unhappy about the prospect of attending for it seemed antithetical to my self-image. Shortly after I entered, however, my world changed. I embraced the culture and aesthetics of Manhattan. The world of art, books and music opened before me and I devoured it. In school, I heard bits of an opera for the first time. I remember it distinctly, the Letter Duet from Mozart’s *Marriage of Figaro*. The next night I attended Tannhäuser at the Metropolitan Opera and thus began a love affair, bordering on an obsession, that has had no end. Twice a week, I stood on line for standing room tickets at the Metropolitan Opera where I was exposed to a cult of similarly obsessed but far more knowledgeable afficionados who taught me the intricate nuances of this rich genre. The great Italian tenor, Franco Corelli, would serve us coffee as we waited and the diva, Joan Sutherland, would invite us backstage.On other days, I would read in a most beautifully appointed place, the Reading Room of the Central New York Public Library on 42nd Street. One passes the pair of sculpted lions, ascends a flight of stairs into a huge high-ceilinged room of impressive silence where I read incessantly without direction but with a newfound fascination that made up for years of illiteracy. I met a coterie of library dwellers, men and women of New York, who spent all of their days in the Reading Room. I did not know who they were or how they came to be there, but they had an insight and understanding of literature that amazed and still perplexes me and they were my teachers. This was New York for me, a city of the culturally obsessed that opened up before me and framed my new world.To support a seemingly extravagant life for a young high school student, I worked. I used my skills as a waiter in a delicatessen in Brooklyn, to wait tables in the cafes and nightspots of Greenwich Village. In the sixties, the Village was the home of the beat generation that through music and poetry and ultimately protest translated discord into meaningful changes in both America and the world. Stuyvesant High School was on the fringe of Greenwich Village and some of its teachers were artists, writers, performers who fueled the politically-fired student body, many the sons of Marxist immigrants. With this array of artistic faculty Stuyvesant nourished my new and voracious appetite.But old worlds die hard. I continued to play basketball in high school and this led to a most memorable and humbling experience. I came onto the court as the starting center, and the center on the opposing team from Power Memorial High School lumbered out on the court, a lanky 7 foot 2 inch sixteen year old. When I was first passed the ball, he put his hands in front of my face, looked at me and asked, “What are you going to do, Einstein?” I did rather little. He scored 54 points and I scored two. He was the young Lew Alcindor, later known as Karim Abdul Jabar, who went on to be among the greatest basketball legends and I became a neurobiologist.My decision to remain in New York and attend Columbia College revealed the provincial but endearing quality of my family. When I chose to accept a gracious scholarship offered by Columbia, my father was disappointed. It was a fact well known that the brightest children of Brooklyn immigrants attended City College. My freshman year at Columbia, I lived with abandon. The opera, the arts, the freedom, the protest left little time for study. In the first semester, I met a student from Tennessee, Kevin Brownlee, who remains a dear friend and is now a Professor of Medieval French at the University of Pennsylvania. Brownlee urged me to redirect this intensity to learning. The world of the arts will remain, but my time at Columbia University was limited. Once again, a new world opened before me. With Kevin as my guide, I became a dedicated, even obsessed, student. My life was spent in a small room lined with volumes of Keats’ poetry at the Columbia Library and I immersed myself in my studies. The study of literature at Columbia in the sixties was exciting in the presence of the poet, Kenneth Koch, the critics, Lionel Trilling, Moses Hadas, and Jacques Barzun. It was largely chance, however, that led me to biology.To support myself in college, I obtained a job washing glassware in the laboratory of Bernard Weinstein, a Professor of Medicine at Columbia University. Bernie was working on the universality of the genetic code. The early sixties was a time shortly after the elucidation of the structure of DNA and the realization that DNA is the repository of all information and from which all information flows. The genetic code had just been deciphered and the central dogma was complete. I was fascinated by the new molecular biology with its enormous explanatory power. I was a terrible glassware washer because I was far more interested in experiments than dirty flasks. I was fired and was rehired as a Research Assistant and Bernie spent endless hours patiently teaching this scientifically naïve, but intensely interested young student. I was torn between literature and science. Dubious about my literary ambitions and fascinated by molecular biology, I decided to attend graduate school in genetics.My plans were thwarted by an unfortunate war and to assure deferment from the military, I found myself a misplaced medical student at Johns Hopkins University School of Medicine. I entered medical school by default. I was a terrible medical student, pained by constant exposure to the suffering of the ill and thwarted in my desire to do experiments. My clinical incompetence was immediately recognized by the faculty and deans. I could rarely, if ever, hear a heart murmur, never saw the retina, my glasses fell into an abdominal incision and finally, I sewed a surgeon’s finger to a patient upon suturing an incision. It was during this period of incompetence and disinterest that I met another extremely close friend, Frederick Kass, now a Professor of Psychiatry at Columbia University. Fred was an unusual medical student, a Texan with a degree in art history from Harvard, who remains a kindred spirit.It was a difficult time, but I was both nurtured and protected by Howard Dintzis, Victor McCusick, and Julie Krevins, three professors at Johns Hopkins who somehow saw and respected my conflict. Without them, there is little question that I would not have been tolerated but they urged the deans to come up with a solution. I was allowed to graduate medical school early with an M.D. if I promised never to practice medicine on live patients. I returned to Columbia as an intern in Pathology where I kept this promise by performing autopsies. After a year in Pathology, I was asked by Don King, the Chairman of Pathology, never to practice on dead patients.Finally, I was afforded the opportunity to pursue molecular biology in earnest. I joined the laboratory of Sol Spiegelman in the Department of Genetics at Columbia University. Spiegelman was a short, incisive, witty man with a tongue as sharp as his mind. Spiegelman was the first to synthesize infectious RNA *in vitro* and this led to a series of extremely interesting and clever experiments revealing Darwinian selection at the level of molecules in a test tube. Sol recognized the importance of the early RNA world in the evolution of life and had recently turned his laboratory to a study of RNA tumor viruses. An immediate bond formed between us and Sol taught me how to think about science, to identify important problems, and how to effect their solution.Although I felt a growing confidence in my abilities in molecular biology, I was naïve in other areas of biology, notably biophysics. Importantly, I had a sense early in my career that my interest in biology was eclectic and that I would need a concomitantly broad background to embrace the different areas of biology without trepidation. I left to begin a second postdoctoral fellowship at the National Institutes of Health, working with Gary Felsenfeld on DNA and chromatin structure. Since I entered medical school to avoid the draft, I had a military obligation that was fulfilled by my years at the NIH and was endearingly termed a “yellow beret.” Gary was great, but the NIH was alien, a government reservation with a fixed workday. As a night person, I found it strange and at some level difficult since I arrived at noon after all the parking spaces were occupied, left at midnight and accumulated an increasing number of parking tickets. In the midst of a molecular hybridization reaction, I was arrested by two FBI agents (the NIH is a federal reservation) for 100 summonses for parking violations.As a fellow in Felsenfeld’s lab studying how chromatin serves to regulate gene expression, I formed close friendships that continue to the present. On the beach at Cold Spring Harbor, I sat with Tom Maniatis and Harold Weintraub and talked about chromosome replication and gene expression and within a few hours a bond formed, a respect for one another and for one another’s thinking, that has lasted for thirty years. Hal, unfortunately, died ten years ago of a brain tumor, but his warmth, his creativity persist.Sol Spiegelman invited me to return to Columbia as an Assistant Professor in 1974 in the Institute of Cancer Research. I was ecstatic to occupy a lab and office adjacent to his. Sol had many visitors in those years, and when he felt bored in a meeting he would excuse himself and hide in my office where we talked science until his visitors finally gave up and left. I was studying the structure of genes in chromatin and had the good fortune of participating in a revolution made possible by recombinant DNA technology. I spent a great deal of time with Tom Maniatis, who pioneered many of the techniques in recombinant DNA. Tom left Harvard for Cal Tech, because he was restricted from performing recombinant DNA experiments in Cambridge, Massachusetts. We learned how to cut and paste DNA, to isolate genes and to analyze their anatomy down to the last detail. We recognized that to understand gene control and gene function, however, required a functional assay. Within months of establishing my own laboratory in 1974, Michael Wigler, my first graduate student along with Sol Silverstein, a Professor at Columbia, developed novel procedures that allowed DNA-mediated transformation of mammalian cells. Michael, even at this very early stage in his career, was conceptually and technically masterful and within a few years he devised procedures that permitted the introduction of virtually any gene into any cell in culture. He developed a system that not only allowed for the isolation of genes, but also for detailed analysis of how they worked. We now had a facile assay to study the sequences regulating gene expression as well as gene function.Michael went off to the Cold Spring Harbor Laboratories and simultaneous with Bob Weinberg at MIT identified the mutant ras gene as the gene responsible for malignant transformation in many cancer cells. My laboratory went off in many directions, first identifying the regulatory sequences responsible for control of specific gene expression. At the same time, a fellow, Dan Littman, now a Professor at NYU, joined the lab interested in two molecules that characterize the major classes of T cells. Dan, along with a student, Paul Maddon, succeeded in exploiting the gene transfer to isolate these two molecules. As often in science, serendipity heightened the interest in these molecules: we demonstrated that one of these receptors, CD4, was the high affinity receptor for HIV, allowing attachment and infection of immune cells.This early work on recombinant DNA was a period of enormous excitement, for it led to a revolution in both thinking and technology in biology. It provided a new tool for the study of fundamental problems and spurred a new and valuable industry, biotechnology. We, who were involved at its inception, were perhaps a bit haughty, aggressive and proud, and were accused by many of playing “God.” As evidence, the press noted that “I baptized my first child, Adam.”Recombinant DNA aroused a good deal of passion and hostility. The notion of tinkering with life was thought to endanger life and this cry became one of the major indictments of modern biology. These experiments raised endless debate because the idea that genes can be taken out of one organism and introduced into the chromosome of another is by itself upsetting. The very notion of the performance of recombinant DNA was linked with the mysterious and supernatural. This conjured up myths that elicited intense anxiety. Recombinant DNA, it was feared, would permit biologists to alter individual species as well as the evolution of species. This controversy emphasized the fact that advances in science may indeed bring harm as well as benefit. In the case of recombinant DNA, as François Jacob said, “Apocalypse was predicted but nothing happened.” In fact, with recombinant DNA, only good things happened. At a practical level, the ability to construct bacteria replicating eucaryotic genes has allowed for the production of an increasingly large number of clinically important proteins. At a conceptual level, gene cloning has permitted a detailed look at the molecular anatomy of individual genes and from a precise analysis of these genes we have deduced the informational potential of the gene and the way in which it dictates the properties of an organism.At a personal level, the emergence of a new discipline, biotechnology, introduced me to a world outside of academia. This important excursion showed me that brilliance is not limited to universities. I met and remain very close to two dynamic leaders of technology development, Fred Adler and Joe Pagano. Despite disparate histories, we remain very close and they continue to fascinate me with lives quite different from that of a university professor.In 1982, I began to think about the potential impact of the new molecular biology and recombinant DNA technology on problems in neuroscience. Molecular biology was invented to solve fundamental problems in genetics at a molecular level. With the demystification of the brain, with the realization that the mind emerges from the brain and that the cells of the brain often use the very same principles of organization and function as a humble bacterium or a liver cell, perhaps molecular biology and genetics could now interface with neuroscience to approach the tenuous relationship between genes and behavior, cognition, memory, emotion, and perception. This thinking was the result of a faculty meeting at which [Eric Kandel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2000/index.html) and I overcame our boredom with administration by talking science. Eric was characteristically exuberant about his recent data that revealed a correlation between a simple form of memory in the marine snail, *Aplysia* and cellular memory at the level of a specific synapse. Molecular biologists had encountered cellular memory before in the self-perpetuating control of gene expression. This led to the realization that this was the moment to begin to apply the techniques of molecular biology to brain function and I would attempt to recruit Eric Kandel as my teacher.A courageous new postdoctoral fellow in my laboratory, Richard Scheller, now Director of Research for Genentech, was excited about embarking on an initial effort in molecular neurobiology in a laboratory with absolutely no expertise in neuroscience. Together with Richard and Eric, we set out to isolate the genes responsible for the generation of stereotyped patterns of innate behaviors. All organisms exhibit innate behaviors that are shaped by evolution and inherited by successive generations that are largely unmodified by experience or learning. It seemed reasonable to assume that this innate behavior was dictated by genes that might be accessible to molecular cloning. It was an exciting and amusing time with myself unfamiliar with action potentials and Kandel uncomfortable with central dogma. Richard Scheller exploited the techniques of recombinant DNA to identify a family of genes encoding a set of related neuropeptides whose coordinated release is likely to govern the fixed action pattern of behaviors associated with egg laying. A single gene, the ELH gene, specifies a polyprotein that is cut into small biologically active peptides such that individual components of the behavioral array may be mediated by peptides encoded by one gene.Watching the story unfold, observing the interface of molecular biology and neuroscience provided great pleasure. More importantly, this collaboration formed the basis of a continuing relationship with Eric Kandel, with his incisive mind, inimitable laugh and boundless energy. In 1986, neuroscience for me was made even richer when Tom Jessell came along. Tom joined the faculty at Columbia and was to occupy a lab adjacent to my own. Not surprisingly, the lab was not ready and I had the great pleasure of hosting Tom in my own laboratory and this forged a long-lasting scientific and personal relationship. Jessell, the understated British scientist with a wry wit and piercing mind, joined a fellow in my laboratory, David Julius, now at the University of California at San Francisco, and together they devised a clever assay for the isolation of genes encoding the neurotransmitter receptors. These experiments, which might have been the last performed by the hands of Jessell, led to the isolation of genes encoding the seven transmembrane domain serotonin receptor, 5HT1C, and more generally provided an expression system that permitted the identification of functional genes that encode receptors in the absence of any information on the nature of the protein sequence. With Kandel one floor above, and Jessell next door, there was no departure from neuroscience. I was surrounded and I did not want to escape. I was beginning to feel that neuroscience was indeed an appropriate occupation for a molecular biologist. To quote Woody Allen, a fellow New Yorker, “The brain is my second favorite organ.”In the late 1980’s I became fascinated in the problem of perception: how the brain represents the external world. I was struck by observations from animal behavior that what an organism detects in its environment is only part of what is around it and that part can differ in different organisms. The brain functions then not by recording an exact image of the world but by creating its own selective picture. Biological reality will therefore reflect the particular representation of the external world that a brain is able to build and a brain builds with genes. If genes are indeed the arbiters of what we perceive from the outside world then it follows that an understanding of the function of these genes could provide insight into how the external world is represented in the brain. Together with Linda Buck, a creative fellow in the lab, we began to consider how the chemosensory world is represented in the brain. The problem of olfaction was a perfect intellectual target for a molecular biologist. How we recognize the vast diversity of odorous molecules posed a fascinating problem. We assumed that the solution would involve a large family of genes and Linda Buck devised a creative approach that indeed identified the genes encoding the receptors that recognize the vast array of odorants in the environment. Linda came to me with the experimental data late one night, exuberant, and I fell uncharacteristically silent. There were 1,000 odorant receptor genes in the rat genome, the largest family of genes in the chromosome and this provided the solution to the problem of the diversity of odor recognition. More importantly, the identification of these 10,000 genes and their expression revealed an early and unanticipated logic of olfaction. Indeed, the subsequent use of these genes to manipulate the genome of mice has afforded a view of how the olfactory world could be represented in the brain, how genes shape our perception of the sensory environment. From that late night moment to the present, it has been a joy to watch this story unfold.It is this work for which Linda Buck and I share the profound honor and good fortune of having been awarded the Nobel Prize in Physiology or Medicine. But there are deeper, more human joys, two sons, Adam and Jonathan, my sister, Linda, a very close coterie of friends, and a new love. Watching, contributing to the growth of my children is not only moving but humbling and puts my intense life in science in perspective. Often this intensity, bordering on obsession, distracted me from fathering and this is a regret. But my sons have emerged from a frenetic teenage into very human college students, extremely unlikely to pursue a career in science. My sister remains a close and dedicated member of an increasingly small family. A new love, Cori Bargmann, a behavioral geneticist now at Rockefeller University, has entered my world. Her intensity for science hides a knowledge and passion for books, music, and art. I have learned much from her but most importantly, Cori has shown me how to combine intellectual intensity with humanity and warmth.Finally, the Nobel Prize was awarded to me not as a man, but for my work, a work of science that derives from the efforts of many brilliant students as well as from the incisive teachings of devoted colleagues. I take equal pride in the science that has been accomplished in the laboratory as in the scientists that have trained with me and are now independently contributing to our understanding of biology. I therefore feel that I can only accept the Nobel Prize in trust, as a representative of a culture of science in my laboratory and at Columbia University. I am deeply grateful for this culture. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview |  |
| Interview |  |
| Q19 | Welcome to meet the Nobel Laureates in Physiology or Medicine 2004, Richard Axel and Linda Buck. First of course like everyone else, congratulations to the prize. You have heard this millions of times in the past days I suppose. This is the afternoon, the day after the big event, so what about the big event yesterday, what are the most memorable moments of the day, Linda? |
|  | Linda Buck: The whole thing was very dramatic and unusual, and it was wonderful to have my family and friends there. It was a once in a lifetime experience.Richard Axel?Richard Axel: I thought that the whole day, the ceremony, the formalism of the ceremony and the grandeur of the evening added a spectacular dimension to what we do, and what we do is try and understand how the world works, how the brain works and to have our work, which we do on a daily basis, celebrated in so grand a fashion, really added a very nice dimension. |
| Q23 | One of the things that really strikes you when you read about your science is the huge proportion of one genome that is used for constructing the nose or the olfactory system. Linda Buck, how come, why do we use so much of our genome for the nose? |
|  | Linda Buck: I think the way evolution works is that if something happens and if it’s useful then it remains in the genome. I think that during evolution of the sense of smell, multiple genes were made, it was advantageous, and they were capped, and you see that some of the genes are disappearing, there are remnants of genes encoding candidate pheromone receptors in humans and those genes are for the most part intact in mice and most of them have become pseudo genes in humans. Now in addition to that though it does seem that in certain invertebrate organisms there are also very large gene families that are used for smell and so it does seem to be a strategy that has worked, perhaps been developed independently in different organisms … |
| Q23 | But happened to be exactly the same systems, in … |
|  | Linda Buck: Yes, but the genes are not really related, they’re genes that encode proteins of the same type but are really quite different. So it does seem to be a strategy that’s perhaps been developed independently several times. |
| Q23 | Was the sensory organ maybe the first … When you look upon evolution, the way to perceive, to react to the external world, chemotaxis came long before phototaxium and maybe phonotaxis if there is any phonotaxium in the biological world. Is that the right, that the smell, the senses of smell was the first one? |
|  | Richard Axel: Chemosensation as you say certainly is the first one. I mean back, every organism, even the most primitive and humble bacterium have to have a way to respond to sense what is in the world around them because that determines how they are going to survive, it determines what their food supply is, how they have to metabolise their food, it determines aversive environments. So all organisms have to have a way to sense the chemical environment and the way they sense the chemical environment has evolved and so we indeed sense it in a different way than does a bacterium but the principle of communicating and responding to the environment is very primitive. |
| Q44 | Anyhow, how is this perception of the chemical environment, how is it mediated into action, how can it be translated to action? What mechanisms is life using? |
|  | Linda Buck: I think in mammals and also in many invertebrate organisms the information travels through a series of relay stations, if you will, in the nervous system and that allows the information from hundreds or a thousand different receptors to be organised in progressively more sophisticated ways and also in different ways. In the mammalian cortex what we see is that there are distinct anatomical areas in the olfactory cortex that are getting information from the odorant receptor family in the nose and those different areas of the olfactory cortex send information to different areas of the brain. We think what maybe happening is that the information from the receptors is being organised, combined, or perhaps modulated in different ways in those different areas before being sent on to yet other brain areas. This parallel processing of information is something that is seen in other parts of the nervous system as well so you can take the same sensory information from the external world and then you can process it in different ways in different parts of the brain to use that information for different things. |
| Q44 | And how do the animals or we perceive all this process? Is it through emotions? |
|  | Linda Buck: The information is targeted to different parts of the brain and some of those structures in the olfactory cortex send information on to higher cortical areas, both directly and indirectly through the thalamus, but in addition there are some parts of the olfactory cortex that send information to the hypothalamus and certain parts of the amygdala and those are parts of the brain that control physiological effects, emotional responses and instinctive behaviours. In fact, we think that using the sense of smell, and using molecular approaches, we can gain access to neurons and neural circuits in those very primitive parts of the brain and perhaps begin to obtain information about the neurons and the neural circuits that control instinctive behaviours and emotions. |
| Q46 | Does that mean that the olfactory system is also sending signals to the brain that we are not aware of, through unconscious levels of our brain? What do you think Richard Axel? |
|  | Richard Axel: That’s a hard question to answer; I mean how do we know that there is the unconscious recognition of scent? We do know, as Linda pointed out, that smell is recognised by cells that project to different areas in the cortex and some of those areas, some of those areas are new brain, cognitive brain and others are old brain, emotive brain. One might think that the odours that activate emotive brain might illicit emotions and innate behavioural responses and neural endocrinal responses without the conscious awareness of those signals. For instance, in animals we know that certain odours can reorganise the time of puberty, can reorganise the menstrual cycle and can illicit or prevent mating. There are studies in humans which are far more difficult to control to suggest that there are olfactory driven changes in the menstrual cycle, there’s a very famous study out of Chicago suggesting that women in a dormitory tend to synchronise their cycles and that’s thought to be olfactory, but those studies are psychophysical not biophysical and they’re much more difficult to prove with certainty. |
| Q46 | What about more everyday life events, is it possible that fear can smell and happiness can smell? That we can register emotions in the room without being really aware of it? Is that a too spectacular question? |
|  | Linda Buck: People talk about it, I think more in literature than in science, the smell of fear and so on and I don’t know, I think maybe that has to do with components of human sweat or it’s not really, it’s not something that we investigate really and I suppose … |
| Q47 | Because in one of your Nobel lectures or Nobel symposia, you talk about your great interest in trying to elucidate how subordination maybe mediated through smells and also aggressiveness and … |
|  | Linda Buck: We are actually looking, using mice, we’re using odours that have particular effects on the animals, we’re just starting to do that now. We’re looking at activation in the brain by a fox odour that causes a stereotype fear response. We’re also looking at effects of different kinds of odorants on the behaviour of the animal and looking at parts of the brain that are activated and we do see that mice don’t like skunk odour any better than we do and there are quite dramatic behavioural differences between their responses to skunk, skunk, fox odour and vanilla so they’ll actually try to get to an input tube that’s, through which there’s vanilla odour and they try to hide from the skunk. They try to hide from the skunk and in response to the fox odour; they just become paralysed with fear. |
| Q47 | Do we know that useful things tend to be preserved throughout the biological fear and maybe … |
|  | Linda Buck: That’s right and it’s clear that in the hypothalamus … The hypothalamus is basically the major control centre of the brain, it’s very primitive, it’s there in animals, it’s there in human and it’s highly conserved in its structure and also in the genes are expressed there and in the neural circuits and most, if not all, instinctive behaviours and emotional responses are controlled by the hypothalamus. |
| Q47 | And the hypothalamus has a direct contact with the nose? |
|  | Linda Buck: There are inputs from, yes; there are inputs from the nose. The hypothalamus actually collects information from all sensory systems, from the other parts of the brain and from the body. It gets input not only from the nervous system, that of course connects the entire body but also through the bloodstream. It measures the temperature, it measures the composition of the blood, it measures sex hormone levels, it controls the menstrual cycle, it controls the stress response. So it’s basically the main control system and of course because odours can cause stress, fear, pheromones and maybe some odours can control sexual behaviour, we can use the olfactory system to try to gain information about those circuits and start dissecting the neural circuits and the individual neurons including the genes that they express, that control those very basic emotional responses and behaviours. That’s where we’re going next. |
| Q16 | Another fascinating information that comes from your science is how the olfactory system is translating scattered molecules of sense into an organised map in the brain, it turns into a physical map, Richard Axel, but who is watching the map inside your brain? How do you make sense out of a physical map from these molecules? |
|  | Richard Axel: That’s a central issue that neuroscientists would like to address and have been attempting to investigate for a very long time as you’ve heard me put it before. This is a central issue in all senses that is the way… There seems to be a conceptual thread that runs through the different senses and that is that in olfaction as well as in vision the image, whether it be a chemical in olfaction or a visual image in sight, is very complex and it needs to be deconstructed into its components before it can be re-established in the brain as something meaningful. So in vision for example, the individual components of a visual image, that is colour, movement, edges, form texture even at the level of the retina in the eye are deconstructed and carried to the brain by parallel pathways. They are relayed in different regions of the brain so there are regions of the brain that are responsive to movement and not colour, other regions responsive to edge and not movement and at some point, there must be an area which consists of ensembles of neurons that can put this information back together. Now the analogy to the olfactory system as a consequence of the efforts of a number of people including Linda, suggest that you transform chemical space into brain space in the very same way that a given odour, even a single molecular species in an odour, will have the capability of fitting into multiple different receptors and those receptors project to different points in the brain so that those points, the receptors that an odour can interact with and the points which they activate in the brain, form a signature and then as you point out, you’re left with the problem. |
| Q16 | Who is watching? |
|  | Richard Axel: The problem of who looks down on these points? Who listens to the music, who sees the activation? As I’ve put it before, it’s an old problem, it’s the problem of the ghost and the machine and philosophers have been addressing this problem now since Plato.Linda Buck: I think this is a challenge for neuroscience in the future and it’s been recognised for a very long time that we do not know how it is that neurons firing in different parts of the brain, active in different parts of the brain, somehow constitute a perception, a percept because it’s clear that not all the information is going to come together in a grandmother cell and when that cell is activated you think “grandmother”. There are indeed neurons that are activated through, in many different parts of the brain and somehow that constitutes a cohesive perception. |
| Q16 | But do you really think … |
|  | Linda Buck: And there’s nobody looking, it’s the way it works. There’s no one who will be looking, it’s the way the brain works, and I think that it is a scientific problem in terms of how physically that might happen but it’s also a philosophical problem, a conceptual problem because I think it’s difficult for scientists to conceptualise how it is that neurons that are dispersed in different parts of the brain could form a percept and it could be that it’s just going to take some kind of a conceptual or philosophical step for people to say, That’s not a problem, we accept that. |
| ID | 0549 |
| Biographical | I was born in 1947 in Seattle, Washington, a city surrounded by mountains, forests, and the sea. My mother was the daughter of Swedish immigrants who had come to the US in the late nineteenth century while my father’s family had Irish roots on one side and ancestors extending back to the American Revolution on the other. I was the second of three children, all girls. My mother was a homemaker who was exceptionally kind and witty and loved word puzzles. My father was an electrical engineer who, at home, spent much of his time inventing things and building them in our basement. It may be that my parents’ interest in puzzles and inventions planted the seeds for my future affinity for science, but I never imagined as a child that I would someday be a scientist.During my childhood, I did the things that girls often do, such as playing with dolls. I was also curious and easily bored though, so I frequently embarked on what were to me new adventures. Aside from school and music lessons, my life was relatively unstructured and I was given considerable independence. I learned to appreciate music and beauty from my mother and my father taught me how to use power tools and build things. I spent a lot of time with my maternal grandmother, who told me magical stories about her girlhood in Sweden and, to my delight, taught me how to sew clothes for my dolls. I was fortunate to have wonderfully supportive parents who told me that I had the ability to do anything I wanted with my life. They taught me to think independently and to be critical of my own ideas, and they urged me to do something worthwhile with my life, in my mother’s words, to “not settle for something mediocre”. I realize now that I internalized those lessons and that they have influenced my work as a scientist.I received my undergraduate education at the University of Washington, which was only a few miles from our home. I had always wanted to have a career in which I would help others, so I initially decided to major in psychology, thinking that I would become a psychotherapist. Over time, my interests expanded and I entertained a variety of different career possibilities. However, none seemed ideal and I was reluctant to embark on something that might prove to be inappropriate. Over the next several years, I intermittently traveled, lived on a nearby island, and took more classes in Seattle. I finally found my direction when I took a course in immunology, which I found fascinating. I would be a biologist.Dallas In 1975, I began graduate school in the Microbiology Department at the University of Texas Medical Center in Dallas. The department had recently undergone an expansion in the area of immunology, making it a major center in this still young area and a stimulating place to learn. I had done a small amount of research at the University of Washington, first in psychology with Walter Makous and then in immunology with Ursula Storb, but it was in Texas that I truly learned to be a scientist. I had a wonderful thesis advisor, Ellen Vitetta, who demanded excellence and precision in research, habits that I believe are important to learn as a student. For my thesis, I compared the functional properties of subsets of B lymphocytes that differed in the class of cell surface immunoglobulin that they used as antigen receptors. In this work and much of my subsequent work, I thought in terms of molecules and the molecular mechanisms underlying biological systems, and sought to gain insight into those mechanisms in my experiments.New York In 1980, I moved to Columbia University in New York City to do postdoctoral work in immunology with Benvenuto Pernis. As a graduate student, I had become fascinated with the unexplained requirement for major histocompatibility complex (MHC) proteins in immune responses, a mystery that was later solved. I decided to explore this puzzle, focusing on class II MHC proteins found on the surface of B lymphocytes. I found that, contrary to expectation, the MHC proteins rapidly accumulated inside these cells when they were activated. My further experiments indicated that they were being internalized from the cell surface and were probably being recycled to it. It was known that antigen is endocytosed with antigen receptors and then degraded. One possibility raised by the internalization and apparent recycling of MHC molecules was that, following internalization, they might be targeted to a specialized microenvironment where they could interact with degraded antigen. The MHC-antigen complexes might then be exported to the cell surface for corecognition by T helper cells.By this time, it had become clear to me that to study molecular mechanisms underlying biological systems, which is what interested me, I needed to learn the recently developed techniques of molecular biology. To this end, I moved to the laboratory of Richard Axel at Columbia University. Richard had begun to work in the area of neuroscience several years earlier through collaboration with [Eric Kandel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2000/index.html), who was also at Columbia. Their collaboration had focused on molecular studies of the nervous system of *Aplysia*, a sea snail. This was the model organism that Eric had used in many of his studies of learning and memory, for which he received a Nobel Prize in 2000. Perhaps not surprisingly, I was interested in searching for genes encoding neuronal cell surface receptors. However, at that time, Richard wanted to continue studying *Aplysia*, so I agreed to a project in which I would try to develop a technique for cloning genes expressed in one *Aplysia* neuron, but not another. After spending a short time learning molecular techniques from Jim Roberts, a student in the lab, I started my *Aplysia* project. Eric Kandel’s group showed me how to isolate giant *Aplysia* neurons that had been assigned names and could be identified by their locations and, within a relatively short time, I began to uncover genes that were differentially expressed among *Aplysia* neurons.While studying a neuropeptide gene expressed in neuron number R15, I discovered that the gene was also expressed in some other neurons, but that its primary transcript was alternatively spliced in different neurons to give different polyproteins. The two polyproteins could generate two different combinations of peptides in different neurons, suggesting a way to produce physiological or behavioral programs with partially overlapping components. While working on the neuropeptide gene, I encountered numerous technical challenges that increased my knowledge of molecular biology and honed my abilities. During this period, I learned a lot of molecular biology from Richard and other members of his lab. I also got to know Eric Kandel, who has continued to be a wonderful source of inspiration and encouragement for me over the years.From my first introduction to neuroscience, I had been fascinated by the brain’s cellular and connectional diversity. In parallel with my *Aplysia* experiments, I sporadically tried to find a way to scan the genome for genes that had undergone gene rearrangement or gene conversion in neurons, thinking that genes that showed this characteristic might be involved in the generation of neuronal diversity. One method that I devised showed promise in *Drosophila*, but was not sensitive enough for the much larger genome of a mammal, which is what interested me. Nonetheless, these efforts were a great source of creative enjoyment for me as I proceeded with the more mundane task of searching for minute alternative exons in the *Aplysia* genome.I was grateful that Richard was tolerant of my high-risk endeavors. He was an unusual mentor in that he gave people in his lab extensive independence in charting their own course once they had established themselves. During this time, I had many colleagues at Columbia with whom I enjoyed long discussions about science. Among these were George Gaitanaris, who has remained a close friend over the years, and Tom Jessell and Jane Dodd, neuroscientists from whom I learned a great deal about neural development.As I was nearing the end of my *Aplysia* project, I read a paper that changed my life. It was a 1985 publication from Sol Snyder’s group that discussed potential mechanisms underlying odor detection. This was the first time I had ever thought about olfaction and I was fascinated. How could humans and other mammals detect 10,000 or more odorous chemicals, and how could nearly identical chemicals generate different odor perceptions? In my mind, this was a monumental puzzle and an unparalleled diversity problem. It was obvious to me that the first step to solving the puzzle was to determine how odorants are initially detected in the nose. This meant finding odorant receptors, a class of molecules that had been proposed to exist, but had not been found. I decided that this is what I had to do as soon as my neuropeptide work was completed.In 1988, I embarked on a search for odorant receptors, staying on in Richard’s lab for this purpose. In a recent commentary in the journal *Cell*, I described what was known about odor detection at that time and the approaches that I tried in the quest to find the elusive odorant receptors. In short, it was known that odorants depolarize, and thereby activate, olfactory sensory neurons in the nose. Although there were varied proposals as to what kind of molecules might interact with odorants, there was compelling evidence that olfactory transduction involved G-protein induced increases in cAMP. After trying several different approaches, I identified the odorant receptor family by designing experiments based on three assumptions. First, since odorants vary in structure and can be discriminated, there would be a family of varied, but related odorant receptors, which would be encoded by a multigene family. Second, odorant receptors would be at least distantly related to the relatively small set of G protein coupled receptors whose sequences were known at that time. And finally, odorant receptors would be selectively expressed in the olfactory epithelium, where olfactory sensory neurons are located. It took some time to devise and develop the methods I used in my search, but in the end they succeeded. Looking at the first sequences of odorant receptors obtained from rat, I was moved by Nature’s marvelous invention. This work showed that the rat has a multigene family that codes for in excess of one hundred different odorant receptors, all related, but each one unique. The unprecedented size and diversity of this family explained the ability of mammals to detect a vast array of diverse chemicals as having distinct odors. In 1991, Richard Axel and I published the identification of odorant receptors.Boston In 1991, I departed for Boston to be an assistant professor in the Neurobiology Department at Harvard Medical School. There, I was immersed in an environment in which I could broaden my understanding of the nervous system. I received excellent support from my chairman, Gerry Fischbach, as I set up my lab. I also developed many excellent colleagues, including [David Hubel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/index.html), whose pioneering studies of the visual system with [Torsten Wiesel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/index.html), for which they received a Nobel Prize in 1981, had always been an inspiration to me. In 1994, I became an investigator of the Howard Hughes Medical Institute, which has generously supported our work for the past eleven years. Over the next decade, I remained at Harvard, gradually rising through the ranks to become associate and then full professor. In 1994, I met Roger Brent, a marvelous intellect and fellow scientist who has been my partner and an important part of my life ever since.The discovery of odorant receptors had explained how the olfactory system detects odorants. My next goal was to learn how signals from those receptors are organized in the brain to generate diverse odor perceptions. I was joined in this endeavor by a series of excellent students and postdoctoral fellows. The discoveries on the organization of the olfactory system that were cited by the Nobel Foundation were made over a period of ten years, during which I was a faculty member at Harvard.The first question we asked was how odorant receptors (ORs) are organized in the olfactory epithelium of the nose. This work was begun by Kerry Ressler, an M.D./Ph.D. student who came to the laboratory for a few months just as the equipment and supplies I had ordered began to arrive in January 1992. I had decided to switch from rat to mouse as a model organism because of the advantage of using isogenic inbred strains for dissecting a multigene family, and the possibility of generating transgenic mice. After cloning and sequencing a series of mouse OR genes, Kerry did our first *in situ* hybridization experiments to examine patterns of OR gene expression. By June, Kerry had returned as a full time student and Susan Sullivan had joined the lab as a postdoctoral fellow. At this point, we began to precisely analyze OR expression patterns and to compare them in different individuals. Prior to the present era of digital photographs that can be stored and analyzed on a computer, this was painstaking work that involved displaying photographic slides on a desktop viewer and recording, on transparencies, the locations of individual labeled cells in different animals. Our studies showed that each OR gene is expressed in about 1/1000 olfactory sensory neurons, that the olfactory epithelium has several spatial zones that express nonoverlapping sets of OR genes, and that neurons with the same OR are randomly scattered throughout one zone. This indicated that signals derived from different ORs are segregated in different sensory neurons and in the information they transmit to the brain. It further indicated that, in the olfactory epithelium, neurons that detect the same odorant are dispersed and those that detect different odorants are interspersed. Thus, there is a broad organization of sensory information into several zonal sets in the epithelium, but, overall, information is encoded in a highly distributed manner. We published these findings in 1993. Similar observations in rat by Richard Axel and his colleagues were also reported that year.Having determined how inputs from different ORs are organized in the nose, we asked how they are arranged at the next structure in the olfactory pathway, the olfactory bulb. In the bulb, the axons of olfactory sensory neurons synapse in about 2,000 spherical structures, called glomeruli. Kerry began to use retroviral vectors to investigate how the axons of neurons expressing specific ORs are organized in the bulb, but then we inadvertently found another way to address the question. While using *in situ* hybridization to identify a number of OR genes expressed in each epithelial zone for chromosomal mapping studies, Susan found that, in one tissue section, an OR probe labeled a single spot in the bulb, which proved to be a glomerulus. Using probes that recognized single OR genes rather than subfamilies of related OR genes, we found that each probe labeled OR mRNAs in sensory axons that were confined to one or a few glomeruli at only two sites, one on either side of the bulb. Different OR probes labeled different glomeruli and those glomeruli had virtually identical locations in different individuals. I still remember a meeting with Kerry and Susan in my office in which I asked Kerry how many sections separated different labeled glomeruli in different bulbs. All of us were stunned by his answer, because it provided the first hint that the bulb might have a stereotyped map of OR inputs and we could not imagine how this could be generated given the organization of OR gene expression in the epithelium. This mystery still has not been solved. These studies indicated that while thousands of neurons expressing the same OR are highly dispersed in the epithelium, their axons all converge in a few specific olfactory bulb glomeruli. The result is a stereotyped map of OR inputs in which signals derived from different ORs are segregated in different glomeruli and in the bulb projection neurons whose dendrites innervate those glomeruli. Remarkably, Bob Vassar in Richard Axel’s lab had concurrently found that different OR probes labeled different glomeruli in the rat bulb. Our two groups published these findings in 1994.Several years later, we began to investigate how the OR family and the patterning of OR inputs encode the identities of different odorants. Using single cell RT-PCR (reverse transcriptase-polymerase chain reaction), Bettina Malnic, a fellow in the lab, had been comparing gene expression in single olfactory sensory neurons. Her work demonstrated that each neuron expresses only a single OR gene, something that we had previously suspected, but that needed to be verified. Bettina was initially focused on the identification of genes that might be involved in OR gene choice or axon targeting in the bulb, but we decided to change course when Takaaki Sato visited our lab and told us about his calcium imaging studies of odor responses in the olfactory epithelium. This was the beginning of a highly successful collaboration in which Takaaki used calcium imaging to define the odor response profiles of individual neurons and Bettina then used RT-PCR to identify the OR expressed by each responsive neuron. These studies demonstrated that the OR family is used in a combinatorial manner. Different neurons are recognized, and thereby encoded, by different combinations of ORs, but each OR is used as one component of the combinatorial receptor codes for many different odorants. As discussed in my Nobel Lecture, these studies also provided explanations for several intriguing features of human odor perception, including how a slight change in the structure of an odorant can dramatically change its perceived odor quality.As soon as we had determined how OR inputs are organized in the olfactory bulb, we began to explore how they are arranged at the next structure in the olfactory pathway, the olfactory cortex. Lisa Horowitz, an M.D./Ph.D. student in the lab, initially investigated connections between the bulb and cortex using classical anatomical techniques. By depositing different tracers in the dorsal and ventral bulb, she determined that these areas project axons to the same regions of the cortex. In agreement with previous findings, this indicated that there could not be a point-to-point patterning of connections between the bulb and cortex. We decided to abandon traditional approaches and to instead ask whether we could chart neural pathways genetically by expressing a gene encoding a transneuronal tracer in olfactory sensory neurons. Lisa found that this was indeed possible. When she made transgenic mice that expressed barley lectin in all olfactory sensory neurons, the lectin crossed two synapses, labeling second-order neurons in the bulb and then third-order neurons in the cortex. This work, which we published in 1999, opened the way to investigating a wide array of questions concerning neural circuits, including those that carry olfactory information.We then went on to use the genetic tracer to examine how inputs from individual types of ORs are organized in the olfactory cortex. To do this, we used gene targeting to generate mice that coexpressed barley lectin with a single OR gene. Lisa, together with a fellow in the lab, Jean-Pierre Montmayeur, prepared the DNA constructs for gene targeting. Zhihua Zou, another fellow, then made and analyzed mice that coexpressed the tracer with different OR genes. The approach worked, but was difficult, with Zhihua investing almost a year in perfecting the conditions needed to detect minute amounts of the tracer in cortical neurons. These studies revealed that the olfactory cortex has a stereotyped map of OR inputs, but one that is radically different from that in the bulb. As I discussed in my Nobel Lecture, the segregation of OR inputs in different glomeruli and neurons in the bulb gives way in the cortex to a complex array of OR inputs in which signals from different ORs partially overlap and single cortical neurons appear to receive signals from combinations of different ORs. This offers a means by which the individual components of an odorant’s receptor code could be integrated at the level of single neurons. This could serve as an initial step in the reconstruction of an odor image from its deconstructed features, which are conveyed by the OR elements of the receptor code. We published our findings on the cortex in 2001.During the ten year period at Harvard in which we did the work described above, my laboratory also investigated a number of other questions. These included studies of the chromosomal organization of OR genes and the evolution of the OR gene family by Susan Sullivan, studies of the development of OR gene expression patterns by Susan and Staffan Bohm, and bioinformatic studies by Bettina Malnic and Paul Godfrey that defined and compared the OR gene repertoires of human and mouse. We also conducted a series of studies on the detection of pheromones in the vomeronasal organ, including studies by Emily Liman and Anna Berghard that revealed differences between transduction molecules involved in odor versus pheromone detection, the discovery of zonal patterns of transduction molecules likely to be involved in pheromone detection by Anna, analyses of vomeronasal responses to pheromones and odorants by Mehran Sam, and the discovery, by Hiroaki Matsunami, of a family of candidate pheromone receptors. During the latter part of this period, Hiroaki Matsunami, Jean-Pierre Montmayeur, and Stephen Liberles also began to explore the mechanisms underlying taste detection, in the process discovering candidate receptors for both bitter and sweet tastes, both of which were also found by other groups at about the same time.Seattle In 2002, I returned to Seattle to be a member of the Division of Basic Sciences at Fred Hutchinson Cancer Research Center and Affiliate Professor of Physiology and Biophysics at the University of Washington. I had always intended to someday return to the West Coast and had already stayed longer in Boston than I had anticipated. When Mark Groudine, then Director of the Basic Sciences Division at Fred Hutchinson, offered me a faculty position there, I gladly accepted. The Hutchinson Center had a reputation for cutting edge science as well as a high level of collegiality, both of which were important to me. In addition, by moving to Seattle, I would be closer to my partner, Roger, who lived in Berkeley, and to my family and friends in Seattle.In Seattle, we are continuing to explore the mechanisms underlying odor perception as well as the means by which pheromones elicit instinctive behaviors. We have also become interested in the neural circuits that underlie innate behaviors and basic drives, such as fear, appetite, and reproduction. We are currently developing molecular techniques to uncover those circuits and to define their composite neurons and the genes they express. In a different vein, we have developed a high throughput approach in which we are using chemical libraries to identify genes that control aging and lifespan, our chief interest being whether there might be a central mechanism that determines lifespan and regulates the aging of cells throughout the body.Looking back Since Richard Axel and I published the discovery of odorant receptors in 1991, it has been immensely satisfying for me to see many laboratories using these receptors in a large scale effort to dissect the mechanisms that underlie the sense of smell and the developmental processes that shape the organization of the olfactory system. Molecular approaches to studying olfaction have extended to other vertebrates as well as to invertebrate species, with Cori Bargmann’s group discovering a large variety of chemosensory receptors in the nematode worm, *C. elegans*, and several groups, including Richard Axel’s, identifying families of odorant and taste receptors in the fruit fly, *D. melanogaster*.Looking back over my life, I am struck by the good fortune I have had to be scientist. Very few in this world have the opportunity to do everyday what they love to do, as I have. I have had wonderful mentors, colleagues, and students with whom to explore what fascinates me and have enjoyed both challenges and discoveries. I am grateful for all of these things and look forward to learning what Nature will next reveal to us.As a woman in science, I sincerely hope that my receiving a Nobel Prize will send a message to young women everywhere that the doors are open to them and that they should follow their dreams. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0549 – Hello.  – Hello, is this Linda Buck?  – Yes, it is.  – Hello, my name is Joanna Rose, I call from Sweden, from Nobelprize.org, which is the official web site of the Nobel Foundation, and I would like to congratulate you so much.  – Oh, thank you, I am so thrilled.  – How do you feel now?  – Well, I’ve just been in a shock for the last hour and a half.  – Oh, I see. Did you expect the message?  – No, I was asleep and I was really quite surprised.  – I understand. Did you ever have the thought, since 1991, that it could be possible to get the Prize?  – Oh, you know, a few people had mentioned it to me and I didn’t really take it seriously.  – I understand. What does the Nobel Prize mean to you?  – I was just going back to sleep … It’s wonderful. It means that others appreciate the work that you’ve done, it’s very gratifying, from that standpoint, and I think that all of us who are scientists do science because we love what we do. It’s out of a sense of curiosity and a desire to understand how things work.  – Do you think that the Prize will affect your future work in any way?  – No, I don’t think so, in terms of the actual experiments that I do. I hope that other women, scientists, receiving a Nobel Prize that will help women, young women, to see that it is possible to accomplish things, and I think it’s very nice from that standpoint.  – Do you think it is harder for women to do science?  – I think it is harder for women to do science, to mix a career, any career, actually, and family, but I think that, in these days it is possible for women to accomplish things, but maybe some women don’t realise that.  – So how do you manage?  – And I think that may help to give them confidence.  – Yes, sure. How would you describe, how do you manage to do science?  – Well I devote most of my time to it. But, you know, that’s my choice, but I think that … I feel very fortunate to be a scientist, because I think it is something that … I feel very lucky to be able to spend my time doing something that I love to do. Not everyone has that opportunity.  – Can you give a message or a piece of advice to others, to young students, whose greatest wish maybe is to receive a Nobel Prize in the future?  – Well, what I always tell my students is that it’s important to do something, to study something that fascinates you. Pick a problem that you’re extremely interested in. That sounds kind of simplistic maybe, but it’s not, because you don’t want to just do a problem because it’s easy to solve, you want to do something that you’re obsessed with, that you just have to understand, because that’s where the joy comes from, and that also, I think, is where the great discoveries come from, for people are really trying to try to figure out things that they don’t understand. And they don’t necessarily know how to do it, but they try very hard and then they succeed.  – So what about you, did you always wish to become a scientist?  – No, I didn’t. When I was young, I wasn’t sure. One thing that was important to me was that I felt that … when I was in my late teens and early twenties that … I felt that it was important to try to help other people, and so I wasn’t sure about science at first, because I thought that it was … maybe it wouldn’t fulfil that requirement and then I decided that it may after all, by learning things and about how biology worked, that would give insight into basic mechanisms. I am not saying that I was that sophisticated in thinking about it, but I thought … I came to the opinion that it was okay after all. In retrospect I could say that, you know what I just said about the basic mechanisms and so on, because I know more.  – What do you think about it today, will your discovery have any clinical applications, for example, to help people in this meaning?  – I think, ultimately. It hasn’t yet, but in terms of olfactory disorders there’s a possibility. But I think that, like in many other biological areas, the information that you gain doesn’t have a direct or immediate clinical use, and rather it gives you insight into biological mechanisms which then can be transferred into other areas. Provide insight into other areas, and also I think that using, as we use the odour receptors as molecular tools to investigate the brain, we may discover things about how the brain works that we don’t necessarily know anything about yet. But of course we won’t know that until we find out how it works.  – It’s a step on this way. I have another question: this is going to be a very long day for you today, what are you planning to do?  – I’m going to go in to work, and talk to the press, and I was going to try to get a couple of hours of sleep, and then answer requests for interviews and so on.  – My last question: have you ever visited the Nobel Prize web site?  – Oh, yes I have, it is a lovely site. Were you a part of building that?  – Yes.  – It’s wonderful. I think it’s excellent!  – The interview is going to be published there. Also I hope to meet you in December in Stockholm.  – Thank you very much. I look forward to meeting you.  – I wish you a nice day today.  – Thank you so much.  – My biggest congratulations.  – Thank you.  – Bye, bye. |
| Interview |  |
| Q19 | Welcome to meet the Nobel Laureates in Physiology or Medicine 2004, Richard Axel and Linda Buck. First of course like everyone else, congratulations to the prize. You have heard this millions of times in the past days I suppose. This is the afternoon, the day after the big event, so what about the big event yesterday, what are the most memorable moments of the day, Linda? |
|  | Linda Buck: The whole thing was very dramatic and unusual, and it was wonderful to have my family and friends there. It was a once in a lifetime experience.Richard Axel?Richard Axel: I thought that the whole day, the ceremony, the formalism of the ceremony and the grandeur of the evening added a spectacular dimension to what we do, and what we do is try and understand how the world works, how the brain works and to have our work, which we do on a daily basis, celebrated in so grand a fashion, really added a very nice dimension. |
| Q23 | One of the things that really strikes you when you read about your science is the huge proportion of one genome that is used for constructing the nose or the olfactory system. Linda Buck, how come, why do we use so much of our genome for the nose? |
|  | Linda Buck: I think the way evolution works is that if something happens and if it’s useful then it remains in the genome. I think that during evolution of the sense of smell, multiple genes were made, it was advantageous, and they were capped, and you see that some of the genes are disappearing, there are remnants of genes encoding candidate pheromone receptors in humans and those genes are for the most part intact in mice and most of them have become pseudo genes in humans. Now in addition to that though it does seem that in certain invertebrate organisms there are also very large gene families that are used for smell and so it does seem to be a strategy that has worked, perhaps been developed independently in different organisms … |
| Q23 | But happened to be exactly the same systems, in … |
|  | Linda Buck: Yes, but the genes are not really related, they’re genes that encode proteins of the same type but are really quite different. So it does seem to be a strategy that’s perhaps been developed independently several times. |
| Q23 | Was the sensory organ maybe the first … When you look upon evolution, the way to perceive, to react to the external world, chemotaxis came long before phototaxium and maybe phonotaxis if there is any phonotaxium in the biological world. Is that the right, that the smell, the senses of smell was the first one? |
|  | Richard Axel: Chemosensation as you say certainly is the first one. I mean back, every organism, even the most primitive and humble bacterium have to have a way to respond to sense what is in the world around them because that determines how they are going to survive, it determines what their food supply is, how they have to metabolise their food, it determines aversive environments. So all organisms have to have a way to sense the chemical environment and the way they sense the chemical environment has evolved and so we indeed sense it in a different way than does a bacterium but the principle of communicating and responding to the environment is very primitive. |
| Q44 | Anyhow, how is this perception of the chemical environment, how is it mediated into action, how can it be translated to action? What mechanisms is life using? |
|  | Linda Buck: I think in mammals and also in many invertebrate organisms the information travels through a series of relay stations, if you will, in the nervous system and that allows the information from hundreds or a thousand different receptors to be organised in progressively more sophisticated ways and also in different ways. In the mammalian cortex what we see is that there are distinct anatomical areas in the olfactory cortex that are getting information from the odorant receptor family in the nose and those different areas of the olfactory cortex send information to different areas of the brain. We think what maybe happening is that the information from the receptors is being organised, combined, or perhaps modulated in different ways in those different areas before being sent on to yet other brain areas. This parallel processing of information is something that is seen in other parts of the nervous system as well so you can take the same sensory information from the external world and then you can process it in different ways in different parts of the brain to use that information for different things. |
| Q44 | And how do the animals or we perceive all this process? Is it through emotions? |
|  | Linda Buck: The information is targeted to different parts of the brain and some of those structures in the olfactory cortex send information on to higher cortical areas, both directly and indirectly through the thalamus, but in addition there are some parts of the olfactory cortex that send information to the hypothalamus and certain parts of the amygdala and those are parts of the brain that control physiological effects, emotional responses and instinctive behaviours. In fact, we think that using the sense of smell, and using molecular approaches, we can gain access to neurons and neural circuits in those very primitive parts of the brain and perhaps begin to obtain information about the neurons and the neural circuits that control instinctive behaviours and emotions. |
| Q46 | Does that mean that the olfactory system is also sending signals to the brain that we are not aware of, through unconscious levels of our brain? What do you think Richard Axel? |
|  | Richard Axel: That’s a hard question to answer; I mean how do we know that there is the unconscious recognition of scent? We do know, as Linda pointed out, that smell is recognised by cells that project to different areas in the cortex and some of those areas, some of those areas are new brain, cognitive brain and others are old brain, emotive brain. One might think that the odours that activate emotive brain might illicit emotions and innate behavioural responses and neural endocrinal responses without the conscious awareness of those signals. For instance, in animals we know that certain odours can reorganise the time of puberty, can reorganise the menstrual cycle and can illicit or prevent mating. There are studies in humans which are far more difficult to control to suggest that there are olfactory driven changes in the menstrual cycle, there’s a very famous study out of Chicago suggesting that women in a dormitory tend to synchronise their cycles and that’s thought to be olfactory, but those studies are psychophysical not biophysical and they’re much more difficult to prove with certainty. |
| Q46 | What about more everyday life events, is it possible that fear can smell and happiness can smell? That we can register emotions in the room without being really aware of it? Is that a too spectacular question? |
|  | Linda Buck: People talk about it, I think more in literature than in science, the smell of fear and so on and I don’t know, I think maybe that has to do with components of human sweat or it’s not really, it’s not something that we investigate really and I suppose … |
| Q47 | Because in one of your Nobel lectures or Nobel symposia, you talk about your great interest in trying to elucidate how subordination maybe mediated through smells and also aggressiveness and … |
|  | Linda Buck: We are actually looking, using mice, we’re using odours that have particular effects on the animals, we’re just starting to do that now. We’re looking at activation in the brain by a fox odour that causes a stereotype fear response. We’re also looking at effects of different kinds of odorants on the behaviour of the animal and looking at parts of the brain that are activated and we do see that mice don’t like skunk odour any better than we do and there are quite dramatic behavioural differences between their responses to skunk, skunk, fox odour and vanilla so they’ll actually try to get to an input tube that’s, through which there’s vanilla odour and they try to hide from the skunk. They try to hide from the skunk and in response to the fox odour; they just become paralysed with fear. |
| Q47 | Do we know that useful things tend to be preserved throughout the biological fear and maybe … |
|  | Linda Buck: That’s right and it’s clear that in the hypothalamus … The hypothalamus is basically the major control centre of the brain, it’s very primitive, it’s there in animals, it’s there in human and it’s highly conserved in its structure and also in the genes are expressed there and in the neural circuits and most, if not all, instinctive behaviours and emotional responses are controlled by the hypothalamus. |
| Q47 | And the hypothalamus has a direct contact with the nose? |
|  | Linda Buck: There are inputs from, yes; there are inputs from the nose. The hypothalamus actually collects information from all sensory systems, from the other parts of the brain and from the body. It gets input not only from the nervous system, that of course connects the entire body but also through the bloodstream. It measures the temperature, it measures the composition of the blood, it measures sex hormone levels, it controls the menstrual cycle, it controls the stress response. So it’s basically the main control system and of course because odours can cause stress, fear, pheromones and maybe some odours can control sexual behaviour, we can use the olfactory system to try to gain information about those circuits and start dissecting the neural circuits and the individual neurons including the genes that they express, that control those very basic emotional responses and behaviours. That’s where we’re going next. |
| Q16 | Another fascinating information that comes from your science is how the olfactory system is translating scattered molecules of sense into an organised map in the brain, it turns into a physical map, Richard Axel, but who is watching the map inside your brain? How do you make sense out of a physical map from these molecules? |
|  | Richard Axel: That’s a central issue that neuroscientists would like to address and have been attempting to investigate for a very long time as you’ve heard me put it before. This is a central issue in all senses that is the way… There seems to be a conceptual thread that runs through the different senses and that is that in olfaction as well as in vision the image, whether it be a chemical in olfaction or a visual image in sight, is very complex and it needs to be deconstructed into its components before it can be re-established in the brain as something meaningful. So in vision for example, the individual components of a visual image, that is colour, movement, edges, form texture even at the level of the retina in the eye are deconstructed and carried to the brain by parallel pathways. They are relayed in different regions of the brain so there are regions of the brain that are responsive to movement and not colour, other regions responsive to edge and not movement and at some point, there must be an area which consists of ensembles of neurons that can put this information back together. Now the analogy to the olfactory system as a consequence of the efforts of a number of people including Linda, suggest that you transform chemical space into brain space in the very same way that a given odour, even a single molecular species in an odour, will have the capability of fitting into multiple different receptors and those receptors project to different points in the brain so that those points, the receptors that an odour can interact with and the points which they activate in the brain, form a signature and then as you point out, you’re left with the problem. |
| Q16 | Who is watching? |
|  | Richard Axel: The problem of who looks down on these points? Who listens to the music, who sees the activation? As I’ve put it before, it’s an old problem, it’s the problem of the ghost and the machine and philosophers have been addressing this problem now since Plato.Linda Buck: I think this is a challenge for neuroscience in the future and it’s been recognised for a very long time that we do not know how it is that neurons firing in different parts of the brain, active in different parts of the brain, somehow constitute a perception, a percept because it’s clear that not all the information is going to come together in a grandmother cell and when that cell is activated you think “grandmother”. There are indeed neurons that are activated through, in many different parts of the brain and somehow that constitutes a cohesive perception. |
| Q16 | But do you really think … |
|  | Linda Buck: And there’s nobody looking, it’s the way it works. There’s no one who will be looking, it’s the way the brain works, and I think that it is a scientific problem in terms of how physically that might happen but it’s also a philosophical problem, a conceptual problem because I think it’s difficult for scientists to conceptualise how it is that neurons that are dispersed in different parts of the brain could form a percept and it could be that it’s just going to take some kind of a conceptual or philosophical step for people to say, That’s not a problem, we accept that. |
| ID | 0550 |
| Biographical | My ancestors apparently emigrated from Europe in the middle of the 19th century; the Lauterburs probably from Luxembourg, and my mother’s people, Wagners and Weingartners, from Baden-Baden or nearby. They settled in northern Ohio, where my mother’s father, Hans Christian Wagner, married Margaret (Maggie) Weingartner. They lived in Tiffin, Ohio when I was a child, where they had raised my mother, Gertrude Frieda Wagner, her twin brother Joseph, and their youngest child, who became a nun with the name Mary Monica. Nearby lived my grandfather Paul Lauterbur who married a woman of Irish descent, Margaret Hillan. They eventually moved south to Sidney, Ohio and had a number of children, of whom my father, Edward Joseph Lauterbur, was the youngest. He later married Gertrude Wagner (the families seem always to have been acquainted) and they had four children, Thomas who died shortly after birth, me, my younger brother Edward Joseph Lauterbur II (Joe) and my sister Margaret.We grew up in a house in Sidney complete with a series of dogs, and as the years went by, birds, turtles, newts, fish, snakes, and other animals, and with interesting yards full of trees, bushes and flowers, as well as a nearby park, open spaces and neighbors, some of whom did not resent children trespassing on their property. It was, in memory, an idyllic time. My father worked in the town, as an engineer and part-owner of the Peerless Bread Machinery Company, and my mother kept house with help of a young woman who did some domestic chores and sometimes cared for the children. Although I attended a parochial school, Holy Angels School, I recall little of it except that the nuns who taught there seemed to value order and discipline over all else, which made it especially desirable to evade their control. More influential in my later interests was, I believe, my aunt Anna Lauterbur, who taught in the demonstration school at Ball State Teachers College (now Ball State University) in Muncie, Indiana, just west of the Ohio-Indiana border. She was fascinated by natural history, always kept a terrarium in her elementary school classroom, and gave me a subscription to Natural History magazine. A very gentle person, always willing to listen to a child, she was my favorite aunt.Because of my parents’ hobby of horseback riding, they had bought a farm just outside of town, and we moved there just as I was transferring to the public high school. The farm, with an old but remodeled house, a barn, various outbuildings, fields, woods, and a little creek, was a small paradise to a teenage boy, even though I acquired many duties, such as caring for the horses, mowing the lawn, cultivating the garden, and helping with harvesting. There was also time, of course, for hunting and fishing, collecting snakes, turtles and caterpillars to raise to butterflies or moths, and for general exploration. School was now more interesting also. Not only did I take up the game of chess as a freshman, but I beat the local champions at it, to their great disgust because they were seniors, and then moved on to play a local adult expert, one of the teachers. Classes were a mixture of pleasure and boredom. One of my teachers, who taught biology and chemistry, had the foresight to excuse me and some of my classmates, who were members of the local science club, from his lectures, so that we were free to use the time to do experiments, both standard and wild, in the school lab. He also had the courage to intervene when some of the dangerous ones came to the attention of the school authorities and we could have been expelled.I met him again recently, and his son recalled that when told of my Nobel Prize, he said, “I always knew he would do something like that.” After graduating from high school, I went on to Case Institute of Technology, an engineering school now part of Case Western Reserve University, in Cleveland, Ohio, about 200 miles north-east of Sidney. My father had recommended it, because, as he observed, he didn’t know what scientists did for a living, but engineers could always get a job. But, given a choice of majors, I chose chemistry.I had had so-called “chemistry sets” of simple chemicals and apparatus since my earliest years (I particularly liked the pungent smell of burning sulfur), and my own home laboratories even before high school. The curriculum at Case was quite general, including all forms of science (except biology) and engineering, including civil, electrical, mechanical, and chemical, and all of the related technologies such as surveying, mechanical drawing, as well as seemingly endless labs of all kinds, for which I have always been grateful. In addition to the excitement and drudgery of academics, there were also the pleasures and stresses of fraternity life, girls, and culture, as well as new friends and foods. Continuing my habit of doing things a little differently than expected, I wrote a Senior Thesis on my attempt to make an organosilicon free radical, but the advisor for it was an organic chemist who specialized in natural products.When I graduated (with a B.S. in chemistry, because I did not qualify for an engineering degree as I had replaced a Unit Operations laboratory course with a graduate course in Quantum Chemistry), I was tired of lectures and professors, and determined to get back to lab work. I knew little about graduate study and the structure of a scientific career, so I accepted an offer to work for the Dow Corning Corporation in their Mellon Institute laboratories, where the emphasis was more scientific than technical. I was also told that I could take graduate courses at the University of Pittsburgh free as an Institute employee. There was much interesting work, I found, in our group at the Institute. Organosilicon synthesis, theories of rubber elasticity, techniques of vacuum distillation, elastomer testing, all were new to me and endlessly stimulating. I was particularly fascinated by the puzzle of how small particles strengthened rubber. I even managed to overcome my distaste for academics and take a few courses.It had long been known that “carbon black” dramatically improved the properties of natural or synthetic organic rubbers, and it had been found that the same was true for silicone elastomers if small particles of silica were used instead of carbon, but not whether surface chemistry was involved or simply physical properties. I addressed one aspect of the problem by substituting phthalocyanine dyes for silica, and they worked perfectly, with their effectiveness decreasing as predicted when the particle size was increased by recrystalization from liquid hydrogen fluoride. Unfortunately, I never achieved a theoretical understanding of the effect, despite intense study of elastomer theory, but I had bright blue rubber and skin.During that period, I also began to learn about nuclear magnetic resonance (NMR) from various visitors and speakers, and to read a little about that new form of spectroscopy as well. It seemed ideally suited, even at that early date, for investigating the structures and electron distributions in molecules, and various physical properties of materials. Therefore, as part of my graduate education at the University of Pittsburgh, in addition to a “literature seminar” on interstellar molecules, I gave one on a paper describing NMR properties of rubber. Before I could begin a planned collaboration on the hydrogen NMR spectroscopy of silicon compounds, however, my deferments came to an end and I was drafted into the Army and my eventual assignment was proposed to be in the SPP (Scientific and Professional Personnel) program, which my B.S. and two years of work experience qualified me for.First, however, I was assigned by mistake to a tank battalion at Fort Knox, Kentucky. After hastily correcting that error, I was given eight weeks of minimal basic training and assigned to the SPP program, as planned, at the Army Chemical Center in Edgewood, Maryland. My specific assignment there was in the Medical Laboratories, where I learned to operate an electron microscope to measure the properties of small aerosol particles meant to carry chemical warfare agents deep into the lungs, and I also proposed, and began to set up, a light scattering apparatus to quantitate vapor absorption on aerosol particles. Another aspect of my duties was to capture and weigh experimental animals meant for chemical weapons testing, so that I became skilled, for example, at catching goats in an open field, for which my farm experience was useful. In time, I learned, from a fellow draftee in my barracks, a Columbia Ph.D., that his unit had purchased an NMR machine, but didn’t know how to use it. I said, “Hey, I know all about that!”, and managed a transfer to help set it up, and arranged for one of my science club buddies, Marlon Shepard, from high school, who had also just been drafted, to join me in the lab, where, among others, we had a drafted Harvard Ph.D. in physical chemistry, Norbert Muller, later a professor at Purdue for many years. We got to work enthusiastically, and I eventually published four papers from our work there, which had turned into a rather unusual opportunity for a young soldier. Perhaps, even more important for my future, I received at least second-hand scraps of a Harvard education, especially the attitudes, from Nobby Muller.When I was mustered out of the Army, I had to decide where to go next. I even considered regular full-time graduate school, but the appeal of Mellon Institute as a familiar supportive working environment won out, especially after my group agreed to buy me my own NMR machine. When I returned to the Institute I arranged that requisition, tested the machine on a standard organosilicon compound (polydimethylsiloxane) at the manufacturer’s laboratory and factory, and impatiently did the initial installation itself when it was delivered. The first critical experiments I did, however, were on 13-C NMR by retuning the instrument, as I had calculated that, if 29-Si resonances could be seen, so could those of 13-C, and a much larger variety of stable carbon compounds existed than of silicon compounds.My first work in that area, a broad survey of carbon compounds, led to many other publications on various classes of organic chemicals, work that absorbed much of my attention for several years and eventually provided the basis for my Ph.D. dissertation. Finally completing those requirements was stimulated in part by my learning of an academic job offer to me that was planned but never made, because the department learned that I did not yet have the degree, and I had begun to be dissatisfied with Mellon Institute because of some restrictions they had placed on my activities. After I obtained that degree, I looked at several opportunities and selected one in academia, because, as I remarked, “I wanted to be free to try any silly thing I decided to do.” One unexpected feature of the job offer, at the State University of New York at Stony Brook, was that it was for the rank of associate professor, so that I went directly to that level, and almost automatic tenure soon after, without even a post-doctorate appointment. I set up another new NMR lab there, and also began to learn the duties and problems of university life while helping to build the department and the institution, and especially, learning to work with students, by that time having gotten over my own distaste for professors by becoming one myself.During the academic year 1969-1970, I took my first sabbatical leave, spending it in Palo Alto, California, in the group of John Baldeschwieler in the Chemistry Department at Stanford. In addition to the scientific opportunities and satisfactions, there were personal activities as well. I had married Rose Mary Caputo in 1962, and although she was not in good health, we sometimes visited San Francisco and we had two children, Dan and Sharon (who later renamed herself Sharyn) who enjoyed the nearly perpetual summer there. I had an undergraduate student doing work back in Stony Brook who began a new project in my lab there, calculating hypothetical 13-C spectra of denatured proteins from data for amino acid spectra. Two graduate students, José Ramirez and Skip Hutton, also remained to continue their research, mostly of isotope effects on NMR spectra, and I flew back to Stony Brook almost once a month to stay in touch with these activities.Back in Stanford, I was trying some new NMR-related things. I went up to the Syntex research labs nearby and began research on 3-H NMR of tritriumlabeled pharmaceuticals. Only one paper on tritrium NMR of organic compounds, by George Tiers, had appeared, so our discovery that one of the “standards” provided to us by Syntex was apparently not labeled in the position they thought it was interfered with our publishing those observations in the limited time we had available, but led to my later setting up a lab, with a chemistry colleague at Stony Brook, to do more such work. I also began collaborative studies at Varian Associates, in that manufacturer’s service labs, of natural abundance 13C NMR spectroscopy of the protein lysozyme in their experimental new superconducting spectrometer, and published the first paper on that subject. I was also working in a lab in the Stanford Medical Center to learn to label a protein, ribonuclease A, with 13C at each of its four methionine residues for eventual NMR study. And, I suppose just to keep busy, I was working with my host, John Baldeschiwieler, and a previous visitor, Barry Shapiro, to his group and friend of mine from Mellon Institute days, to commercialize 13C isotope-enrichment technology developed at Los Alamos National Laboratories. We even started a company, “Kivatec,” to use Los Alamos underground distillation methods for that purpose.It is clear that I was actively beginning to consider biomedical NMR as a new area for application of my skills and knowledge of NMR, partly stimulated by the activities of Oleg Jardetzky, a new member of the Stanford faculty. My intense and detailed involvement in biomedical applications of NMR came, however, from an entirely unexpected direction.After I returned to Stony Brook, by a long, leisurely automobile drive from California with my family, and settled in again to my department (where I found the same arguments continuing that had been going on when I left) another unexpected event occurred. It had its beginning several years earlier, when a field service engineer for Varian, the leading NMR company, saw an opportunity and asked for my opinion on his idea of starting his own company to make or distribute specialized NMR equipment and supplies. His business plan seemed reasonable, and I encouraged him to go ahead. For a time the company thrived, and I was a member of the Board of Directors.In May of 1971, however, some other members of the board compared notes with the company’s banker and found that the company had engaged in some very dubious business practices and was, in fact, bankrupt. At a hastily-called Board meeting, appropriate actions were weighed, and the banker, there as a guest, threatened to close the company that day unless someone he trusted could be persuaded to take over as President, Chairman of the Board, and Chief Executive Officer. I was the only academic on the Board, the semester had just ended, and the others believed that I was free for the summer, so that I was asked to take the job. I agreed, flew to the company headquarters in New Kensington, PA, near Pittsburgh, at the beginning of each week and back to Stony Brook and my family and students for the weekend.The developments at the company could supply the plot for a novel, but the incident that is important for my purpose here is that a post-doc arrived with tumor-bearing rats to check the proton NMR relaxation times of their tumors and normal tissues and organs. I was there to observe the experiments, and noted that large and consistent differences were observed for specimens from all parts of the sacrificed animals and that the experiments seemed well-done. Some individuals were speculating that similar measurements might supplement or replace the observations of cell structure in tissues by pathologists, but the invasive nature of the animal procedure was distasteful to me, the data too complex, and the sources of differences too obscure, to be relied upon for medical decisions. As I pondered the problem that evening, I realized that there might be a way to locate the precise origins of NMR signals in complex objects, and hence to form an image of their distributions in two or even three dimensions. That story, and its consequences, is told more fully elsewhere.Shortly afterwards, I returned to my university for the fall semester, and a colleague took over my company responsibilities. The beginning of the new academic year was a very busy time, and I found some quiet moments to test my ideas about a mathematical approach to such imaging during attendance at seminars and then to consider other practical aspects of the idea as the semester proceeded. In the meantime, I began dropping in on the new medical library of the university, which I passed each morning on the way to work, to spend a few minutes reading, in journals and books, about new developments, problems, and questions in medicine that a new imaging method might address. As I became more confident that these techniques could be both practical and useful, I gradually reoriented most of my research in that direction, then spent almost 30 years on developing its techniques and applications, while chemistry as such became mostly a subject to be taught to students.An exception, later to be significant, was my general interest in evolution and the origin of life, a topic that I addressed in guest lectures in my university and in selected teaching experiments for undergraduate laboratories. During this period, of course, my children were growing up, as they do, but my marriage was disintegrating. I began to be recognized for my imaging work, and my earlier scientific accomplishments began to be overshadowed by this new direction. At the same time, my efforts to expand the imaging studies, now named MRI by medical doctors, began to be seriously inhibited by administrative and political problems at Stony Brook. My marriage ended in divorce, and I formed a new personal attachment with Joan Dawson, an American physiologist, working at University College, London, whose field was muscle biophysics and physiology, as studied mostly by NMR. If we were to be together, either she needed a new position at Stony Brook or we both needed new jobs elsewhere. After looking at several possibilities, and getting married in 1984, we accepted offers at the University of Illinois.We moved to Urbana in 1985, with a new baby and high hopes for our professional lives, which were immediately dashed. A plan to share our time between the Urbana and Chicago campuses was foreclosed by technical and political problems in Chicago, and my intended equipment in Urbana, a new whole-body MRI machine associated with a hospital there, was unavailable because of a legal dispute. That problem was never resolved. The hospital eventually sold the machine, but I obtained a small animal-scale machine from the university and began new experiments. My laboratory was organized as the Biomedical Magnetic Resonance Laboratory, initially located in a rented building near campus. When the landlord, a hospital, decided to demolish the building to further its own plans, a small new building was built for my laboratory.In the late nineteen nineties, that building, including my office, my laboratories, my staff, and all of my equipment, including that provided from university funds in 1985 and those items purchased from external grants over the years, were transferred to another university operation. My wife and I considered looking for new positions, but, in addition to having spent a great deal of time and money building a house, our daughter was in a very good high school, so we stayed. I had a joint appointment in the Department of Chemistry, and moved there, because I had already begun to think about a new approach to the origin of biology from chemistry and wanted to pursue that line of research. Thus, by the time the long-awaited Nobel Prize for MRI was awarded, I had left that field for another (and my daughter had entered college). I am now not only actively pursuing my new research interests, but learning the new skills in time management required of a Nobel Laureate.Selected references (out of 319)“Filler Phenomena in Silicone Rubber,” E.L. Warrick and P.C. Lauterbur, Ind. Eng. Chem. *47*, 485-491 (1955).“Nuclear Magnetic Resonance Field Shifts of Si29 in Various Materials,” G.R. Holzman, P.C. Lauterbur, J.H. Anderson, W. Koth, J.Chem. Phys. *25*, 172-173 (1956).“Nuclear Magnetic Resonance Spectra of Phosphorus Compounds,” N. Muller, P.C. Lauterbur and J. Goldenson, J. Am. Chem. Soc. *78*, 3557-3561 (1956).“C13 Nuclear Magnetic Resonance Spectra,” P.C. Lauterbur, J. Chem. Phys. *26*, 217-218 (1957).“Some Applications of C13 Nuclear Magnetic Resonance Spectra to Organic Chemistry,” P.C. Lauterbur, Ann. N. Y. Acad. Sci. *70* (4), 841-857 (1958).“Anisotropy of the C13 Chemical Shift in Calcite,” P.C. Lauterbur, Phys. Rev. Letters *1*, 343 (1958).“Sn119 Nuclear Magnetic Resonance Spectra,” J.J. Burke and P.C. Lauterbur, J. Am. Chem. Soc. *83*, 326-331 (1961).“Magnetic Shielding and the Electronic Structures of Aromatic Molecules,” P.C. Lauterbur, Tetrahedron Letters, 274-279 (1961).“Nuclear Magnetic Resonance Spectra of Elements Other than Hydrogen and Fluorine,” P.C. Lauterbur, Chapter 7 in *Determination of Organic Structures by Physical Methods*, Vol. 2, edited by F.C. Nachod and W.D. Phillips, Academic Press, New York, NY, 1962, pp. 465-533.“13C Nuclear Magnetic Resonance Spectroscopy. VI. Azines and Methyl Azines,” P.C. Lauterbur, J. Chem. Phys. *43*, 360-363 (1965).“Solvent Isotope Effects on Chemical Shifts of Ions in Aqueous Solutions,” A. Loewenstein, J. Shporer, P.C. Lauterbur and J.E. Ramirez, Chem. Commun., 214-215 (1968).“Pseudorotation in Trigonal-Bipyramidal Molecules,” P.C. Lauterbur and F. Ramirez, J. Am. Chem. Soc. *90*, 6722-6726 (1968).“13C NMR Spectroscopy of Biopolymers,” P.C. Lauterbur, E.J. Runde and B.L. Blitzer, in *Magnetic Resonances in Biological Research*, C. Franconi, editor., Gordon and Breach, London, England, 1971, pp. 355-364.“Image Formation by Induced Local Interactions: Examples Employing Nuclear Magnetic Resonance,” P.C. Lauterbur, Nature *242*, 190-191 (1973).“Zeugmatographic High Resolution Nuclear Magnetic Resonance Spectroscopy. Images of 243 Chemical Inhomogeneity within Microscopic Objects,” P.C. Lauterbur, D.M. Kramer, W.V. House, Jr. and C.-N. Chen, J. Am. Chem. Soc. *97*, 6866-6868 (1975).“*In Vivo* Zeugmatographic Imaging of Tumors,” P.C. Lauterbur, C.-M. Lai, J.A. Frank and C.S. Dulcey, Jr., Physics in Canada *32*, Special July Issue: Digest of the Fourth International Conference on Medical Physics, Abstract 33.11 (1976).“NMR Studies of the Protein-Solvent Interface,” P.C. Lauterbur, B.V. Kaufman and M.K. Crawford, in *Biomolecular Structure and Function*, P.F. Agris, editor, Academic Press, New York, NY, 1978, pp. 329-351.“Augmentation of Tissue Water Proton Spin-Lattice Relaxation Rates by *In Vivo* Addition of Paramagnetic Ions,” P.C. Lauterbur, M.H. Mendonca Dias, and A.M. Rudin, in *Frontiers of Biological Energetics*, P.O. Dutton, J. Leigh and A. Scarpa, editors, Academic Press, New York, NY, 1978, pp. 752-759.“The Sensitivity of the Zeugmatographic Experiment Involving Human Samples,” D.I. Hoult and P.C. Lauterbur, J. Magn. Reson. *34*, 425-433 (1979).“On Two Approaches to 3D Reconstruction in NMR Zeugmatography,” R.B. Marr, C.-N. Chen and P.C. Lauterbur, in *Mathematical Aspects of Computed Tomography*, Vol. 8, G.T. Herman and F. Natterer, editors, Springer-Verlag, 1981, pp. 225-240.“The Use of Paramagnetic Contrast Agents in NMR Imaging. II. *In Vivo* Studies,” M.H. Mendonca Dias, P.C. Lauterbur and E.J. Brown, Jr., *Abstracts*, First Annual Meeting of the Society of Magnetic Resonance in Medicine, Boston, MA, 1982, pp. 105-106.“Aspects of Cardiac Diagnosis Using Synchronized NMR Imaging,” E. Heidelberger, S.B. Petersen and P.C. Lauterbur, Europ. J. Radiol. *3*, 281-285 (1983).“NMR Technology for Medical Studies,” T.F. Budinger and P.C. Lauterbur, Science 226, 288-298 (1984).“Ferromagnetic Particles as Contrast Agents for Magnetic Resonance Imaging,” M.H. Mendonca Dias, M.L. Bernardo, Jr., R.N. Muller, V. Acuff and P.C. Lauterbur, *Abstracts*, Fourth Annual Meeting of the Society of Magnetic Resonance in Medicine, London, England, 1985, p. 887.“Cancer Detection by Nuclear Magnetic Resonance Zeugmatographic Imaging,” P.C. Lauterbur; Accomplishments in Cancer Research, 1985 Prize Year, General Motors Cancer Research Foundation, J.B. Lippincott Co., Philadelphia, (1986); also in Cancer *57*, pp. 1899-1904 (May 1986).“Microscopic NMR Imaging,” P.C. Lauterbur and L. Kyle Hedges, *Abstracts*, XXIII Congress Ampere on Magnetic Resonance, Rome, Italy, 1986, pp. 24-27.“SLIM: Spectral Localization By Imaging,” X. Hu, D.N. Levin, P.C. Lauterbur and T. Spraggins, Magn. Reson. Med. *8*, 314-322 (1988).“Three Dimensional Electron Spin Resonance Imaging,” R.K. Woods, G. Bacic, P.C. Lauterbur and H.M. Swartz, J. Magn. Reson. *84*, 247-254 (1989).“Relaxivity and Stabilities of Metal Complexes of Starburst Dendrimers: A New Class of MRI Contrast Agents,” E. Wiener and P.C. Lauterbur, *Works-in-Progress Abstracts*, Ninth Annual Meeting of the Society of Magnetic Resonance in Medicine, New York, NY, 1990, p. 1106.“NEUROVISION: A Software Tool for Functional MRI Neuroimaging Analysis,” C.S. Potter, M. Banich, N. Cohen, A. Kramer, P.C. Lauterbur and H.D. Morris, *Abstracts*, SMRM/SMRI Functional MRI of the Brain Workshop, Arlington, VA, 1993, p. 243.“ChickScope: An Interactive MRI Classroom Curriculum Innovation for K-12,” B.C. Bruce, B.O. Carragher, B.M. Damon, M.J. Dawson, J.A. Eurell, C.D. Gregory, P.C. Lauterbur, M.M. Marjanovic, B. Mason-Fossum, H.D. Morris, C.S. Potter and U. Thakkar, Computers & Education Journal *29*, pp. 73-87 (1997).*Principles of Magnetic Resonance Imaging: A Signal Processing Perspective*, Z.-P. Liang and P. C. Lauterbur, IEEE Press, Piscataway, NJ (1999).“The Structure of Chemical Matter and the Germs of Life,” Second Astrobiology Symposium, NASA Ames Research Laboratory, April 7-11, 2002, poster.“The Chemical Origins of Biologies: Bootstrapping toward Life,” P.C. Lauterbur, (in preparation). |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0550 |
| Interview |  |
| Q19 | Today it’s the afternoon, the day after the big day, it’s almost a little cruel to ask you to come here to answer a lot of questions but what are your feelings today after this big event? |
|  | I’m beginning to believe it’s real. It’s a very overwhelming experience, the whole week, which is almost over, but my wife and I were discussing just last night that there is a sense of unreality almost, because of course not our usual working day or week and you never know exactly what it is going to be like. |
| Q43 | What will be the strongest memories you will bring back home from these days? |
|  | The first thing that comes to mind is some of the guests I arranged to come here, some people I’d not seen in many cases for many years who were very important in my early work and making it possible and encouraging me and collaborating with me. In general I was happy to see them all and happy that they all enjoyed one another’s company as well. |
| Q43 | One of the strongest memories I will remember is the way you described how your science emerged and the sort of struggle between the chemist and physicist in the early days. |
|  | Oh yes. Of course I’m happy that the Nobel organization has been relaxed about the official designation of laureates in various categories, which it was not always I understand from history, 50–100 years ago, there were sometimes serious debates about whether someone is a proper scientist of a certain kind but so far as I could tell from the selection of laureates in recent years the Nobel people really do understand in their hearts how unified the various disciplines are. |
| Q38 | When the idea came up of using magnetic resonance, what did the physicist say about your idea? |
| Q23 | It has passed some time since the first ideas come up and the first experiments were done so there is the possibility to put this into perspective. What would you say is the greatest significance of the possibility of using magnetic resonance imaging? |
|  | The first reaction at least was always scepticism, including the reactions of Nobel Laureates. However, unlike some other people the second reaction, sometimes within minutes, was I was mistaken. Now that shows a quality of mind that was able to live with the fact that you have made a public error in a major matter and to apologise for it immediately. Not everyone has the self-confidence and largess of spirit to make it possible for them to do that. Some of the most vigorous objections were some people who quickly became the most intelligent about it. |
| Q23 | But it was a very big shift in paradigm going from radiology to magnetic phenomena? |
|  | The shift of paradigm was that there was no previous example of applying the kind of techniques to making images that I was proposing and, as is the case with any good idea, one of the first responses of many people was oh of course, why not, those who were not totally sceptical but that again is a well-known phenomenon that the better the idea is the more simple and intuitive it seems to be to some people which makes them think it’s trivial. However, if it really is trivial why did not some of the best people in the world who are doing the work think of it in the previous 20 years? |
| Q23 | And why didn’t they? |
|  | Because they were thinking about physics in a too limited way. As I used to say, it was good to be working with undergraduates in my laboratory because they had not yet learned too much to believe in what we were doing. |
| Q23 | Ignorance might sometimes be a help. |
|  | People who are intentionally educated but have not risen beyond their education have a tendency to mistake practical approximations in using calculations for fundamental principles. That is one of the things that you try to bring to students in a proper education and it doesn’t always work but it’s a difficult trick of mind to have worked hundreds of homework problems with a professor telling you you’re making mistakes about something and then to have someone propose something that says all of this work that you’ve been doing is simply a practical approximation to a calculation trick and you’re supposed to think beyond that, which is not always easy. That’s why there’s a long apprenticeship in science and most people continue even after years relying upon what is called in English, I don’t know about Swedish, a rule of thumb, approximations that simple calculations and problems to make them easier to do but that is not the real science, that is just a helpful trick. |
| Q47 | The history of science is very often connected to new instruments and hands shift in paradigm or quite a new way of looking on the world. I mean Galileo and the telescope and Leeuwenhoek and the microscope. So what about the MRI and Lauterbur? |
|  | Not quite the same. There are many ways of doing science but I had been working with the basics of nuclear magnetic resonance essentially all of my professional life and doing chemical structure and analytical measurements using nuclear magnetic resonance with no reference whatsoever to imaging because if anyone thought about it they didn’t even think it was impossible, it did not occur to them whether there was anything there to think about. |
| Q47 | But in what way do you think that the possibility of looking into the body and looking into the brain, will it in a way change the way we look upon ourselves and the life we live or give us new explanations? |
|  | What forced me to think about the problem seriously was that I saw that such a non-invasive method would be very useful, but I had never heard of any way of solving that problem, not a hint. The actual idea formulated itself in a way that does have some generality, that is by looking at a problem metaphorically instead of right side up, upside down. I was in the middleof a sentence, which one of my guests here, who was there at the time, reminded me of. I was describing how it was impossible to do any such thing because of certain problems with the physics of the measurements. Halfway through that sentence I realised that those problems were in fact the solution to the fundamental problem. At that point, right in the middle of a sentence was a paradigm shift and of course it took more than just one instant to work out a lot of the practical details but there was a moment where essentially was seeing a problem has actually been its own solution. |
| Q47 | Which is chemistry. Have you started to formulate some new hypothesis about how life originated on earth? |
|  | Yes, but it’s very early. It’s something I’ve been officially working on only for about two years or so and so it’s premature to talk about.You couldn’t give us a hint?Paul Lauterbur: It’s very technical also. It involves a part of chemistry that people have known about for some years but no-one has thought was any significance and so there’s a paradigm shift there too but really I’d rather not talk about it because we’re trying to do some of the necessary experiments in my laboratory right now. I don’t know if at this exact moment, but I hope my students are working hard back home but if there’s one thing that you learn, you know, a lifetime in science, even though an idea seems very good to you, the personification of nature, mother nature, can say, Naughty boy, you have not been listening to me, you are totally wrong and you always have to go back to what nature is able to do. |
| Q36 | But let’s, for a short while go back then to magnetic imaging. What is your prospect for the future? I mean how far can imaging be done? Or can you always find some new phenomena that could be used for imaging? |
|  | There are many kinds of results that are being found in a preliminary way, which I’m not actively involved with at the moment. I don’t have even a normal understanding of where some of these very new things will go since I have not been following them for two years or so. I don’t know where they will be going in the immediate future. I know there were things that I was working on a few years ago, as well as other people were, that seemed to me to have a great deal of potential, some of which I don’t really have any idea whether they are just clever tricks or whether they have real fundamental potential. I will have to wait, like everyone else, to find that out. |
| ID | 0551 |
| Biographical | I was born on 9th October 1933 in Lambeth, London, the youngest of three brothers. I grew up in Camberwell, ten minutes walk from Camberwell Green, the epicentre of the Borough. My father, Sidney George Mansfield was the eldest son in a family of five sons and four daughters.My father worked for the South Metropolitan Gas Company, as a gas fitter. My mother, Rose Lillian, was the youngest of three daughters. At the time of my birth she was not working, but looked after me and my two brothers, Conrad William, the eldest, and Sidney Albert.Outbreak of World War II In September 1939 when war broke out I was nearly 6 years old and my memory of this period is now hazy. However, I do recall very clearly the first time the air raid siren sounded on the day war was declared. I was playing in the street nearby and ran home asking what the strange wailing sound was. In the months that followed plans were instigated to evacuate all children from the London area.I was evacuated from London on three occasions during the war years. The first was a relatively short period spent in Seven Oaks. Later I was sent to Torquay, Devon and stayed with the Rowland family. During a lull in the air raids I came back to London for approximately one year, then returned to Torquay shortly after the commencement of the V2 bombardment of London and was fortunate to be able to stay again with the Rowlands.Secondary education Back in London after the war I was hurriedly told by my school master that I should take the 11+ examination, something I had never heard of before. There was no preparation because time was too short. I took the exam and failed, but not completely. The mark I received was not quite high enough to get me into the local Grammar school, but it was sufficient for me to go to a Central School in Peckham. However, this situation lasted for approximately one year. Then all Secondary schools, in London at least, were completely reorganized so that Central schools were dispensed with altogether and pupils from Secondary schools and Central schools were merged into new schooling arrangements which were called Secondary Modern schools, (these were later renamed Comprehensive schools, but after I had left).Rocket science I left school at age 15 and started work as a printer’s assistant. This took me almost to the age of 18. Because I had developed an interest in rocketry I applied for and obtained a job in the then Ministry of Supply at the Rocket Propulsion Department in Westcott, Buckinghamshire. I remained in this position for around 18 months and was called up for National Service to serve in the army for two years, returning to Westcott after National Service in 1954. I studied for Advanced Levels part time for approximately two years and gained University entrance.University education In 1956 I entered Queen Mary College, University of London. My subject was Physics and in my third undergraduate year we were given individual projects to pursue instead of the normal practical laboratories which we had taken during the first two years of the course. My individual topic was set by Dr Jack G Powles. It was to build a portable NMR spectrometer to measure the earth’s magnetic field. This had been done previously using valve technology, but my task was to build a transistorized version. I knew very little about transistors at this time since it had not formed any part of the electronics course that we had undergone in physics. My experience was very much in valve technology. Nevertheless, I enjoyed the project very much and of course learned a great deal about transistors. Towards the end of my undergraduate studies I was approached by Jack Powles, who offered me a position in his research group working on NMR.At that time Jack Powles was a Reader in Physics and I felt greatly honoured to be asked to join his research group. Jack Powles’ main interest then was in studying molecular motion in a range of materials, mainly liquids. My task was to build a pulsed NMR spectrometer to study solid polymer systems. It was during this period that I discovered what we later called ‘solid echoes’. This was towards the end of my three year doctoral studies and we were only able, therefore, to produce a short paper on solid echoes observed in a single crystal of Gypsum.The American adventure Towards the end of my studies I was asked whether I would be interested in going to the United States for a short post-doctoral period. Jack offered to arrange a position working with Professor Charlie Slichter in the University of Illinois at Urbana, Illinois.I married my wife, Jean Margaret Kibble, on 1st September 1962 and we left to join the University of Illinois in October 1962. Charlie and his first wife Nini met us at the airport at Urbana-Champaign and installed us in what turned out to be temporary post-graduate accommodation at Orchard Downs. Orchard Downs was about two miles from the campus centre and was therefore within walking distance, so I thought. Of course I had not taken in to account the weather. In late October early November the typical air temperature in early morning could reach minus 20 degrees Centigrade even though the skies above were clear blue. I remember attempting to walk in one morning and I got roughly half way to the campus when the frost began to effect me. I continued to walk briskly and by the time I got to the Physics Department my limbs were beginning to seize up with the cold. My eyelids crunched when I blinked and I was extremely thankful that I managed to get to the Department before anything serious happened.The research work that I was involved in during my stay at Urbana was the NMR study of doped metals. A scientific paper by Kohn and Vosko had predicted that conduction electron scattering around zinc centres would behave in a periodic manner so that the resonance shifts of copper atoms would vary in shells around the zinc scattering centres and these shifts would be measurable by looking for low amplitude side bands in the copper resonances of the two copper isotopes. My task was first to build a double resonance spectrometer capable of looking at the copper resonances in a pulsed mode and secondly, to produce single crystals of doped copper as suitable samples to be studied. Building the apparatus was relatively straight forward since I had already built a pulsed spectrometer back in London, but the production of a single crystal of copper with sufficient surface area to give a measurable free induction decay signal was a novel experience for me. It involved growing a single crystal and slicing it into thin plates to give sufficient surface area. The slicing process was done with an electro-spark cutting process which left the surfaces severely disturbed so that it was necessary to etch the damaged surfaces away to reveal a clean undamaged surface.I worked as a post-doc for approximately two years and made several samples and did many experiments on these samples but could not see the predicted effect. But the experience that I gained on this project and the knowledge and background that I learnt during my stay in Illinois were invaluable.In Charlie Slichter’s laboratory, I was not able to pursue the solid echo work started in London, but a colleague from Jack Powles’ laboratory, Doug Cutler, who came over at roughly the same time as we did was working with Professor Ted Rowland in the Metallurgy Department at Urbana. The apparatus that Doug Cutler was using was very similar to the equipment that I had left behind in London. Towards the end of my stay in Urbana I persuaded Doug Cutler to perform a couple of experiments for me on pure aluminium powder. He was able to see solid echo effects and I produced a short mainly theoretical paper extending the theory of solid echoes to systems with spin greater than a half. In the same paper I also included solid echo effects on the two spin species system, NaF. My colleague, Dr John Strange (now Professor), while working as a post-doc at Cornell University, also allowed me to include some of his preliminary experimental data.While I was busy in the Physics Department my wife took a post working in the University Health Centre as a Secretary. She quickly made friends with a number of other secretaries and introduced me to people with whom I would not otherwise have come in contact. We saw her friends on several occasions and had an enjoyable interaction with them. Of course we also interacted with the Slichters and the other members of the group.The wanderers return After the two year period we were sad to leave Urbana and the various friends that we had made there during our stay. But we were also pleased to return to London to see our respective parents after such a long period away. I had been approached by Professor Raymond Andrew while we were still in the States. He had recently moved from Bangor to Nottingham and in a letter to me in July or August of 1964 he wrote to offer me a Lectureship at the University of Nottingham. I had had other offers including one from Jack Powles who had recently taken the founding Professorship in Physics at the University of Kent at Canterbury, however I decided that I liked the offer from Nottingham and accepted. After several weeks in London my wife and I made our way to Nottingham to meet Professor Andrew and to take up his offer. I was still quite interested in pursuing my earlier ideas developed during my PhD studies in London and so I was given a room where I was able to set up equipment to pursue my studies in multiple-pulse NMR.Life in Nottingham I was extremely fortunate to be offered a Canadian research student shortly after my arrival at Nottingham. His name was Don Ware and he came from UBC in Canada. He had an MSc in NMR from the Chemistry Department at UBC. His MSc supervisor was Basil Dunell. Don had little experience in pulsed NMR but was keen to learn so I proposed that he build a pulsed NMR spectrometer capable of performing multiple-pulse experiments. This was in 1964. A year or so later Jack Powles came to Nottingham to give a colloquium talk in the Physics Department. Afterwards he was shown around the various research groups. By that time Don and I had managed to perform our first multiple-pulse experiments and we were pleased to demonstrate these results to Jack. During the course of his visit he said he thought he had seen something similar from a pre-print that he had been sent by John Waugh from MIT. But he wasn’t sure whether it was the same or not, and that he would contact me when he got back to Canterbury. A week or so later a copy of John Waugh’s pre-print to Jack arrived on my desk. By then I had already drafted a letter of our own which was duly sent off for publication to Physics Letters. Our paper was published shortly after John Waugh’s paper and its appearance triggered a period of inter-group squabbling that continued on up to the early 70’s.In 1972 Dr Alan Garroway, an American post-doc, joined my group to study multi-pulse techniques. He had carried out his PhD studies at Cornell University. His work had been concerned with using NMR to study fluid flow. He and his first wife, Mary (now deceased), arrived in February 1972, and on the day they arrived we invited them to dinner, but the country was in the grip of a series of electricity power cuts so that Alan and Mary’s first experience of Britain was a candle lit dinner. Earlier in 1971 I had received an SRC research grant to pursue multi-pulse NMR and included in the equipment support was money for a mini-computer. I had, therefore, purchased a Honeywell computer with 4 k bytes of magnetic memory and had spent quite a bit of the summer of 1971 adapting the machine so that we could connect it to the experimental apparatus in a computer controlled mode. One of the first things that Alan was engaged in was the implementation of the Cooley-Tukey fast Fourier transform algorithm so that transient signals could be rapidly captured and transformed into a spectrum. This work was very successful and later in 1972 we were regularly using the computer controlled spectrometer to study the response of a number of suitable compounds including Calcium Fluoride. Computerization of the NMR spectrometer meant that we were able to pop specimens in for extremely rapid analysis and as a result we quickly ran out of suitable compounds to study with interesting chemical shift anisotropies. It was at this point in early summer of 1972 that I started to think seriously about applications of the line narrowing process.The birth of MRI In those days coffee and tea breaks were taken in the tea room of the Physics Department. It was an opportunity for members of staff and students, sometimes in different research groups, to interact and exchange ideas. On this occasion all other people had left the tea room except for me, Alan Garroway and my student Peter Grannell. We had exhausted all the readily available materials for studying chemical shift anisotropy. Among the results that we had obtained was an extreme elongation of the free induction decay of Fluorine in a single crystal of Calcium Fluoride. It suddenly occurred to me that by removing the dipole-dipole interaction in Calcium Fluoride it ought to be possible, at least theoretically, to look at the atomic structure of Fluorine by imposing an external magnetic field gradient. Alan, who had worked with gradients during his PhD studies, was skeptical, but Peter Grannell was more amenable to the idea. I rushed away from this meeting and wrote up several pages of calculations showing the theoretical possibilities and handed them to Peter Grannell. Peter was in the last year of his PhD studies which finished formally on the 1st October 1972. We had already discussed the possibility of him staying on as a post-doc and I suggested that one of the topics he should work on was NMR diffraction studies along the lines of the calculations I had already produced.Alt Heidelberg du Feine I had also made arrangements for sabbatical leave to work in Professor Karl Hausser’s group in Heidelberg starting in October 1972. My family and I left for Heidelberg in late September 1972 with the plan that Peter and I would continue to interact via post while he prepared to do some experiments on NMR diffraction. I had already decided that there were extremely difficult problems to overcome using real single crystals of Calcium Fluoride and that a simulated approach was called for initially. In this approach a model lattice was to be constructed with several plates of camphor separated by thin sheets of plastic. Although a solid, camphor contains a large number of highly mobile protons which rotate to give a relatively narrow absorption line. The sheets separating the camphor plates contained far fewer mobile protons which gave virtually no signal component to the free induction decay. Our first experimental results were obtained as early as November 1972, and they showed the diffraction effects when the magnetic field gradient was switched on. When the gradient was turned off a single absorption line shape was observed with no splitting. After repeating these results many times during the early part of 1973, the results were written up for presentation at the First Specialized Colloque Ampère in Krakow, Poland in September 1973. At the same time a more formal publication was submitted to the Journal of Physics, C which appeared in November 1973.Journey to Krakow My wife and I made the long journey to Krakow by coach stopping overnight in Leibzig. My talk at the Conference was scheduled as the first invited lecture entitled “Multi-pulse Line Narrowing Experiments: NMR Diffraction in Solids?”. My recollection is that the paper was well received and created some discussion afterwards. One person in the resulting discussion asked if I was aware of similar work that had been carried out by Professor Paul Lauterbur. In fact I was completely unaware and asked where I might find this work. I also asked whether it was concerned with imaging in solids and was told that it was not, that it was concerned with imaging of water in test tubes. The person raising the matter was none other than my old sparring partner, Professor John Waugh. When I returned to England I looked up the relevant publication in the library and decided that the approaches though completely different were not entirely unrelated. The paper by Paul Lauterbur had been published several months earlier in the year. But there were several concerns that I had concerning Paul’s approach to imaging liquids and indeed our own approach to imaging in solids. The first which applied to both techniques, was the question of defining an active slice of material. In the case of Paul’s work he had used the method of projection reconstruction to obtain an image and in that technique a large number of experiments needed to be conducted in order to extricate the image with reasonable resolution. This took valuable time. In my own approach my first concern was the complication of producing images from multi-pulse experiments. There was also the question of defining a slice. We very soon decided that the pursuit of imaging in solids was perhaps ahead of its time and could be deferred for future work. It would be so much easier to look at biological specimens where the relaxation times were shorter and where the line widths were generally speaking narrower.Passage to India Early in 1974 a number of colleagues from the Physics Department travelled to India for an International Conference on NMR. Among these were Dr Bill Moore and Raymond Andrew’s post-doc, Dr Waldo Hinshaw. At this conference Paul Lauterbur gave a talk on his work on imaging which created some excitement and provoked quite a bit of discussion among the Nottingham group during their return flight to England. Shortly afterwards they conceived a different approach to imaging which was called the “sensitive point” method of imaging. By applying time dependent magnetic field gradients along two orthogonal axes they were able to define a point volume of the specimen which could be swept thereby interrogating the whole plane, point by point, to produce an image. Inevitably this was an extremely slow process.The slice of life I was still very much concerned with imaging speed and also the question of sliced definition. After a lot of thought and discussion with Peter Grannell we came up with a method of slice selection which looked as though it might work reasonably well. Alan Garroway also came up with a different method of slice selection using a string of short pulses to define the slice and between us we thought that the sensible approach would be to combine our efforts and publish a short note on the general technique of slice selection. This was sent to the Journal of Physics and was published in the form of a letter. The question of imaging times was still concerning me and during the course of 1974 I spent a great deal of time turning over my thoughts on how this may be achieved. One way forward was what I called line scan imaging. In this method a line of magnetization in a specimen was selectively excited and read out. This process was repeated until the object had been scanned. The technique was much faster than the sensitive point scan method of Hinshaw and also turned out to be faster than the projection reconstruction method of Paul Lauterbur, but I was still not satisfied. Nevertheless, line scanning was used to produce a number of images and in particular it was used to scan the finger of one of my early research students, Dr Andrew Maudsley. The scan times for these finger images were 15-23 minutes. These were the first images of a live human subject and were presented at a special meeting of the Medical Research Council which was convened in 1976 to review the work of the several imaging groups that had sprung up both at Nottingham and also in Aberdeen. All groups were vying for MRC support and this meeting was called specially to review the topic and to decide how best to support the work. The images demonstrating live human anatomy were annotated by Professor Rex Coupland, then head of the Department of Human Morphology. They produced a startling response at this meeting and convinced the MRC that our work should be supported. We produced a grant application requesting a substantial sum of money to produce a whole body MRI machine.The application was handed to Professor Andrew for his comments before sending it off to MRC. In fact the application was delayed by a month or so with no comment or explanation. However I learnt subsequently that Raymond Andrew himself had already sent in a research grant application to MRC and he had decided that he should wait until he had received a decision from MRC before allowing my application to go forward. His application, which was granted, was concerned with building an intermediate size imaging machine with a sample access diameter of about 10 cm. The intention was to establish an intermediate step between the small scale approaches that we had already demonstrated and the whole body machine which I was keen to press on with. My grant application was sent in subsequently and considered at the following round of grants. The application was successful and the result was announced in 1977.The delay in the submission of my MRC grant created some acrimony which continued in one form or another for several years until Raymond took early retirement and left for the University of Florida in 1984. During this period strife within the Andrew group occurred when Bill Moore decided that he wanted to split his imaging activities away from Raymond’s group. This occurred in the late 70’s when a whole body magnet was obtained with a grant from the Wolfson Foundation and Bill Moore together with Neil Holland decided that the results of this new work should be independently managed. Thus a period of internecine squabbling broke out between Raymond Andrew’s remaining group, which included Dr Paul Bottomley and a member of staff, Dr Peter Allen, who was loosely associated, and the third group headed by Bill Moore. After a while, under this new regime, matters began to settle down again in a quasi steady state.Blacksburg Dr Peter Morris, who in 1977 had just finished his PhD studies on multi-pulse NMR in solids and liquid crystals, stayed on at Nottingham as a post-doc for two years or so. This occurred at approximately the time when the MRC funding was granted. He together with Dr Ian Pykett were heavily involved in the installation of our first 0.1 T electro-magnet and subsequent RF and gradient coil designs. We had all been working flat out to get a large scale image in time for the ENC Meeting in Blacksburg, Virginia in April 1978. In the event, the night before we were due to fly out, I volunteered to climb into the machine for an attempt at imaging my abdomen.Just a day or so before, I had received a typewritten draft of a piece from Professor Tom Budinger of the University of California at San Francisco suggesting that the gradient levels and switching rate that we were proposing to use to produce my abdominal image, were potentially dangerous. I personally did not believe the calculations and had performed alternative calculations which suggested that the expected induced transient currents flowing in response to the gradient switching were much lower than those predicted by Tom.I climbed into the machine and signaled to Peter and Ian to push the button for a single pulse. There was an audible crack but I felt nothing. I then signaled to start the scan. The magnet was enclosed in aluminium sheeting forming an RF screen. Due to lack of time there was no light inside. I was therefore clamped in the magnet vertically and in pitch darkness for 50 minutes until the procedure was completed. Our wives and fiancées were present ready to haul me out of the magnet in an emergency, but the whole experiment went well and images were recorded. Photographs of the raw images were taken, but the film was processed in a local store in the USA a day or so before the presentation.Trouble ahead During the early 80’s there were growing difficulties within the University of Nottingham concerned mainly with the promotional prospects in the various departments on campus. This meant that aspiring members of staff were being artificially held back because of arbitrary constraints introduced by the government of the day and forced upon the Vice-Chancellor, Professor Basil Weedon. These constraints induced a feeling of great uncertainly throughout the University which was heightened when calls were made to introduce an early retirement scheme in order to reduce the over staffing levels that were considered extant in many Departments. These considerations produced a rash of requests for early retirement which in some cases carried a substantial early retirement premium especially for younger members of staff. In the exodus that followed the Department of Physics lost four members of staff to early retirement. These were Professor Andrew, Dr Moore, Dr Peter Allen and Dr Bill Derbyshire. Dr Moore went to the United States to take up a Professorship at the Brigham and Women’s Hospital in Boston, Massachusetts. Dr Allen went to the University of British Colombia in Canada to set up a medical imaging group there and Dr Derbyshire took a Senior Lectureship at Sunderland Polytechnic. Sadly Dr Moore collapsed and died while playing tennis approximately six months after taking up his new position. Raymond Andrew died of cancer in 2001 at the age of 78. Dr Peter Allen successfully created his own MRI group and continues to research his particular interests in medical imaging. Dr Derbyshire later took a position working with Rank-Hovis and is now retired.With all these staff changes occurring over a 1-2 year period, my group was the only one in MRI to survive in Physics at Nottingham. In fact in 1984, I myself was courted to return to the States with no fewer than three offers, from the University of Alabama, University of Illinois at Urbana and the University of Maddison, Wisconsin. I decided to stay at Nottingham despite the attractive offers.A new start Shortly after my return to Nottingham, I received a call from the Department of Health telling me that there was some funding available to purchase a 0.5 T superconductive magnet – was I interested? I accepted immediately and later in 1984/5 the magnet arrived and was installed in a small extension of the Physics Department. These events helped to settle me firmly in Nottingham and removed all doubts I may have had about moving elsewhere.I had been greatly concerned about our proposals to use the 0.5 T magnet for EPI. My major worry was whether rapid magnetic gradient switching within the close confines of the magnet would induce the static magnetic field to quench. I had been thinking seriously about the problem for several months prior to the arrival of the magnet, but with no clear solution in mind when it arrived. Shortly after installation of the magnet, I recall rushing down to the laboratory in great excitement to announce to my post-doc, Dr Barry Chapman, that I believed I had solved the magnetic problem by introducing a magnetic screen between the gradient coil and the inner bore of the static magnet. The idea was that the screen, itself, would be another coil designed to make the total magnetic flux from the screen and the primary gradient coil zero beyond the screen, thereby removing any interaction between the gradient coil and the magnet.We hurriedly put together some calculations and filed the idea as a Patent. Meanwhile, Dr Robert Turner, who had joined my research group to learn about MRI in general and EPI in particular, had been thinking about the problem from a different view point, using a so-called annealing algorithm, but without success. I mentioned my approach to him and within three months or so, he together with Dr Roger Bowley, a theoretician in Physics, had come up with a much more rigorous mathematical analysis of my idea. This material was added to the Patent within the one year allowed before final filing. So active magnetic screening was born and quickly applied to the development of EPI at Nottingham. Once published active magnetic screening was rapidly taken up by the MRI industry and forms the basis of all commercial MRI machines today.The golden era The 10 year period from 1980-1990 was exceptionally fruitful in terms of research output, development and medical applications of high speed imaging. Considerable effort was put into the implementation of EPI, initially by two research students, Roger Ordidge and Richard Rzedzian (now deceased), then later by several other students including David Guilfoyle and Mark Doyle. While this was going on, other work continued in non-medical applications of MRI principally by Stephen Blackband and Richard Bowtell. Other types of whole body imaging were tried out by Volker Bangert, a German student from Berlin who had a grant from the Deutsche Akademische Austauschdienst. The major effort made in EPI produced increasingly better images as a result of further work carried out by research students Martin Cawley and Alistaire Howseman. Whole body EPI work with a series of patients became possible with the help of Dr Michael Stehling, a medical graduate from Germany who came to Nottingham, initially as a visitor with a grant from the Deutsche Forschungsgemeinschaft, but later decided to stay on to study for a PhD in MRI.By the end of the 80’s the quality of EPI data had improved dramatically so that most regions of the human body could be studied rapidly, bringing relief to many patients. It was at about this time that Dr Penny Gowland joined the group and made substantial contributions to our work on foetal imaging.This was the end of a Golden Era in the development of MRI at Nottingham. There were, of course, further developments well into the 1990’s and beyond including the trial experiments using EVI at 0.5 T, carried out by Paul Harvey, and at 3.0 T, carried out by Paul Glover, Ron Coxon and Jonathan Hyking.Following my retirement in 1994 from teaching in the University, I continued my research activities both at the University and with the help of my small company, General Magnetic. Our main interest has been concerned with MRI safety matters. In particular we have tried to reduce the acoustic noise levels generated by the gradient coils when pulsed in EPI. This work, started in the University by Joanna Beaumont and Ron Coxon, has subsequently been further developed by Dr Barry Chapman, and my son in law, Brett Haywood.Another safety issue also related to gradient coils is the unwelcome level of electric field that naturally accompanies high levels of changing magnetic field. Electric fields are responsible for neural stimulation induced in patients when being imaged. Currents flowing within the patient may induce peripheral muscular twitch for relatively mild stimulation levels. However, for larger and faster gradients applied to the thorax, induced cardiac fibrillation is a real and serious danger. This aspect of our work is a joint venture between the University of Nottingham and General Magnetic and involves Professor Roger Bowley and Brett Haywood.None of the work in MRI could have been achieved without the enthusiasm and dedicated support of a highly motivated team of technical and academic staff, research students and post-docs sustained over the period from 1972 – to the present day. I wish also to thank my three secretaries, Mary Newsum-Smith, Lesley Key and Pamela Davies for their unstinting help and the patience shown to me over the course of a long and exciting career. Last, but no means least, I would like to thank my wife, Jean, and my family for their unfailing and unswerving support during the good as well as the not so good times. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0551 |
| Interview |  |
| Q43 | I would very much like to know of course what will be the strongest memories you will be bringing back home from this event. |
|  | I think the last day or two, especially meeting the King and Queen, the actual prize award ceremony, the banquet – it’s all been fabulous and most enjoyable, but very tiring. I just don’t know how the Royalty can keep this up either. |
| Q43 | One of my strongest memories will be from your Nobel Lecture on Monday when you described how this terrible sound that is produced by the magnetic resonance imaging camera could be reduced, nearly go extinct. |
|  | Yes, it’s something that we’re really working on still, it isn’t a complete working system at the moment, it was just an example such as we have at the moment that shows what is possible in principal. |
| Q32 | But your delight when you showed this to the audience, and you also came back to it in your thanks speech at the dinner. Is it very important for you, this? |
|  | It’s important to make it quieter because one of the problems of course is that the machines are very noisy. I personally find the noise disturbing at those very very loud levels, so I think anything that one can do which can reduce the noise level and make the safety and comfort of the patient better improve that. I think it is extremely valuable in terms of the usage of the machine. For example, somebody who is extremely sick does not want to be upset or concerned or cowarded by huge levels of noise and if one can make it more pleasant, then so much the better. But there is a serious side to this as well and that is that the noise level is actually at a point where it is dangerous. |
| Q16 | But is the driving force here your curiosity about the phenomena behind the science behind it, the phenomena behind it, or is the welfare of the patient? |
|  | It started out with the welfare of the patient in the first instance. These machines are very noisy and as one goes to much higher magnetic field strengths, the noise gets louder so there is a serious point to this. It happens also to be of interest to me from the physics point of view, how one can go about reducing the noise level in a way which satisfies the requirements of the patient and does not upset the imaging capability of the machine. You can always turn the machine off, but that doesn’t make any noise at all, do you see what I’m saying. You’ve got to get the balance right. That’s what we’re trying to do, come up with a technique which will not impede or impair the image quality but make the whole process more pleasant for the patient. |
| Q41 | Some time has passed now since the first discoveries were made and technology has substantial developed. You can put it in perspective now, I suppose. What is the real significance, what is the big paradigm shift that has come about through this technology? |
|  | I think it’s a different type of image that one can produce and an image which carries with it much much more information about the disease state, the disease process and produces this in a very very clear manner, in a manner which is easily recognisable so that to my mind is the major contribution. |
| Q41 | When you see it back in the history of science the paradigm shift is very often connected with the development of instruments. If you look on Galileo and the telescope, it changed our world view totally. You had Levenhuk and the microscope, it also changed our world view totally. What about this? |
|  | I think this will perhaps not be quite so important on broad spectrum as some of the examples that you’ve given, but I think it’s important for the patient and for the diagnosis to have a really good, clear understanding so that intervention for example can be done in a minimalist way, in a way which doesn’t cause further problems, but solves the immediate medical problem. In that sense I am always thinking I have to say, about the patient and patient comfort. |
| Q23 | This is of course fundamentally important but aren’t you a little bit modest when you play it down this way because looking into the brain and see how we think and maybe also could make images out of our most spiritual experiences. Don’t you think that will somewhat change the way we probably look at courses? |
|  | I’m going to play it down a bit more I think.Alright.Sir Peter Mansfield: I’m going to say that imaging of the brain for the study of the mechanism and the way in which the brain works has only just started and it’s extremely difficult for me or anyone else for that matter to predict how this will turn out ultimately. But the first core on imaging is to look at the diseased brain in terms of tumours or other problems associated, other medical conditions associated with this and try to bring relief to the patient so again I’m not really being modest, I think that’s what imaging is about. There may be other important applications but at the moment I think they remain to be demonstrated, it’s to the very early stage. I’m not saying it won’t happen, all I’m saying is that at the present level of development, the major, major application of MRI is going to be in treating sick people. |
| Q23 | But you’re using some very extraordinary phenomenon, down to the nuclear level of atoms and to the electron level of atoms. Do this phenomena exist or are they just measures in your instruments? Does spin exist? |
|  | That’s a very deep question and I can’t give you an exact answer. All I can say is that matter behaves as though it has a spin and at the very very tiniest level maybe there is no such thing as spin. It may be that nature conspires in such a way to give one the impression but at the end of the day we have to observe nature and interpret it in a sensible way and when one does this mathematically, it turns out that the best description is one where atoms, the nuclear atoms, actually have spin, but whether they are actually spinning I think is something that I can’t answer. |
| Q36 | But are there all sorts of phenomena deep down in atoms and the molecules and electrons. Can you foresee other phenomenas in other part of matters of behave that could be used for even more spectacular imaging techniques coming in the future? You just talk about protos, what about all the other atoms? |
|  | Again I think we’re limited in the materials that have the right sort of microscopic ‘behaviour’ and there is no response to many many materials which where the nuclear have apparently no spin. We are looking for something which at the nuclear level behaves as though it’s a spinning top, but quantum mechanically of course we know that it’s only a manifestation of some deeper state, a deeper state of matter. Maybe nothing is spinning anywhere. |
| Q36 | But when it comes to functional imaging we have seen some spectacular films on moving hearts and intestine moving. How far can this be driven do you think? There are hormones running around in our body, there are nerve impulses going around. Will it ever be possible to make imaging of the way life is functioning in such a detail ever? |
|  | I would say not. I don’t want to spoil somebody else’s Nobel Prize for the future but I think the problem with people, ordinary folk and particularly film makers, is that you give them something and they always want more. They are not satisfied with the wonders that can already be achieved, they want to push the science if they can and get people to make comments which you can’t possibly substantiate. That’s the problem, I think, with interviews of this time, you always want that little bit more, you won’t be able to push the topic beyond comfort level and that’s all I can say. |
| ID | 0552 |
| Biographical | An autobiography published a few years ago[\*](https://www.nobelprize.org/prizes/medicine/2002/brenner/biographical/#not) records many of the salient events in my life which led me to become a scientist and my Nobel Lecture covers the intellectual background and consequences of the research work for which the Prize has been awarded.In this somewhat compressed version, I start with my birth on the 13th January 1927 in a small town, Germiston, in South Africa. My parents were Jewish immigrants from Eastern Europe; my father came to South Africa from Lithuania in 1910, my mother, from Latvia, in 1922. My father was a shoe repairer and our first home was in some rooms at the back of his shop. He never learnt to read or write but, in addition to English, Yiddish and Russian, he learnt to speak Afrikaans and Zulu. I learnt to read at an early age, and a customer of my father, Miss Walkinshaw, persuaded my father to allow me to go at the age of five without charge to her kindergarten. I completed the first three years of primary school in one year and was admitted to the local school the age of six directly into the fourth year, some two years younger than all my contemporaries. After 4 years in primary school, I went to Germiston High School where I matriculated in December 1941, just before turning 15.During this time I discovered the Public Library in Germiston, one of the many libraries set up all over the world with funding from Andrew Carnegie’s endowment. It was here that I found a source of knowledge and the means to acquire it by reading, a habit of learning which I still follow to this day. I also became interested in chemistry and gradually accumulated enough test tubes and other glassware to do chemical experiments, using small quantities of chemicals purchased from a pharmacy supply house. I soon graduated to biochemistry and tried to discover what gave flowers their distinctive colours. I made the (to me) astounding discovery that the pigments I extracted changed their colours when I changed the pH of the solution.I was fortunate in that the Town Council of Germiston gave me a bursary of 60 pounds per year that allowed me to go to the University of the Witwatersrand in Johannesburg to study medicine and, in 1942, at the age of fifteen, I began the course studying Physics, Chemistry, Botany and Zoology. I lived at home and I cycled every morning to the railway station to travel by train to Johannesburg followed by a walk to the University, carrying sandwiches for my lunch and returning in the evening the same way. My Uncle Harry had given me a microscope as a present which allowed me to continue my personal explorations of the living world. This was the beginning of my contacts with the real science. In my second year, after moving to the Medical School, I began the courses of Anatomy and Physiology. I had begun to see that I was interested in cells and their functions.It was noted then that I would be too young to qualify for the practice of medicine at the conclusion of my six year medical course and I was allowed to deviate and spend one year in a Medical B.Sc. course in Anatomy and Physiology. This was heaven. The small group of about a dozen students inhabited a small room in the Anatomy Department where we each had a small laboratory bench. We learnt how to do research by working in small groups with more advanced researchers in the Department. I learnt physical chemistry with Joel Mandelstam (later Professor at Oxford University), microscopy with Alfred Oettle, and neurology with Harold Daitz who became a close friend and who died at a very early age in Oxford. Raymond Dart and Robert Broom taught me anthropology and paleontology, and the man who inspired all this activity was Joseph Gillman, a histologist who had created a centre of research in that isolated place. He invited me (I needed no persuasion) to continue with research and I stayed on for two more years doing an Honours degree and then an M.Sc., supporting myself by working part-time as a laboratory technician. I read many books and taught myself many subjects during this period, learnt how to build equipment and how to do experiments, and had many arguments and discussions with Joe Gillman. I also began to publish papers. My scientific bibliography begins in 1945 with a paper published with Joe Gillman and his brother, Teddy, but my first paper as sole author appeared in 1946. This paper dealt with a histochemical reaction, and it was the first of several which reflected my growing interest in a subject which I later called cell physiology. My M.Sc. thesis was in the field of cytogenetics, another self-taught subject, and this was the beginning of my research in genetics. This background was to serve me well in later years when I became a molecular biologist.In 1946, W. Le Gros Clark visited South Africa and invited me to come to his Department of Anatomy in Oxford, but I was advised by everybody to finish my medical course, because it was believed then that a medical qualification would be essential for a research position later. I did go back to my medical studies but I continued working in the Department of Anatomy and moved to the Department of Physiology when Joe Gillman became Professor there. I was not a good medical student and had an erratic career, brilliant in some subjects, absolutely dismal in others. In my final year I failed Medicine, scraped through Surgery but got a First Class in the third subject, Obstetrics and Gynecology. I had to go back and repeat Medicine and Surgery and six months later, in July 1951, I finally received the degrees of MB BCh. I had already decided that I would do research and that I needed to go abroad. CH Waddington, who had earlier visited South Africa had advised me to go to Cambridge. I applied to the Department of Biochemistry and never even received a reply. I had decided that the subject I was interested in was molecular biology which, of course, did not exist at the time, and when I was awarded a scholarship by the Commission for the Royal Exhibition of 1851, H. Raikes, head of the University of Witwatersrand, who was originally an Oxford trained chemist, advised me to write to [C.N. Hinshelwood](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1956/index.html), the Professor of Physical Chemistry at Oxford University, who had interests in the applications of physical chemistry to biology. That sounded closer to what I wanted to do. Hinshelwood had written a book called the “Chemical Kinetics of the Bacterial Cell” which I read and thought was in the direction I wanted to go. He accepted me and suggested I work on bacteriophage resistance in bacteria. I immediately began to read about bacterial viruses and in October 1952 I arrived in Oxford to do a Ph.D. in the Physical Chemistry Laboratory.There was still food rationing in England and life was difficult all through my 2 year stay in Oxford. In addition, I and the others were outsiders three times over; we were scientists, we were research students and we were colonials. Many of my friends in Oxford shared these stigmata and the only compensation was the opportunity to join Halifax House and lunch there. This was where I met Jack Dunitz, a crystallographer, and through him Leslie Orgel, a theoretical chemist, both of whom have remained lifelong friends and colleagues.We had many discussions on DNA, for I had come to Oxford with two half ideas both of which were more than half wrong. One was a way of working out the structure of DNA using dyes and the other was how nucleic acids could participate in the synthesis of proteins. I can remember in November 1952 Jack telling me about two fellows in Cambridge who were going to solve the structure of DNA. When in April 1953, Jack told us that these two fellows in Cambridge, [Francis Crick and Jim Watson](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html), had indeed solved the structure of DNA, Jack, Leslie and I drove to Cambridge on a day between the 16 and 18th April to see the model.This was the watershed in my scientific life. The moment I saw the model and heard about the complementing base pairs I realized that it was the key to understanding all the problems in biology we had found intractable – it was the birth of molecular biology. It was a revelation reinforced by conversing with Jim Watson at greater length during a walk we took together, when I realized that working with bacteriophage had put me on the right road to enter this exciting new field, even though what I was doing was trivial.My wife and I were married in London in December 1952 and she was also engaged in doing a Ph.D. in Psychology in London. She was allowed to move to Oxford and, until June 1954, we lived in a flat in Woodstock Road working on our theses, had a child in addition to my stepson, Jonathan, dreaming all the time of food and the warm climate of our native South Africa.An opportunity to visit the United States came about when Dr. M. Demerec, the director of the Carnegie Institution Laboratory at Cold Spring Harbor visited Sir Cyril Hinshelwood. It was Demerec who invited me to Cold Spring Harbor and who helped me to obtain a Carnegie Corporation Travelling Fellowship which enabled me at the end of the summer in Cold Spring Harbor to make a trip across the United States to visit other laboratories. I drove across America with Jim Watson to Cal Tech and I then had a period of research at the Virus Laboratory in Berkeley, working with Gunther Stent. I also had made a short visit to Washington, D.C.My visit to America was important because through it I met many of the then important workers of the Phage School, Seymour Benzer, who became a lifelong colleague and friend, [Max Delbrück](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1969/index.html), the founder of the phage school, [Salvador Luria](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1969/index.html) and many others who were destined to play important roles in the development of of the new science of molecular biology.I had also met Francis Crick again in Woods Hole and Cold Spring Harbor and visited him in Cambridge in December 1954 on my way back to South Africa. At this meeting we discussed how I might join him in the future and I returned to South Africa at the end of 1954 as I was committed to do so by the terms of the Carnegie Corporation Fellowship.I set up a laboratory in the Department of Physiology in the Medical School in South Africa and begin to try to find a bacteriophage system which we might use to solve the genetic code. I also continued to work on some theoretical aspects of the genetic code and during this period was able to prove the impossibility of all overlapping triplet codes which was circulated in an RNA Tie Club note and later communicated to the Proceedings of the National Academy of Sciences by George Gamow. Francis worked hard to get me an appointment at the Medical Research Council Unit in Cambridge and in December 1956 we left South Africa for a new career in England. I did all of my work on molecular genetics in the Cavendish Unit and its successor, the MRC Laboratory of Molecular Biology, where the work on *C. elegans* was initiated and developed. I spent 20 years sharing an office with Francis Crick and many new and exciting ideas (both right and wrong) were generated from our conversations. The centre point of our interests had begun to diverge and whereas we were both interested in the nervous system, I was far more interested in finding a simple experimental system which might tell me how brains were constructed, whereas Francis wanted to know about the complex activities of higher nervous systems. He left Cambridge in 1976 to join the Salk Institute where he pursued an entirely new career in neuroscience.In 1977, I was appointed proleptic Director of the MRC Laboratory to succeed [Max Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/index.html) on his retirement in 1979. However, I immediately took over the financial management of the laboratory and spent several years in trying to get the finances on a proper basis. These were times of hyperinflation in Britian and not enough attention had been given to the rising costs of our research. I often referred to myself as the epileptic Director. During this period, I became interested in how the new techniques of cloning and sequencing DNA could influence the study of genetics and I was an early and active proponent of the Human Genome Sequencing Project. By 1985, I found that the administrative load of the Director was becoming tiresome and interfering with what I still wanted to do in research and so when I was asked whether I wanted to continue as Director after 1987 when my term of appointment ended, I jumped at the opportunity and left the laboratory in 1986 when my successor took office. The MRC gave me a small Unit and, with some added resources, I set up a Unit of Molecular Genetics based in the Department of Medicine where space was provided for me by Professor Keith Peters. It was in this Unit that the pufferfish project began. The Unit was closed by the MRC in 1992 when I was 65 but I continued the laboratory with other support for some years thereafter. In the meantime, it became imperative for health reasons that I spend the winter months in a warmer climate and Richard Lerner made this possible by giving me a part time appointment in The Scripps Research Institute in La Jolla, California. Here I found I could pursue new interests in chemistry and especially in the interface between chemistry and biology. I also became involved in a company in the San Francisco Bay Area called Lynx where together with another friend, Sam Eletr, we developed a new massively parallel method for sequencing DNA. In 1995, I founded The Molecular Sciences Institute with a gift from the Philip Morris Company where I hoped that we could create an environment where young people could pursue science in an atmosphere of harmonious purpose and high intellectual challenge. I retired from the Institute in 2000 and in 2001 was appointed a Distinguished Professor in the Salk Institute in La Jolla where I rejoined Francis Crick.I owe a great debt to the many people who have helped me in my life. My parents would have preferred me to become a surgeon or a physician but were most understanding of the ambitions of their son. My wife and family have borne the burden of a preoccupied husband and father for fifty years. Living most of the time in a world created mostly in one’s head, does not make for an easy passage in the real world. Throughout my scientific life and in all my projects I have been joined by many scientists, young and old, whose work was absolutely essential for the success of our scientific endeavours. Many have gone on to do important scientific work but all remember those wonderful times when we and our science were young and our excitement in meeting new challenges knew no bounds. I believe that a scientist should be judged by the quality of the people he has helped to produce and not by prizes or other honours bestowed on him. Let my works speak for themselves.I am still, at the age of 76, excited by scientific research and the prospect of what can be done in biology. Science is something one is tied to for life and one should never retire from anything until one has secured one’s next job. The endless quest for knowledge will continue as long as humans exist. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0552 |
| Interview |  |
| Q49 | “Man is but a worm,” that was the satirical, ironic comment that was given to Charles Darwin when he presented his theory of evolution. The same quotation was used in the [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2002/horvitz/lecture/) by Robert Horvitz, and I suppose, Robert Horvitz, that there was a hidden meaning in you showing that picture and doing that quotation. |
|  | Robert Horvitz: I don’t know that the meaning was specifically hidden but the point was that it reflects in fact the findings of the three of us combined. Because as we have learned more and more about biology, we find that the biological principles, the biological mechanisms, the precise genes and proteins that one sees in a worm of the sort that we’ve studied, or probably in any other organism, are remarkably similar to those that are present in human beings. |
| Q49 | “Science is at a crossroad,” is another quotation from the [Nobel Lectures](https://www.nobelprize.org/prizes/medicine/2002/sulston/lecture/). ”Either you decide to do science by press releases or you do science by publication.” That quotation came from the lecture given by John Sulston, what was the meaning of that quotation? |
|  | John E. Sulston: I think to be honest probably it’s more biology at the moment. It’s an old issue with science I think, whether one is going to simply make claims. In a previous discussion we were saying how the alchemist practiced science by press release, and he didn’t do very well. The point about press releases is you don’t check the facts behind and what you should do with press releases is to say: Show me your data. Biology is now finding itself in this position because suddenly biology is of commercial value and there’s a great temptation to try to gain financial advantage by issuing statements but not publishing them properly. We’ve had some experience of this with genome work and so that’s why I made a particular point of this, that we must publish openly, show the data and that’s the way science proceeds properly. |
| Q49 | “We’re drowning in an ocean, or a sea of data but we are starved from knowledge.” That is a quotation from Sydney Brenner’s [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2002/brenner/lecture/). Sydney Brenner, could you expand a little on that? |
|  | Sydney Brenner: Yes, I think we now have unprecedented ability to collect data about nature. Generated of course by our ability to sequence the genomes of complex organisms. You might say that we could in principle make an atom-by-atom description of what there is in nature, but there is now a crisis developing in biology that that completely unstructured information does not enhance understanding. What people want is to understand, which means you must have a theoretical framework in which to embed this. It is interesting that the word science and the word knowledge actually is the same word, so that people who just collect data are not doing science in that sense. I think that this problem will occupy our attention for certainly the next coming decades. Because we need it not only for understanding, but to communicate it and teach it. |
| Q34 | By this you have introduced yourselves, all the three Nobel Laureates in Physiology and Medicine. And welcome to the Nobel e-Museum and this interview on your prizes and the science around it. Let’s go back to this issue about differences between knowledge and data, Sydney Brenner. What are the great challenges that lie ahead of bioscience now when the human genome is almost, because it would always be almost completed? |
|  | Sydney Brenner: It was originally said that sequencing the human genome would be like sending a man to the moon, and if you reflect on it, it’s exactly the same. Because sending a man to the moon is very easy, it’s getting him back that’s the problem. I think the metaphor now extends, which is how can we get the human genome back from the moon, because we’ve done the first half. I think everybody knew that the major task would be to find the meaning of the genome, to interpret it. And I think that for more of the more sober people in this field, they’ve realised that the major part of the task still lies ahead. I think that that is going to be absolutely essential. Now there is a tendency in our science to say that everything could be done by this type of factory organisation, that was necessary to sequence the human genome and the other genomes. And there is now an idea afoot that we could just set up all of this to study proteins, to study cells, to study everything. But I’m a great believer in the fact that factories are not necessarily intelligent. And I think that what we’re going to need is human intelligence. I think the belief that we will put all this data into a computer and it will tell us the answer, this is ill-founded.John E. Sulston: I think it’s a minority who really feel that. I think what you have to guard against is this tendency that people put “-omics” on the end of everything and feel that it’s a new field and it really isn’t. Truth to say, although much drama was made of it and this was really because of the issue of the data release, there was never a very large fraction of science funding spent on the sequencing and I think that’s probably the rule. I think one should continue with large scale projects which have to be highly justified, but always with regard to the problems that they’re going to address. I think it should always be the case that by far the larger part of the funding should be spent on individual problem-solving efforts. If we can keep that balance, then I think we’re alright.Robert Horvitz: I would absolutely agree with that. One of the comments that echoes in my mind is the comment “don’t forget the biology”. The sea of information indeed does sometimes mask, and the excitement of the acquisition of such amounts of data, sometimes masks the fact that this is simply the foundation. To understand, we do need the basic inquiry. I think that what is really vital is to keep in mind creativity as being much of the source of future progress. Creativity is not the product of either a factory or a committee, the creativity really comes from an individual or sometimes a very small group of individuals, and we must make sure in all contexts that we keep those paths to creativity as open and as supported as we possibly can.John E. Sulston: I’m particularly pleased that we made a clear expression of this, since we’re here on behalf of the worm, the way the worm DNA sequence was published, it was entitled “A platform for investigating biology”. And there was a rather short paper about the genome itself surrounded by many other papers which were making the first steps towards the analysis that Sydney was speaking of. I’m very pleased that we did that because I think it expresses our feelings very well. |
| Q23 | Does that mean that we are focusing in a way too much on the genes? There might be much more interesting knowledge to be gained from complexity and the interaction between all the other things that are around the gene. Who is deciding over the genes? |
|  | Sydney Brenner: I think the complexity problem is the problem. It’s going to be even more enhanced in later years as we begin to tackle such questions as how does the brain work? I think that we need to, and biological systems are unique in that they can encode their own complexity within themselves, so biological systems will be the ones where this new science can be investigated in an objective manner and will form a bridge between the complex systems we ourselves invent, in economic systems and the law governed systems that you find in physics and chemistry. I think biology will occupy intellectually a pivotal role.Robert Horvitz: I think genes are very important but as we talk about biology, we are of necessity talking about biological complexity, and there are different levels of complexity. We have complexity at the level of genes; we have complexity at the level of cells; we have complexity at the level of networks of cells. As we talk for example about the nervous system, certainly genes provide the framework and the foundation for all that goes on, but some of the problems of the nervous system are probably best addressed not at the level of genes, but rather at the level of cell networks and neural networks. It’s only part of the problem, the genes, and we certainly want to understand at that level but my statement again is don’t forget the biology. The biology is much broader than genes. And some of the studies absolutely have to be carried at these higher levels. |
| Q23 | But the exciting thing is that it sounds as if there were some general knowledge to be harvested from this theory of complexity that could be applied even to economics and to associated questions or to other complex systems. What is your idea on that, John Sulston? |
|  | John E. Sulston: I’m not sure. People talk a lot about complexity theory. There’s a web thing that keeps being sent to me and I’m not sure that I believe in this abstraction. But of course people should try, if they think they can produce generalisable rules that may be right. One other point, I think the construction of devices is immensely important. I must say, when we come to talk about the human brain, I am one of those who regard it as least as important, the attempt to make intelligent devices. At the moment the words are being misused because none of our devices are intelligent. But nevertheless, as soon as you begin to make machines that learn and indeed evolve in some fashion, then I think we are beginning to use messages from life. In that sense you might be saying that we are using some similar ideas. But whether or not some real understanding of complexity will emerge, or it will be rather the case as Sydney has often said, that you cannot make a description which is shorter than the thing itself. I think we have to find out. But I think we have to explore. I do emphasise, it’s so important that we should use our creativity in this way. I think it’s actually particularly important, it came to light in a comment the other day that maybe Mozart had a completely different sort of creativity from scientists because without Mozart the music wouldn’t have existed, whereas with science we only discover and it’s there. I don’t think that’s true as we go forward in the areas we’re talking about now, because I think our creation will be as important as our discovery.Sydney Brenner: The answer to the Mozart thing is that the sounds exist in nature and he found the language to put them together in an interesting way. We could take exactly the same view which is that the objects exist in nature and it is the language that we use, whether it’s mathematics or scientific theory, to put them together. I don’t necessarily believe that there is a fundamental difference between them. I think the important thing is that it seems to me, that there are still enormous puzzles in this that are quite difficult to grasp. Because we have now systems of enormous complexity, like the human brain, which has arisen by an evolutionary process from the systems and shows continuity with *C-elegans*, that something came from *C-elegans* to reach this level of complexity by a process of mutation, accretion, but not by a process of design, which is the difference between this and man-made objects. And I think that that says to me that there must be some architecture within this that permits that flexibility because for many other systems, we know that if you change them, the most probable consequence is you break them. Whereas through this evolutionary process, nature has achieved something and to comprehend that I think is really a big challenge.John E. Sulston: The major thing of course is the rearrangement of the parts. I think we now understand that that’s the most likely key role of sexual reproduction. It’s an old puzzle for the geneticists, how organisms are inconveniently diploid, they have two copies of everything. The reason is probably that every generation can get a great rearrangement. Although the process is blind, in fact evolution is indeed arranging the parts. This is more likely to be productive than mutation which is usually destructive or merely adding new bits, and where do you get the new bits from? But if you rearrange old parts which work together in slightly new combinations, you can make much more rapid progress. And I think it’s right to say that’s how evolution has proceeded.Robert Horvitz: I think evolution is also a key word in the context of the question you raised a few moments ago about complexity. And the question is biological complexity likely to provide models for complexity of other systems? I think the answer is that evolution has done the work of generating a number of solutions and that if we understand those solutions, we can then see at least some cases in which complexity has been defined and we can then ask whether we can apply that knowledge, that framework, in other spheres. My guess is actually that we will be able to do so but probably not in ways that we’ll anticipate until we see what the answers really are. I think in part about devices that have been made in bioengineering, where people have made a variety of prosthetics and other devices, always with the notion that they’re copying biological systems but by and large, what is done before the knowledge of the biology is actually very unlike the biology. But the knowledge of the biology can then change what one can do in the future. I’m perhaps a little bit more optimistic than John of the general principles emerging, but we don’t know ahead of time what they are. Evolution has solved problems.John E. Sulston: The reason I speak about it negatively, I do feel that complexity is now a buzz word just as chaos was about 10 years ago and it annoys me. It’s like “-omics” over again. Let’s just find out how it works |
| Q34 | Along the path you understand more and more about how life works, but what would you say would be the most serious challenge to our ethics? What is the most controvert ethical question that will arise out of the science that you are a part of? |
|  | John E. Sulston: I think the challenge to the ethics is ourselves and our social systems actually. I don’t think inherently we are creating worse ethical problems with biology than we did by, for example, inventing nuclear weapons. But in both cases, if we don’t apply the democratic process properly, and of course we do have to bear in mind all the time, as [Winston Churchill](https://www.nobelprize.org/prizes/literature/1953/churchill/facts/) said that “Democracy is most awful way of governing ourselves until you think about the alternatives.” I think it’s very true that we don’t have any alternative to democracy and unless we apply it properly, and that means a rather full democracy, not a microsecond response referendum but a full democracy in which everybody has a chance to learn and to participate, then I think we might be in some trouble through discrimination of various kinds, and people have painted various horror stories of how we might actually specie-ate ourselves, if the rich ought to start breeding themselves in some clever way. I believe that properly applied social democracy will be a sufficient check on excesses of that kind.Robert Horvitz: One comment that was made really can be seen in a book written some years ago by [Jacques Monod](https://www.nobelprize.org/prizes/medicine/1965/monod/facts/), which he entitled *Chance and Necessity*. In that he took this topic that Sydney has alluded to, and that is the knowledge that essentially biological organisms have not been designed, they have evolved by chance. And what we see before us just is the consequence of a large number of random events and the selection of those that happened to work better than others. That may, as Monod very well discussed, interface with the issue of ethics because we have to begin to think of ourselves in different ways than perhaps much of human society has thought in the past. Particularly in the context of religion and ethics that are driven by religion. I think what we’re going to need is basically an ethical foundation that is humanity driven as some of these concepts really change with time. But I think those ethics inherently shouldn’t be altered by knowledge, but it’s the responsibility of all of us to make sure that the ethics are very much front and centre stage. |
| Q50 | Given that reproductive cloning could be done as safely as IVF and IXa today without any risk for the child or for the mother. Would reproductive cloning fit into that ethical framework in the future? Sydney Brenner? |
|  | Sydney Brenner: I think your assumption has to be questioned, whether it could be done. No, because I think that I can imagine a society that would accept that. There was a tremendous row over the case of *in-vitro* fertilisation and many people thought that it was unethical. Of course the argument was that this was of great benefit to a certain group of individuals. In that way now the machinery exists for those people to benefit from it and it’s a safe procedure. What worries me more is that the objectives of human beings in different countries differ, and we have to sit and ponder not so much on the ethics of any procedure, but the ethics of spending large resources say on cardiac transplantation, just to keep away from the genetics, and very little on famine. And I mean it’s that that worries me more, that the world is not a uniform place with a uniform set of standards. I think we have to be careful when we are thinking which leaf is higher than another leaf to be sure which branch we are standing on.John E. Sulston: In fact I think I would go a little further than that, I would say that the world is in danger of being pushed towards a uniform standard. The standard of the unadulterated marketplace, where indeed the money will continue to be spent on cardiac transplants and drugs that are used mainly by the rich countries, because that’s where the markets are, and the others are neglected. I think in a sense we have a uniform principle and I think it’s wrong. I think we’ve got to have a new principle where we deliberately try and spread the healthcare more evenly and I think this is something we desperately need today. |
| Q50 | And you have a recipe or any road ahead for that? |
|  | John E. Sulston: The road ahead? I’m afraid I have to say democracy again, because in the end if it’s not a democratic voice then it won’t work. But I think what’s happening is that our great world organisations, the World Trade Organisation and also the World Health Organisation, are much more nearly one vote, one dollar than one vote, one person or one country as they should be. I think it’s up to us. I think we actually share a rather higher platform than we did a couple of months ago for speaking about these matters, so it’s important that we do think about them. I think that we should press for this.Robert Horvitz: I think democracy is a key word, but I think what we need is an enlightened democracy, because in a democracy there is always the risk of the rule of the majority to the detriment of the minority. In this case we’re talking about the rule of the minority to the detriment of the majority, so it’s more extreme. But I think even in the case where it’s a majority we have to make sure that the rights and privileges of the minority are very well maintained and supported. I think that we need education. I think we need leadership to really inform and perhaps even persuade the majority of people who are making decisions that it is in their interest as well as in the interest of humanity in general to follow the kinds of paths that have just been described. |
| Q49 | When the genome project was almost finished, President Clinton and the British Prime Minister met at a press conference announcing this completion of the genome. Then President Clinton said: “Now, maybe we have seen the language in which God created Man”, and Sydney Brenner, you wrote a comment on that. |
|  | Sydney Brenner: I think that what I wrote on that is in the same way we could view the Bible as the language which man used to create God. That was just a comment like that. I think that that’s a very, how shall I say, exaggerated way of putting it.Your saying or Clinton’s saying?Sydney Brenner: Clinton’s saying. Because I think it has to pay respects to certain views in society and it’s not the language which anybody used to create man.Because you have said very clearly that the architecture is inside the structure.Sydney Brenner: The architecture is inside and I still think that that is the question of how this … This is why I think ordinary people don’t believe in evolution because we’re telling them by random changes that we can change a black and white television set into a colour television set. And everybody says there’s no way that can happen because if I try and change a television set, I’ll break it. That’s what will happen. And that is why a lot of questions about the internal architecture become important. That mutation happens but certain mutations carry a greater value than others. And we need to understand, so clearly mutations which affect the language of gene regulation are going to be more profoundly important than ones which just might affect the function of a protein. |
| Q51 | Maybe Robert Horvitz, couldn’t Sydney Brenner’s statement about the Bible be interpreted seriously? Given the mutations work finally gives us consciousness and awareness and we have created God or made him. The Bible was the language in which we describe what we think is the higher meaning for life. |
|  | Sydney Brenner: Exactly, yes, it’s a deeper thought than is done in terms of what it was alluding to. It was double edged, and one edge was what you said, the other edge was to say, it’s a more comic way of looking at the human genome.John E. Sulston: I think that there is a serious point there. But incidentally, what I would like just to replace the President’s remark with is that what we’ve done is to read the language of evolution. As Sydney emphasises, and he’s absolutely right, we don’t understand it. But nevertheless, we have the hieroglyph, we know how we brush the sand off the hieroglyph and now we’re working on its interpretation, I think. But to the other point, I think we do have, and that’s why I agree so much with what Bob said about trying to develop a real humanist basis for ethics. Because after all it’s not just the Bible, it’s the Koran, it’s a zillion other writings, all of which are more or less contradictory, all of which incidentally are very capable of leading people to physical combat and really serious warfare over points which were written in these books. I think we can develop serious humanism, but we do only have a limited amount of time because I do think we are going to understand the workings of our brain in much greater detail. I do think that we’re going to come much closer maybe to have a full understanding of what we really mean by self-consciousness and free will. By understanding what I mean is, and it is going to be complex, that in some fashion we’ll be able to write down all the components. Now the question is what will that mean? How can one comprehend oneself? It’s like trying to understand the Klein bottle. It’s a real paradox.I suspect the way we shall do it is to actually understand all the pieces but nevertheless not be able to hold an image of how it works all at once in our own heads. You can sort of trace around the pathway and do each bit at a time. I think most of us actually feel like that thinking about relativity, I certainly do. I can do the bits but just getting the whole thing, it just won’t gel for me. Now the reason I say it’s urgent is that I think we are going to, at the same time, be increasing our physical power, our power of the biological world and we have got to come to a way of making responsible decisions about how to use these things, and to come to the point where we’re going to do it in the knowledge where we really cannot sustain the idea reasonably of us being driven all the time by some higher thing, but rather seriously regard ourselves as products of the evolution. I think we are going to have to have that sort of social ethical revolution. It’s going to be needed over the next 50 years or so. I think it’s a very, very urgent matter and one that’s very worth paying attention to, to try and contribute. |
| ID | 0553 |
| Biographical | “He can’t even throw a baseball!” was the way my cousin Harvey greeted me soon after my birth on May 8, 1947. Looking forward to a fellow athlete, Harvey, age three, found me ill prepared for sports. I suspect the disappointment continued, as Harvey progressed to become one of the star little league players in Chicago. I did not.Family history Chicago is my hometown. My mother Mary Savit Horvitz was born in Chicago, and my father Oscar Horvitz was born in the neighboring town of Joliet. Both of my parents were first-generation Americans, the children of Jews who left Eastern Europe around the turn of the century. My maternal grandfather David Savit (Savitzky) was born in 1879 and came to Chicago in 1904 (via Liverpool, Halifax and Detroit) from Oster, Russia, in present-day Ukraine about 40 miles north of Kiev. He was the second oldest of ten children, and his widowed mother Malke Zolotar Savitzky and his eight younger siblings followed him to Chicago. David was a dress manufacturer and a grocer, but I remember him most reading, playing chess (sometimes with me) or standing at his newstand selling newspapers. The family held him in awe as a gentle and caring human being, and as a scholar.My maternal grandmother Rose Bleiweiss Savit came to Chicago from Galicia, Austria, around 1902. She was from an area that was alternatingly Austrian and Polish, from a town that is now Debica, Poland, about 60 miles east of Cracow. I always thought of her as Polish. She was one of the lucky members of her family, as her father Hersch David Bleiweiss and at least three of her siblings were murdered by the Nazis. Rose married David Savit in 1908, and my mother Mary Savit was born in 1921, the youngest of four girls, after Ann, Sylvia and Esther. In the early 1950s, David and Rose moved to Miami because of Rose’s ill health, but after David’s death in 1957 Rose returned to Chicago. She lived with us from 1963 until her death in 1968. Like David, Rose played chess, but she enjoyed poker more and sometimes joined poker games with my friends and me. Before I left for college in 1964, I spent one year living with Rose and during this time heard many stories, most of them about Chicago speakeasies during the 1920s.My father’s parents were Samuel and Celia Horvitz. Sam’s original name was Solomon ben Mikhail Gourevitch, but, like many other immigrants to the U.S., he found his name altered upon entry to the country. Sam was from a Jewish village called Shchedrin, located near Minsk, in what was then Russia and is now Belarus. Sam was from a wealthy Russian family. His father ran a lumber business but, being Jewish, was not allowed to own any land himself. Sam spoke Russian, Polish, Yiddish and German. He married his first wife (not my grandmother) in Poland in 1902 and went to Chicago to avoid the 1904-1905 Russo-Japanese War. Once in the U.S., Sam worked in the garment trade as a presser. In 1910, he was blacklisted for participating in the four-month long Hart, Schaffner and Marx labor strike. Hart, Schaffner and Marx was a giant clothing manufacturer, the largest company in Chicago at that time. Employees were subjected to excessive work hours, miniscule wages and subhuman working conditions, and a strike at the company became the basis of a city-wide violent clash between businesses and the unions. Sam kept a hat with a bullet hole in it, a souvenir of a shot taken at him during a union rally. He became an insurance salesman, and it was because he was working for a Polish insurance company that from 1917 to 1920 he lived in Joliet, which had much industry, many steel mills and large numbers of Polish immigrants. Later, Sam operated a Chicago dry cleaning business, which I remember visiting once, just before he died in 1951.Sam’s first wife died in 1908, and he and their two daughters moved in with cousins, where my paternal grandmother Celia Bolotin was a boarder. Celia was from Novgorad-Syovorsk, about 150 miles northeast of Kiev in Russia. Celia was generally called by her Hebrew name of Tzipporeh, which means “little bird.” In Russia she had lived in a one-room house, which her family shared with the domestic animals, for mutual warmth. As a young girl, Celia was unusual. First, unlike most girls in her town, she learned to read. Second, she was rather stubborn and independently minded. Because in one of the books she had read a girl was cruelly mistreated by her step-mother, when young Celia’s widowed father remarried and was loading a cart to take his family and possessions to another town to live with his new wife, Celia refused to go, and moved in with an aunt. Both a desire for knowledge and a strong will are family characteristics that have endured. In 1905, Celia, not yet 20 years old, was involved in the first Bolshevik uprising and was captured by the Czar’s police. Knowing that they were executing people who knew how to read or write, she feigned illiteracy. They released her, but informed her if caught again she would be killed. Celia left Russia, traveling via Rotterdam to Chicago. She and Sam were married around 1909, and she raised Sam’s two daughters (Faye and Bess) as well as two daughters (Pearl and Diana) and two sons (Mike and my father, Oscar) from their own marriage. My father, like my mother, was the youngest. My father’s family moved a lot – about every three months – because landlords offered three months free rent to attract tenants. I never knew either of my father’s parents very well, as Celia died before I was three and Sam when I was four. My father and Sam were not on good terms, both because Sam left Celia for another woman and because Sam failed to provide any support for the large family he deserted during the Depression. I think both Celia and Sam influenced me greatly through my father, who learned about responsibility from his mother and about the costs of irresponsibility from his father.My father was born on November 3, 1918, just before the signing of the armistice ending World War I. His parents were delighted that the war was ending, and named him Oscar Freedom Horvitz. My father never liked and never used his middle name, signing things as Oscar F. or, more often, simply as Oscar. He grew up on the north side of Chicago, but nonetheless became an ardent fan of the south-side Chicago White Sox baseball team. Dad himself wanted to be a professional baseball player, but his eyes went bad when he was young (as did mine) and his family could not afford to buy eyeglasses. Eventually, one of his teachers purchased a pair of glasses for him. As a teenager, my father worked as a milkman’s helper, and many weeks the family lived on the butter, eggs, milk and cottage cheese he was allowed to bring home from whatever was left over at the end of the daily run. After my father finished high school, he went to work to support both his mother and himself. He took a job with an advertising agency, clipping ads from daily and weekly newspapers around the country. He found the job tediously dull, and to amuse himself he memorized the names of every town and its newspaper. He remembered these names throughout his life, and I think back fondly how years later people would express amazement that he knew not only the locations of their hometowns but also the names of their hometown newspapers.My mother Mary Savit was born on June 5, 1921. Not given any middle name, she decided to adopt the middle initial “R,” because it gave her the initials “MRS.” She lived in a variety of neighborhoods in Chicago’s north side. My parents met at a Christmas party in 1938, when my mother was 17 and my father 20. While in high school, my mother worked for 25 cents per hour as a sales clerk in a dimestore. In college, she had a part-time job as a bookkeeper and telephone switchboard operator at a company that made and sold uniforms for military officers. My mother obtained a teaching certificate in elementary education and then a B.A. in English from the Chicago Teacher’s College. She began substitute teaching in the Chicago public schools. My father changed jobs, working next at a mail-order house, and attended night school to study chemistry, which he loved. However, he soon realized that he could not afford the continued schooling that would be needed to allow him to make a living as a chemist. He switched to accounting. In 1941, my father passed the civil service exam in accounting and was hired by the General Accounting Office of the U.S. Government for a job in Washington, D.C. To be together, he and my mother decided to get married. Because he could not afford and my mother did not want a diamond ring, my father bought a ring for my mother in a dimestore. He returned to Chicago for the wedding, which was on June 30, 1942. They lived in Washington until 1945, when they moved back to Chicago. While in Washington, shortly after my parent’s marriage, my father was hit by a car, soon thereafter leaving him with a steel pin in his shoulder. He later told me that without this accident I might never have existed, as otherwise he would have been drafted into the army and who knows what would have happened to him if he had gone to war. In Chicago my father continued working with the General Accounting Office, while my mother continued the employment she had begun in Washington, D.C., with the Social Security Board of the U.S. Government.Growing up I was born in 1947 and given the name Howard Robert Horvitz. My first name, which started with an “H,” was in memory of my great-grandfather Hersch, who had been shot a few years before by the Nazis. “Robert” my parents simply liked, in fact so much that they decided to call me “Bobby” and registered me for kindergarten as “Robert H.” Later, when I went to university, I reverted to the name on my birth certificate and became known as “H. Robert.” As I grew up my parents mostly called me “Bob,” reserving “Robert” for times of disapproval and “Rob” or sometimes “Robin,” by my father, as terms of love. I begged my parents for a baby sister, and, on October 5, 1950, my sister Carol Cecile was born. She was named for my grandmother Celia, who had died earlier that year. I remember awakening the day my sister was born, surprised to find myself in my parent’s bed next to my Aunt Ann, my mother’s oldest sister. Ann died of Alzheimer’s Disease many years later, one of a number of my personal reasons for becoming interested in neurodegenerative disorders. We lived on the north side of Chicago, which led to my becoming a fan of the Chicago Cubs baseball team, unlike my father, whose loyalty to the White Sox continued. My parents saved their money and moved repeatedly to find better homes for themselves and their family. When I was born, we lived in a one-room kitchenette near Lake Michigan, and I slept behind a screen while they ate, entertained or slept. We moved some miles west in 1948 to a one bedroom, four-room apartment. After my sister Carol was born, we moved again a few blocks away to a five-room bungalow on Rockwell St. Sometimes at night Carol and I secretly crawled out through her window to play in the back yard with friends who lived next door. One of the great delights of my receiving the Nobel Prize was that I was contacted by many old friends with whom I had lost touch, including one of these next-door neighbors on Rockwell St.  The Rockwell St. house is where I feel that I grew up, living there from ages five through 12. The neighborhood at that time was a mix of 1920s bungalows and apartment buildings, and was mostly Jewish. Author [Saul Bellow](https://www.nobelprize.org/nobel_prizes/literature/laureates/1976/index.html)‘s father lived a few houses south of us. I was a member of a club we named the Epics, without having any idea what the word meant but simply because we liked its sound. The year after I moved out of Chicago, the Epics became the Commodores, a gang. Rockwell St. was also important for me because it was while living there I became good friends with Ira Zarov, who lived across the street and whose mother was my Den Mother in Cub Scouts. Ira and I remain very close, exchanging e-mails almost daily and spending a week of most summers with our families together at his family home along the south shore of Lake Michigan, near Chicago.  I went to the DeWitt Clinton Elementary School and got into trouble repeatedly for small misdemeanors, particularly in the third grade. One transgression was my insistence upon crossing in the middle of the street to walk to school with Ira. Another involved the fact that Ira and I had acquired vast quantities of gumballs as a consequence of having found a cardboard circle that could substitute for a penny in the gumball machine in the local candy store. A few years later Ira and I were stopped at knife point by a boy trying to rob us. He was no bigger than we were. Ira and I moved apart and pointed out to our assailant that we had him outnumbered. He left.  In 1960, my family moved to the northern Chicago suburb of Skokie, because the schools were better. I attended eighth grade at East Prairie Grammar School. Because I had come from the Chicago school system, I was placed in the lowest of the three academic tracks for all of my classes. Within a few weeks, each of my teachers moved me to the highest track. The consequence was that I got to know, and become friends with, most of the eighth grade students very rapidly. My eighth grade English teacher, Marcia Wachs, is particularly memorable and engaged me in the reading of proper English literature. A year after I left her class, she sent me a book accompanied by a very nice note: “How many times I have thought of you and wondered how you were enjoying high school. … You seem to have a talent for writing, and I thought you might profit from reading this book. It’s a gem … .” The book was “The Elements of Style” by Strunk and White. I still have both the book and her note, and I use the book to this day (particularly when I try to educate members of my laboratory concerning the usage of “which” and “that”).  In 1947, the year I was born, my father became a Certified Public Accountant. His professional life thereafter was that of an accountant. My father loved numbers, a love I learned from him. Eventually, he became the Vice President and Treasurer of a major trucking company based in Chicago. Whenever we went on family trips, Carol and I always watched for Spector trucks, sometimes reminded by my father that the stock he had purchased for us was almost enough to say that we owned one of the tires on the truck. He was President of the Motor Carriers Accountants Society of Chicago. I was always very proud of the fact that he had published a book, which was an income tax guide for farmers. He also authored a chapter in a book about data processing. Published in 1957 and focused on the accounting machines and punched cards of the era, his chapter noted, “Long-range studies of electronic computers are being made at the present time.” In 1989, my father died from amyotrophic lateral sclerosis (ALS). His illness moved me to become actively involved in research involving this horrific neurodegenerative disease.  A sense of my father is reflected in a dedication written by my sister and me to an ALS Resource Book, the publication and distribution of which we funded. We wrote: “Dad was a humanitarian, not only in his values, but also in the actions of his everyday life. He cared deeply about people and always had the time to listen and provide insight. He was happiest when he was making someone else happy. In our family, Dad created an environment filled with a love of knowledge and the joy of inquiry and discovery about the world around us. Not a day went by without his learning something new and our learning something from him. So many things interested him: foreign languages, exotic places, history, new words, opera, baseball, people. He was equally excited by an exchange of smiles with little children as by a beautiful piece of music or by some scientific discovery. He also had a way with languages and often surprised people by speaking with them in their native tongue or talking with them about some detail of their country that few would know about. He once dreamed of being a major-league catcher, and then of being a research chemist. Numbers were his friends, and he chose accounting as his profession. However, his love of science continued and was infectious, giving both of us the opportunity and encouragement to study and lead lives dedicated to scientific inquiry. Dad was a wonderful mentor. He always strove to do his best, and he always brought out the best in those around him.”  My father’s illness and death were an immeasurable loss to me. My father was a major cornerstone of my life. It was my father who came to talk with the elementary school principal with me after my more serious infringements. It was my father who – after at age 15 I had attempted unsuccessfully to drive the family car using a “borrowed” key and knocked down a wall of the garage – convinced me over the telephone not to run away from home and who then came home from work not to punish me but rather to console and comfort me. It was my father who would sit with me and amaze me as he solved diagramless crossword puzzles and double acrostics by simply reading the clues and writing in the answers to each as he read them. It was my father who, throughout my adult life, prepared my income tax returns and who, once ill and dying, taught me how to prepare them myself. I think it was when my father died that I really grew up. I also became more introspective and much closer to both my sister and my mother during his illness. This closeness has continued.  My mother began working as an elementary school teacher in 1948, stopped in 1950 when my sister was born, and then resumed teaching in 1955. She first taught in the third grade and then progressed through the grades with me until she stopped as a seventh and eighth grade teacher of math and science. Her training was in English, and her interest in science and her desire to be a good teacher led her to take part in a program supported by the National Science Foundation in which she spent a summer studying astronomy. Later she returned to school and obtained an M.A. in guidance and counseling, after which she worked as an elementary school guidance counselor. My mother retired in 1988. My mother has been a wonderful model for the professional woman – a loving mother dedicated to both her family and her work. She inspired me, made me proud and developed in me an enormous respect for women in general. My mother chose teaching as a profession in part because it would allow her to be home with her children as they grew up. Nonetheless, to this day, she asks me if she ruined my life by returning to work too soon after my birth. I tell her I do not believe that I turned out so badly.  I could always depend on my mother. She is capable, organized, practical, logical and absolutely reliable. Although she is a worrier, my mother never loses her sense of purpose or her ability to deal with difficult situations. When I was hit in the eye with a baseball, it was my mother who took me for stitches (after leaving my father the succinct note: “Took Bob to the hospital. Don’t worry.”). When friends and I rode our bicycles to O’Hare Airport (a trip far beyond the confines we were supposed to traverse) and one of the others got a flat tire, it was my mother who came and brought us home. It was also my mother, with her interest and knowledge as a science teacher, who encouraged my first experiences with experimental science. My sixth grade science project, which I think was her idea, was entitled “Electricity Produces Light through Heat” and won a third prize. My ninth grade project, in which I used the fruit fly *Drosophila melanogaster* to replicate Gregor Mendel’s famed 3:1 and 9:3:3:1 inheritance ratios, required my mother to relinquish her bathroom for my breeding experiments. She helped me prepare the fly food, which smelled awful, and tolerated the fact that to anesthetize the flies I used ether, which smelled worse. This project also won a prize, and earned me a trip to the Illinois State Science Fair, in Champaign-Urbana. My mother saved the (written) project intact, and when the announcement was made that I had received the 2002 Nobel Prize in Physiology or Medicine, my mother showed a local reporter my 1961 science fair poster, one panel of which was then reproduced in the Chicago Sun-Times on October 8, 2002 (next to my high school graduation photograph).  My mother’s strength and independence became clearest to me as she nursed my father during his illness and as she has coped with and redefined her life after his death. My mother, now age 81, is impressively active and completely engaged in the events of the world. She regularly takes brisk walks for exercise and particularly enjoys walking at a nearby botanical garden. She is a bridge player, and loves the theater, the symphony, movies and art. She has long been politically active, and for some years has supported local and national actions of the National Council of Jewish Women. My mother has many friends, some of whom, albeit sadly a diminishing number, she has had for decades. My parents traveled together extensively, and my mother has continued her travels on her own, for example touring Australia, New Zealand and China. She also has visited Greece, Turkey and Costa Rica with my sister Carol. Their descriptions of the trip to Costa Rica, to see one of Carol’s field stations in the tropical rainforest, were somewhat divergent. Whereas Carol described the site as the Hilton of field stations, my mother emphasized the primitive conditions that she had experienced. Carol never told my mother that each night before going to sleep she would check my mother’s bedding for deadly snakes and spiders. After my father died, my mother for 10 years taught English as a second language on a volunteer basis to immigrants from all over the world. She also has taken countless adult education courses, on topics as diverse as international relations, world religions, poetry, music appreciation and money management. She has very recently obtained and begun to learn to use a computer. My mother is highly organized, and both her home and her person are well-kempt. She has been described as “an elegant woman.” She is constantly sending me newspaper clippings, sometimes about the world but more often with advice about foods, health, finance or child-rearing. Generally, the advice is very good.  My father and my mother were a team, in raising my sister and me and in life in general. Together they instilled in me a sense of responsibility, of commitment, of determination, of fairness, of pride, of ambition, of optimism and of love. People, particularly family, came first. Knowledge and learning were revered. We were all always expected to do our best. Prejudice was unacceptable and attributed to ignorance. Time together and family vacations were important, and we traveled together extensively within the U.S. Without doubt, my parents defined the priorities and many of the interests that came to be central in my life.  Growing up with my sister Carol was a special delight, except perhaps during a few of my teenage years when I regarded her at best as an intrusion. When little we would play together, and I would make up long stories of flying horses and imaginary friends. Carol voiced progressive views at an early age. When she was about five, she was listening to a conversation between my father and me. After he told me “Everything is made of atoms,” she immediately cried in response, “That’s not fair! Isn’t anything made of Eves?” Carol and I were quite divergent in our interests, with her gravitating toward the artistic and poetic aspects of life, whereas I was more focused on math, science and schemes to make money. Carol also was more rebellious, first against our quite secular home – she adapted the orthodox Jewish custom of lighting candles and saying prayers on Friday nights and went to a Hebrew overnight camp – and later politically, leaving Barnard College (at Columbia University) with the plan of becoming a left-wing political activist. Our parents intervened, and she registered at highly liberal Antioch College in Ohio, which because of its work study program allowed her to be almost any place but Ohio. While she was a student at Antioch, Carol spent time in Colombia, South America, and developed her passion for botany, Spanish and Latin culture. During this period Carol was rescued rather dramatically and against her will by our parents from a nearly fatal disease and an ill-fated engagement to a Colombian merchant marine, after which she stayed briefly in Chicago. I invited her to come to Boston, and she moved in with me, living on a front porch that we insulated for her and working at the Harvard Herbarium. Carol then went back to school and obtained a Ph.D. degree in biology, just like me. It is amazing, given our backgrounds and interests, that we both became biologists. Carol married Randy Nutt, an artist also from Chicago, and the two of them now live in Miami, Florida, where Carol is on the faculty of the University of Miami. Carol has spent much of her life in the tropical rainforests of Mexico, Central and South America. I believe we have always been close and mutually supportive, and I often think about the different view of life held by those who are not lucky enough to have siblings.  In addition to my family, there was another constant presence in my young life that I believe influenced me greatly. At age two and a half, I acquired asthma. For many years thereafter, nights (in particular) could plague me with a shortness of breath that made me feel (and occasionally wish) that I was dying. When I was small, my father would carry me in his arms through the night. Later I would just lie in bed, waiting for the dawn and hoping for the relief that often came with daybreak. I had tests, medications, and shots. The asthma continued and affected my life in many ways. Most sports seemed precluded. At age 10, I insisted upon going away to Camp Chi, an overnight camp in nearby Wisconsin, and spent almost the entire two weeks in the infirmary, with an adrenaline inhalator next to my bed. Despite these stresses, instead of becoming increasingly afraid of life, I think I became more and more determined to experience and conquer it. Nothing, I thought, could be worse than what I had already suffered. I became fearless, unafraid to go anywhere and try anything and determined to persevere, even when my shortness of breath made my physical suffering so great I could barely force myself to move.  In retrospect, I think back to growing up in Chicago with the impression that I had far more freedom and independence than I would allow a child today. After school, my friends and I wandered the neighborhood, which was assumed to be and probably was safe. For a while, Ira and I went house-to-house selling magazine subscriptions, hoping to earn all sorts of wonderful prizes. We rang every doorbell within the distance we could walk between school and dinner. We never sold a single subscription, but we did meet and talk with lots of people. For greater distances, my bicycle was my major source of transportation. Bicycle explorations went far beyond my local neighborhood and as often as possible into unknown areas. These adventures perhaps helped kindle the wanderlust that stays with me today.  In high school, the means of my explorations progressed from bicycles to cars. Before I could drive, I hitch-hiked through Chicago, simply going wherever the drivers were headed. Once the first of my friends turned age 16, we had access to cars, and a much greater world was opened. We went north to the expansive Lake Michigan beaches of wealthy Chicago suburbs and once even to Wisconsin (discovering in the process how fast a station wagon could go). We went south into the heart of the Chicago slums. 14th and Peoria, reportedly the site of various houses of ill-repute (we never got out of the car, so I never ascertained if that was true), was a favorite target.  As a high school student I did well academically. My introduction to biology was in the ninth grade, when I did my *Drosophila* breeding experiments. The class consisted almost entirely of dissections of formaldehyde-preserved animal corpses. The teacher was allergic to formaldehyde (or so he told us), and left us on our own each day. Mostly, I played dots with my laboratory partner. Based upon this experience, I never would have guessed that I would later become a professional biologist. For a project for this class, I made an extensive insect collection, which the school kept and displayed. While collecting insects in Chicago’s Humboldt Park, Ira and I were mugged by two older boys. They put their arms around our necks, and one said, “Your money or your lives.” Ira and I laughed, which was the wrong response. They squeezed more tightly, and I relinquished my butterfly net and thirty-nine cents.  As a sophomore, I received my first B, which was for one quarter of a summer school World History class. It was traumatic. I had been encouraged at home to have high expectations. Later B’s were less upsetting. I tended to work reasonably hard and developed a method of study that consisted of my trying to think of every possible question the teacher could ask followed by my writing both the question and the answer to the question on paper, which then allowed me to review both easily. This approach took some time and presumably reinforced the various facts I was supposed to be learning. I was the Assistant Editor-in-Chief of the school newspaper, The Nilehilite, which was my main extracurricular activity.  While I was in high school, my parents became convinced I would later become an entrepreneurial businessman. I had a variety of money-making plans. I published a magazine that I called Brigand (again, I simply liked the sound of the word), using a mimeograph machine for mass production. I sold advertisements for Brigand to local merchants and sold the magazines to friends, neighbors and relatives – mostly relatives. In another scheme, a shipment of sweatshirts had been damaged in one of the trucks from the trucking company at which my father worked. The trucking company had to buy the sweatshirts, which I purchased and resold at a profit. I also had a number of part-time jobs. For a while, I worked at an insurance company, looking at a handwritten number on a new insurance application and stamping that number onto the upper right hand corner of the first page the application. My most memorable job was at the large discount house E. J. Korvette’s, where I was employed in the record department and was able to buy records at wholesale prices. My boss was a bit of an eccentric, and every day after the store oficially closed he would play at maximal volume his favorite album, “The War Whoops of the North American Indians.”  I did not have a clear idea about either where I wanted to go to college or what I wanted to study. I enjoyed science, particularly math and chemistry, but I also liked English and working on the school newspaper. It seemed likely that I, like most of my classmates who chose to continue their education, would attend the University of Illinois in Champaign-Urbana. Alternatively, some of the best students went a bit further away, to the University of Michigan in Ann Arbor. I applied to both schools. However, a guidance counselor insisted that I also apply to “some school in the East.” I said that I would be happy to do so and that she should pick the school. She picked MIT, and I applied. I visited the University of Michigan the weekend of a Michigan vs. Michigan State football game, and the beer and partying convinced me this was not where I wanted to be. I was scheduled to visit the University of Illinois one weekend in November, but on Friday, November 22, President John F. Kennedy was assassinated, and my trip and much of the rest of what was happening in the U.S., were cancelled. The upshot was that when I was accepted to MIT, I saw no reason not to go there (except for the pleas from my English teacher, who warned me that my intellectual development would cease if I went to such a technical school).  The assassination of JFK for me, as for so many others, was an enormously deep shock. I was 16 years old and simply could not believe such things could happen in the country in which I lived. This event was one of a small number that no doubt are etched deeply in the minds of many, causing us all to remember precisely where we were at the time. In this case, I was in my high school cafeteria. Five years later, when JFK’s brother Bobby was shot, I learned the news from the radio upon awakening in my apartment in Brighton, Massachusetts. Much more recently, on September 11, 2001, I was at a meeting of the Howard Hughes Medical Institute in Chevy Chase, Maryland, sitting next to the HHMI President, Tom Cech, when Tom was called outside to be told what was soon to be announced to the entire group about the attacks on New York City and Washington, D.C.  MIT, the first time I flew from Chicago to Boston to begin life as an undergraduate student at MIT in September, 1964. At the freshman orientation, Dean Fred Fassett (whom I later got to know better after getting into some trouble) said “Look to your left. Look to your right. One of you won’t be here when the rest of you graduate.” My undergraduate years were a mix of academics and extracurricular activities, more of the latter than the former. I became Features and then Managing Editor of the MIT student newspaper, The Tech, and had the great excitement of scooping the Boston daily newspapers in getting a story and the paper out the morning after the great blackout in the northeast in 1965. I was very active in student government and was a member of a variety of committees and councils. When I became a candidate for student body president, I learned the names, hometowns, faces and majors of all approximately 3500 undergraduates. I spent full-time campaigning, met lots of people, and won the election. The next year I lived in a three-piece suit and had endless meetings with MIT administrators and, less often, with students. I talked with James Killian (President Eisenhower’s Science Advisor), Jerry Wiesner (President Kennedy’s Science Advisor), Jay Forrester (the inventor of magnetic core storage) and other MIT luminaries. Professor Forrester offered the view that everyone should change professions every seven years, a comment I have thought about many times since. I felt that I was grooming myself for a career in law and politics or possibly in business.  My coursework probably suffered, not in my grades, particularly, but in what I was learning. Mostly I would wait until the night before an examination, stay up all night, and learn what I needed to know to answer the questions the next day. For some courses I did nothing whatsoever until the week before the final examination. When one of my professors penalized me for turning in all of my problem sets at the end of the course, I thought he was being quite unreasonable. I majored in mathematics, with an emphasis on its theoretical as opposed to its applied aspects. However, I knew that in contrast to some of my classmates, I was not a mathematician in my soul. I had sufficient credits to graduate after three years, but did not want to do so, in part so that I could continue with my extracurricular activities and in part because I was simply having too much fun to want to leave. I decided to earn a second undergraduate degree, in economics. I then had the enormous good fortune to be able to write my undergraduate thesis under the tutelage of [Bob Solow](https://www.nobelprize.org/nobel_prizes/economics/laureates/1987/index.html) of the Economics Department. Bob was amazing. I would struggle for two weeks, get stuck, go talk with him for 30 minutes, and be set back on course for the next two weeks. The title of my thesis was “The Profit-Maximizing Utilization of Exhaustible Resources,” and in short what it said was that left to their own devices with a profit motive as the only goal, businesses would deplete natural resources (such as oil, timber or minerals) as rapidly as possible, with no reason for or thoughts of conservation for the future. I enjoyed this project very much, and thought about becoming an economist. My minors, which were called something different, were computer science and psychology.  My computer background was enhanced by my undergraduate summers, when I worked for IBM. My first summer (1964) I spent wiring panels for accounting machines. A friend of my father’s had arranged the job, and I was employed by the IBM Chicago Transportation Office. Weekly business meetings were held at 7:30 a.m. Monday mornings, and the office was over an hour’s drive from my home in Skokie. Business attire was suit and white shirt, with socks and tie that matched each other in color. The second summer I wrote computer programs for an IBM 1440 computer. There was lots of spare time, and I wrote a program that would randomize a virtual deck of cards and deal bridge hands. (I had started playing in duplicate bridge tournaments with my friend Ira.) The summer of 1966 I taught computer programming in the language Autocoder to business executives at the IBM Chicago Education Office in downtown Chicago. I still wonder what these high-level executives felt when they entered their first class and saw a 19 year-old standing in the front of the room. One special aspect of these summers was driving between Skokie and Chicago each day with my father. (The day I forgot to fill the gas tank and ran out of gas on the expressway during rush hour was particularly memorable.) My last summer in college, I stayed in Boston and worked at the IBM Boston Programming Center helping to develop CPS (Conversational Programming System), an early timesharing system that used the first computer language that looked more like English than algebra. CPS was never released, but I had a great time and many good lunches.  It was that last summer in Boston that I met Joe Schwarz, one of my closest friends. A year later, Joe and I became roommates, as I began graduate school and he continued his graduate studies of astrophysics. Despite the fact that Joe and his family lead complicated two-city lives – splitting their time between Munich, Germany, and Milan, Italy – we see each other often and have shared family vacations on Cape Cod a number of times.  During those summers in Chicago, my friends and I continued a tradition we had started in high school – Saturday night poker. A group of us would gather at Ira Zarov’s house – Ira had been my closest friend since third grade – to play poker, whether Ira was there or not. (Often he was not.) My father’s accounting approaches had taken root in me by then, and I kept a detailed log of my winnings each night, to the penny. (During this same period, I also kept a log of the precise time I went to bed and woke up each day, to the minute.) I say winnings, because there never was a night that I lost. I had studied the odds and poker strategy, and I was disciplined and cautious. In fact, after a year or two, I became obsessed with winning and distressed by the possibility of losing on a single night. I altered my play toward the end of evenings to ensure that I would be ahead when we finished. I realized that this state of mind was not healthy, and one day I decided that the next time I played I would lose, no matter what. I did so, and after that I sometimes won and sometimes lost when I played what I believe was both a better and a more enjoyable game of poker. Ira, as I recall, lost more often but may well have won more overall, and later became a successful professional poker player for a period of time. [Marty Chalfie](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/), long a friend and later a colleague in the *C. elegans* field, sometimes joined the game.  Typically during these games we would break for a while so that someone could pick up pizza. During one such break, those of us who had stayed behind started talking about how we were wasting time. Each Saturday we sat playing cards and trading our money back and forth. We should be able to come up with something more productive to do. We sat, and we thought. Then I had an idea. When our pizza-buying group returned, they were surprised to find the rest of us reading telephone directories. The idea was simple. The Chicago Daily News was running a contest called “The Wizard of Odds.” Each day during the week the newspaper published a one-digit number. On Saturdays, the paper would publish three letters. Anyone with a telephone number that ended in four digits included in the five published numbers and with a last name that included all three of the published letters would share in that week’s prize, which like a lottery grew during weeks when no prize was claimed. All we had to do was to read the phone books and find winners. So we did. We telephoned people and told them they had won a substantial cash prize and that we would tell them what it was if they agreed to give us one-third. People, not surprisingly, were exceedingly dubious. However, almost everyone agreed to meet with us and when they saw the newspaper description of the contest were convinced of our legitimacy. Only one person refused to pay us. Another invited me to tour the Chicago Mercantile Exchange and offered me a job there with him. One of my college roommates came to visit for a weekend and made a fair amount of money by joining us.  I was very unsure about what I wanted to do after graduation. Having worked each summer for IBM, I probably was expected either to join the company or to continue my education in the area of computer science. Graduate school in mathematics or economics as well as law school or business school also seemed to fit my undergraduate experiences. But the time was the late 1960’s, and I wanted to do something “relevant,” particularly if it did not involve wearing a three-piece suit. I began to think about medicine. However, I knew nothing about biology. A roommate, Al Singer, now a physician-scientist at the National Cancer Institute, convinced me that modern biology was more than formaldehyde-fixed specimens, and during the first term of my senior year I took the introductory course in biology. I loved it. As a text, we used [Jim Watson](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html)‘s “Molecular Biology of the Gene.” My interest in medicine became secondary to a growing intrigue with biology. Six weeks into the course I went to the professor in charge, Cy Levinthal. “Professor Levinthal,” I said, “I am a senior, all I know about biology is what I have learned during the past six weeks from you, and I’m thinking about going to graduate school in biology. Am I crazy?” “I went to graduate school in physics,” Professor Levinthal replied, “And I’m teaching your course. You’re starting early.” Biology it was. The next semester I took a course in Genetics from Maury Fox, and was captivated by Sturtevant and Beadle’s “An Introduction to Genetics.” I also took a laboratory course, which introduced me to neurobiology and to the electrophysiological methods used in the classic studies by [Haldan Hartline](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1967/index.html) of the eye of the horseshoe crab *Limulus*. I applied to Harvard, MIT and Stanford, was accepted at all three, and decided to simply move the mile up Massachusetts Ave. to the Harvard Department of Biology.  The summer after my graduation from MIT was an adventure. With three friends, I set out in June with a car, a tent and four sleeping bags. Our first stop was Chicago, where we earned some spending money doing office jobs for my father’s trucking company. Our only subsequent obligation was a wedding in Omaha, Nebraska, in early August. We traveled across the Midwest, into the west, up to western Canada, down the west coast and back across the country. We met many people, and had a wonderful time. Even the night we spent in the Butte, Montana, jail was interesting. (We had befriended a boxer from Monterey, California, or so we thought. He was staying next to our campsite. When we returned from town, he and our sleeping bags had all disappeared. We went to the police station to report the theft, and the police kindly offered us a place to stay for the night.) Three of us had been math majors, and as we drove we studied the recently published book “Beat the Dealer,” by Edward Thorp. From this book we learned how to play a winning game of blackjack and also how to spot a stacked deck of cards. We discovered such a stacked deck in a well-known Las Vegas casino and proudly told the dealer. He called the pit boss, who was very friendly and asked us accompany him to another room. There he became less friendly, and informed us, “If I ever see any of you in here again, no one else will ever see you after that.” We left. I was not winning much money anyway. The other book I remember reading while traveling during the summer of 1968 was Jim Watson’s autobiography, “The Double Helix.”  At the end of that summer, I returned to Chicago in time to experience the Democratic National Convention, where the peace platform calling for an end to the Vietnam War was defeated and the pro-peace protestors were considered enemies of the country and in particular of Mayor Richard J. Daley’s Chicago. Meeting Alan Ginsberg, standing face to face with the National Guardsmen, trying to help slow down the crowds running from the tear gas, watching the Chicago police beating innocent people, escaping by hiding in the back seat of a car driven by a resident of a nearby black ghetto through a neighborhood that on other occasions I might have feared entering – there are many images and memories engraved in my mind. These days still make me ashamed of my city and my country.  Graduate school at the Harvard Bio Labs In September, 1968, I entered graduate school in the Harvard Department of Biology, located at The Biological Laboratories, or Bio Labs, in Cambridge. I felt like a fish out of water. Everyone else seemed vastly more prepared, more knowledgeable about biochemistry and biology and more engaged. Because of my limited background, I was assigned mostly to undergraduate classes. In a cell biology course taught by Keith Porter and Dick McIntosh, the first exam had a question involving ribosomes. I had no idea what a ribosome was. In [Konrad Bloch](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1964/index.html)‘s biochemistry course, one of the few graduate courses I was taking, we focused every day on how electrons moved in the series of biochemical reactions of the [Krebs](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1953/index.html) cycle. I had never heard of the Krebs cycle. In a genetics seminar course, I was simply lost. The experimental approach to problem solving was completely unlike the way I had been trained to think as a student of mathematics. I was a teaching assistant in an introductory biology course taught by Lynn Riddiford and Carroll Williams. For the dissection laboratory, the students had to choose between rats and lobsters. I encouraged them all to study lobsters, although I had no idea what was inside either a rat or a lobster, because after class the TAs were allowed to cook and eat the dissected lobsters. I decided that if at the end of the first year my understanding of biology had not improved substantially, I would leave and do something else. However, my comprehension increased, and I stayed. My advisor was Matt Meselson, and I was supposed to begin working in his laboratory my first summer, in 1969. However, I had long planned and was very excited about spending that summer in Europe. The only foreign country I had ever visited was Canada – once during my trip the summer before and once during my freshman year at MIT when I had rather cold experience hitch-hiking to Montreal from Boston in January – and foreign travel appealed to me enormously. No one told me that in graduate school you were supposed to work in the laboratory over the summer. Matt was incredulous that I planned to be away during the period my professional training was supposed to begin. Still, I went, and had a wonderful time exploring new places, foods and peoples. The only downside was my continuing problem with asthma, which left me in bed for days at a time in Paris, Milan, Malaga and on the island of Skiathos in Greece, from which I had to be carried on a stretcher through the village to get to a boat back to the mainland and to a hospital in Volos, where I stayed for some time.  In the fall, I continued with my courses and began research in Matt’s laboratory. I had no idea what I was doing, and had to ask a fellow graduate student, Patricia Foster, to show me how to use a pipette. Pat and I had gotten to know each other as teaching assistants in the introductory biology course, for which she and I had been exiled together to the cold room to grind spinach for chloroplast preparations. Pat very much educated me about and encouraged me to persevere in biology. We became a couple in 1970, and lived together for the next 13 years.  Matt Meselson is a great scientist, but he was more focused on the crucially important issues of chemical and biological warfare than on his laboratory. Matt was spending much of his time in Washington, D.C. as an advisor to the U.S. government. I had to be in an alternative environment to acquire the training I needed. I considered changing schools. I was intrigued about the idea of living in Europe and thought about a number of European laboratories. However, my cousin Ed Brody (eight years older than me and an older brother of Harvey, of Chicago little league baseball fame) convinced me that staying at Harvard was a better idea. It was one of a number of times Ed had a major influence on my life. Ed is a physician-scientist who trained at the University of Chicago, did postdoctoral work in Geneva, Switzerland, and then ran a research laboratory in Paris, France for many years. It was Ed who obtained for me the fruit flies I used in my high school science fair project.  I talked with Wally Gilbert and Jim Watson about transferring from Matt’s laboratory into theirs. Jim had recently become Director of the Cold Spring Harbor Laboratory on Long Island, New York, and he suggested I go to the annual Cold Spring Harbor Symposium to be held in June, 1970, to become exposed to the field of molecular biology in a professional way. The meeting was focused on transcription, and was very exciting, with cutting edge research being presented in a way that made me want to know what was coming next. At the end of the meeting, still unsure if I was going to be accepted to join Jim’s laboratory, I asked him what I should do. Jim told me to return to Cambridge and talk with Klaus Weber, another Harvard professor who with Jim and Wally ran a joint laboratory, about a project. I gathered his answer was yes.  The Watson-Gilbert-Weber laboratory at Harvard offered an unparalleled training experience. The three of them were all exceptional scientists, and they were highly synergistic in their approaches and talents. Jim has a superb biological intuition, and it was he who defined the problems most of the students embarked upon. Wally has profound critical abilities, and could see the flaws in any experimental design or interpretation. Klaus has magic fingers, and could devise ways – old or new – to make any experiment work. It could not have been more stimulating, or more challenging.  My thesis project derived from Jim’s interests in transcriptional regulation. He had written in his 1970 edition of “Molecular Biology of the Gene” about how development was likely to involve differential gene expression. With this in mind, Jim had focused a part of his laboratory on RNA polymerase, the enzyme responsible for synthesizing RNA from DNA. Jim’s laboratory had shown that the enzyme consisted of two major components, a multi-protein complex that did the work of transcribing RNA and a more loosely associated protein that conferred specificity, i.e. that caused the enzyme to begin at specific sites along the DNA. This specificity factor they named sigma, and Jim’s model for development was that a sequence of sigma factors defined a temporal series of distinct transcriptional products. The experimental basis for this model was some recent observations made in the laboratory concerning *E. coli* phage T4. These studies suggested that the bacterial RNA polymerase with a bacterial sigma factor transcribes a first set of T4-specifc RNAs, called “pre-early”; one of the pre-early genes encodes a viral-specific sigma factor, which then reads the “early” genes; and finally, a second T4 sigma factor encoded by one of the early genes reads the “late” genes. In this way, a series of three sigma factors defines three distinct developmental phases of T4 gene expression. However, no such factors had actually been isolated, and the evidence for this model was rather circumstantial. My project was to identify T4- specific sigma factors.  To begin, I purified *E. coli* RNA polymerase from bacterial cells infected with T4 and examined the subunit composition of the enzyme. I worked with the expert, constant and generous guidance of Klaus Weber and graduate student Chris Goff. (Chris was studying another change in the T4-modified *E. coli* RNA polymerase.) Indeed, the host RNA polymerase had a number of new subunits, as had been recently reported by Audrey Stevens at the Oak Ridge National Laboratory. In a cleverly designed experiment (the clever design was that of a postdoctoral scientist working next door, Jeff Roberts), I was able to show that one of these subunits was the direct product of T4 gene 33. Other studies had indicated that gene 33 regulated the transition from the early to the late stage of T4 development, so this result was quite exciting and led to my first publication, in *Nature New Biology*. I was very proud of this achievement. However, my enthusiasm was dampened a bit by a conversation with Larry Gold, a T4 researcher at the University of Colorado in Boulder. Larry knew how hard I had worked to prove that this small RNA polymerasebinding protein was the product of gene 33 and also knew the data that had suggested this was likely to be the case. Was it worth, he asked, working so hard to prove something that was clearly very likely to be true? Could I not have been better spending my time to find something that was unexpected, rather than something that was expected? Larry’s questions were provocative – I’m still not sure I know the best answer – and I have thought about them often in designing further research projects.  Most of my days as a graduate student were spent in a cold room at 4°C, purifying RNA polymerase. After some time, I devised a rapid method for isolating small quantities of enzyme based upon precipitating RNA polymerase with antibody that had kindly been raised by Chris Goff. (Although I had tried, I proved to be too allergic to inoculate and bleed the rabbits myself.) Then I could work in my laboratory room at a normal temperature. To visualize changes in the enzyme, I used radioactivity, and routinely did bench-top experiments in the open laboratory involving 25 millicuries of radioactive phosphate or sulfate. I also worked with comparably high levels of radioactive iodine. Such experiments today would have to be done under special conditions, but during the early 1970s, scientists were much less cautious. After some years, I officially became Wally’s student, as Jim left Harvard to spend full-time at the Cold Spring Harbor Laboratory.  I published four papers as a graduate student, all involving T4-induced modifications of the *E. coli* RNA polymerase. I was the sole author on all four publications. Both Jim and Wally put their names only on papers to which they felt they had made major and direct contributions. These papers were assembled into my Ph.D. thesis, which included an introductory chapter focused not on the biochemistry of RNA polymerase but rather on the biology of phage T4. I liked thinking about T4 as an organism, just as more recently I have enjoyed thinking about all aspects of the biology of the nematode *C. elegans*.  Life at Harvard was intense, which suited me well. Work started early in the morning and ended late at night. Students in the group were highly independent, relying more on other students and postdoctoral researchers than on faculty for input. “Sink-or-swim” seemed to be the prevailing attitude. If you managed to swim, you really learned to do science. However, there were a number of students who sank who I believed had outstanding potential. We had three group meetings a week, over lunch on Mondays, Wednesdays and Fridays. For each session, one student or postdoc presented his/her most recent findings. These were serious times, as an audience of Jim Watson, Wally Gilbert, Klaus Weber and often Mark Ptashne and David Dressler (two other Harvard faculty members) left little uncritiqued. Giving my first public talk, at a phage meeting at Cold Spring Harbor, was a very gentle experience by comparison. If you could survive a Harvard group meeting, you could survive anywhere. In preparing for these group meetings, I acquired a habit that I have continued to this day – writing a complete text of my presentation. I find this practice helps me organize my thoughts and time my talk, gives me an aide for those moments when I go blank on-stage and allows me to prepare a related talk at a later date very easily.  Some years into my graduate studies, our Harvard group meetings acquired a name. One of the underground Boston newspapers, either the Phoenix or the Real Paper, did a story about Wally Gilbert and entitled it “Stalking the Secret of Life.” Thereafter, our group meetings were always labeled “Stalking the Secret of Life: Part 247,” “Stalking the Secret of Life: Part 248,” etc. I learned an enormous amount as a Ph.D. student, both about how to do and how not to do experimental biology. I came away with two beliefs that have driven my research ever since. First, do the do-able; working on an important but intractable problem would not suit me. Second, engraved in me from Jim Watson: since it is no harder to work on a problem that is important than on one that is not important, always choose the former.  Studying the bacterial virus T4 introduced me to a community of interactive and cooperative scientists. During one visit to Chicago to see my family, I went to the University of Chicago to talk with a fellow T4 researcher, who kindly gave me a set of mutant strains I needed. My mother supplied a small mayonnaise tub for me to use to transport the glass vials. I carried the tub in my hand as I boarded the plane at O’Hare Field for my return to Boston. The woman sitting to my right was curious, and asked what I was carrying. “Oh, nothing important,” I said, “Just some viruses.” This was an error. “VIRUSES!!” she yelled. After considerable subsequent conversation, the viruses flew to Boston in the cockpit, and the woman to my right said not another word to me the entire flight. On another occasion, I visited biochemist Ray Gesteland at the Cold Spring Harbor Laboratory to ask for his advice about an experiment I had planned. As I spoke with Ray, he was emptying rack after rack of test tubes from a large refrigerator and pouring the contents down the sink. “Ray,” I finally said. “What are you doing?” “Oh,” he replied, almost gleefully. “These are my last six months of experiments. They didn’t work, so I’m going to start something new.” To me, six months literally down the drain seemed like a disaster. To Ray, they offered an opportunity to explore some exciting new idea. Ray was a scientist, and I still had a lot to learn.  As a graduate student, I lived in north Cambridge, sharing the top two floors of a house with my friend Joe Schwarz and a cast of others. After a year, Pat Foster also moved in. Our roommates were interesting and varied and included graduate students in biology and astrophysics, people who worked at a great diversity of occupations and people who did not work at all. At one point, both the front and back porches were rented, someone was sleeping on the living room couch and a total of 14 people (including my sister Carol) called our five-bedroom house their home. For a while, we also had a German Shepherd and, briefly, her 11 pups. We took turns cooking. Because I had the only car, I did the shopping. We joined a food co-operative and when handed a form that asked for “Name,” I wrote “Bob.” After that, our house became known as a commune called “Bob.”  I began to think about what I wanted to do after completing my Ph.D. I had a strong desire to spend some time in Europe, and visited a number of laboratories there. Jim Watson thought I should go to Stanford – there was a regular exchange of graduate students and postdocs between Harvard and Stanford at that time. Klaus Weber had an alternative thought and suggested that I talk with Sam Ward, who had just moved to the Harvard Medical School from [Sydney Brenner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/index.html)‘s group in Cambridge, England. Sydney and Sam had been using the nematode *Caenorhabditis elegans*, an organism that had been little studied previously, to pursue problems in neurobiology. I had long been intrigued by the nervous system, in particular by complex issues, like the mechanistic basis of learning, memory and consciousness. As an undergraduate I had taken a course given by Jerry Lettvin entitled “The Biological Basis of Perception and Knowledge,” which had whetted my appetite but supplied few answers. As a graduate student, for a course about protein synthesis taught by [John Hershey](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1969/index.html), I had written a term paper entitled “A Research Proposal on Protein Synthesis and Learning.” Sam told me about Sydney’s efforts to reconstruct the worm’s nervous system from serial section electron micrographs, promising to reveal the complete wiring diagram of a nervous system for the first time. *C. elegans* was eminently suited for genetic analysis, and I had become enamored with the power of genetics from my studies of T4. After a number of conversations with Sam, I wrote Sydney, and asked if I could join his laboratory. My expressed interests were developing methods for studying *C. elegans* at the molecular level and using genetics to analyze memory and learning. His response was “As far as I know, all attempts to show learning in nematodes have failed,” but that I was free to choose my research project when I arrived. After some further correspondence, he wrote, “Go ahead and apply for fellowships.” This meant “yes.”  There were a number of other factors that influenced my decision to join Sydney’s laboratory. First, Chris Goff, with whom I had worked closely, had gone there and raved about the place. Second, I wrote Ed Brody, in Paris, and asked him for his views of “Brenner and his nematodes,” noting that the phrase “sounds like a new rock band.” Ed was encouraging. Third, Pat was delighted at the prospect of living in England. Cambridge indeed was a great place to live, and the Laboratory of Molecular Biology a fantastic place to do science.  When I told Jim Watson that I planned to go to Cambridge, England, to study the neurobiology of *C. elegans* he asked me if I knew anything about neurobiology. I had to admit that I did not. Jim then suggested an immersion education – three consecutive Cold Spring Harbor summer courses in neurobiology. I enrolled in and took three such courses during the summer of 1974: An Introduction to Neurobiology, taught by John Nicholls; Experimental Methods in Electrophysiology, taught by Enrico Stefani and Dante Chiarandini; and The Neurobiology of *Drosophila*, taught by Bill Pak. Each course was intense and stimulating. I learned an enormous amount, and made many friends. Cold Spring Harbor courses have a reputation for being both exhilarating and exhausting, and I have been told that I am the only person who has ever taken three in a single summer.  England and worms Sydney Brenner was my fourth official research supervisor, after Bob Solow, Jim Watson and [Wally Gilbert](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1980/index.html). Amazingly, they, and I, now all have Nobel Prizes.  Pat and I arrived in England just before Guy Fawkes Day (November 5) in 1974. Chris and Eleanor Goff, friends from our Harvard days, kindly provided our initial lodging. My first assignment for laboratory space was a two-foot wide area of benchtop in a room in which biochemists on each side of me were labeling tRNAs using vast quantities of 32P-labelled phosphate. As I began my studies of *C. elegans*, I wondered whether the worms, or I, might acquire mutations as a consequence of the nearby radioactivity. Soon I moved down the hall, into a room that I shared for the rest of my stay with a number of scientists, including [John Sulston](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/index.html), a young staff member in Sydney’s group.  I had received a fellowship from the Muscular Dystrophy Association of America. The fellowship was for a much greater amount of money than Pat and I needed to live in England, and I deposited half of the funds I received into a Swiss bank account, believing this would guard us against an unstable British economy and also against currency fluctuations between Europe and the U.S. This account remains untouched. My fellowship application had focused on an analysis of the chemosensory nervous system of *C. elegans*. However, studies of nematode chemosensation had been begun by Sam Ward, and I decided I should do something different. My interests and my MDA support both drove me to want to study aspects of worm biology that might relate to human neuromuscular disorders. In particular, just before I left the U.S. I had a moving conversation with a close friend of my parents who was dying of ALS. I did not know anything about the disorder, but could see that it was terrible. Her last words to me were, “I know it is too late for me, but please try to do something for others who suffer from this horrible disease.” Beyond studying the worm’s musculature and/or nervous system, I had no idea how to try to do so, and in any event it was the basic biology that intrigued me.  Sydney suggested I study muscle cell growth, in particular that I try to determine how individual muscle cells add new myofilaments as they increase in size. The problem sounded interesting, and remains unsolved. However, I had begun conversations with John Sulston and found a topic that excited me more. John had recently found that he could directly observe cell divisions in living *C. elegans* larvae and in this way determine aspects of the worm’s cell lineage, the pattern of cell divisions and cell fates that occurs as a multicellular organism develops from a single-celled egg. So far, he had examined only the development of part of the nervous system. John and I decided that together we would explore more of the worm’s cell lineage, with the goal of determining the complete pattern of cell divisions that generates the adult animal. I began by examining the musculature, in part because of my MDA fellowship. John had already noted that the number of muscle cells in the main body musculature increases as the animal develops from a newly hatched larva. My first goal was to determine the precise number of body muscle cells in the young animal and the cell lineage responsible for adding additional muscle cells during larval development.  Counting muscle cells proved more challenging than I had anticipated, in part because using Nomarski optics one visualizes nuclei, and the difference between the nucleus of a muscle cell and that of certain non-muscle cells was not always obvious. More importantly, the worm was not designed the way I thought it should have been. The animal is shaped like a tube, with four quadrants of muscle: dorsal-right, dorsal-left, ventral-right and ventral-left. It never occurred to me that these four quadrants might contain differing numbers of muscle cells. So I counted, recounted, re-recounted and finally asked John to count, too. The upshot was that the superficially radially symmetric young animal contains 21 muscle cells in each dorsal quadrant, 20 in the ventral- right quadrant and 19 in the ventral-left quadrant. By tracing the postembryonic cell lineages involved in muscle development, I discovered that to this number is added an additional 14 muscle cells, three in each dorsal quadrant and four in each ventral quadrant. I learned that preconceived notions in biology can be very misleading. Only observation and experimentation can reveal biological truths.  Life as a postdoctoral researcher at the Laboratory of Molecular Biology was exceedingly stimulating, great fun and involved far more conversation than did life at the Harvard Bio Labs. Morning coffee and afternoon tea on the second floor, where the Division of Cell Biology was housed, were key, whether or not one drank coffee or tea. These breaks were opportunities to talk, to think, to listen and to learn. Sitting in the tea room with Sydney Brenner after lunch never failed to be both amusing and interesting. Sydney has an incredible wit, an amazing breadth of knowledge and always enjoys a good conversation. Latenight science – and sleep – were often endangered by Sydney. A number of times when I was working at 2 or 3 a.m. and desperate for a cup of tea, I would go to the tea room only to find myself soon joined by Sydney, attracted by the rattle of the spoon in the tea cup. In Sydney’s (but not my) view, 2 a.m. was an excellent time to talk! I learned to stir silently.  Lunch was an especially good time for scientific interaction. Everyone in the building went upstairs to the top floor to a cafeteria run by Gisela Perutz, the wife of the famed structural biologist [Max Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/index.html). Here one would pick up lunch – bangers, spuds, faggots, toads-in-the-hole or whatever (I quickly saw that despite the U.S. and England ostensibly sharing a common language, much of the English spoken in England was completely foreign to me) – and sit at whatever table had an open seat and talk about whatever science came to mind. I had the opportunity to meet many outstanding scientists. One of these lunches, with fellow worm researchers Jonathan Hodgkin and John White, led to an experiment by Jonathan that revealed a fundamentally new aspect of *C. elegans* sex determination. Monday nights were special. Dinner at the University of Cambridge’s Clare Hall, hosted by [Tim Hunt](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2001/index.html) and often led in conversation by [Francis Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html), was followed by a research seminar, in which Peter Lawrence and/or Michael Ashburner, two *Drosophila* developmental geneticists, would invariably ask the speaker why he or she had bothered to do whatever it was that he or she had done. Friday evenings involved a short walk to the Frank Lee Center, for a pint (or more) of England’s best brew.  The worm group was very much the center of my scientific and much of my personal life. I worked most closely with John Sulston, who became a mentor, a friend and in some ways a hero. I had the impression that John could do anything. He was warm, personable, unassuming and completely dedicated. Often after his bicycle ride to the laboratory (John bicycled to reduce the pollution that results from driving cars), insects and other debris would fall from his long beard onto his samples. John argued passionately that research biologists should receive salaries much lower than those of trash collectors, because the former have so much more fun. I made many other friends, including Jonathan Hodgkin and John White. Toward the end of my stay, I had the opportunity to renew my high-school friendship with Marty Chalfie for the months that we overlapped. I developed scientific collaborations with Jonathan, John and Marty. The collaboration with Jonathan was particularly instructive to me. He had discovered a class of *C. elegans* mutants abnormal in the segregation of the sex chromosome during meiosis, and I had isolated a number of additional mutants of this sort. We decided to characterize our mutants together. We sat down, agreed upon a set of experiments, and assigned one of us to do each experiment. However, neither of us had ever collaborated in such a way before, and we each felt that we would trust our own data more than data from someone else. When we met again to examine our collected data, Jonathan had done all of his experiments as well as all of mine, and I had done all of mine as well as all of his. Luckily, our results agreed. The upshot was a paper in which we had counted precisely 183,001 worms for the published data alone. This experience made it easier for me later to trust the data of my students without having to repeat everything they did. (Even so, in the early days of my laboratory, there were some experiments I did repeat, privately, just to be sure.)  Pat and I lived first in Cambridge, not far from the train station, and later in the village of Great Shelford. Going to and from the lab meant driving past open farmland, which was highly refreshing after having lived my previous 27 years in Chicago and Boston. I found the whole area, with its charming villages, thatched cottages, beautiful flower gardens and comparatively slow pace, extremely appealing. The nearby village of Grantchester, with The Green Man pub and a lovely tea garden, was a particular favorite. One could punt to Grantchester from the center of Cambridge and stop for a pub lunch or just a pint of beer. For food, Indian cuisine seemed vastly better than in the U.S., and the Curry Queen in Cambridge was a common target. Pat, who had left Harvard to work in what was a very early version of a biotechnology company (she was the Biology Department), resumed her studies as a Ph.D. student at the University of Cambridge, which gave us both the opportunity to partake of life at Wolfson College. Pat and I used Cambridge as a base for travel, and visited most of Britain and much of Europe during my three years in Sydney’s laboratory. I considered staying in England, but decided that a return to the U.S. would allow me greater flexibility in developing an independent research program. My job at MIT came about through a misunderstanding. Sydney had visited Brandeis University, and he suggested that I apply for a faculty position there. I did not want to leave England yet, but I could not pass up such an opportunity. I sent my curriculum vitae and a statement of research interests, but no publications, as I had not yet published any of my postdoctoral studies. I decided that if there was a possibility that I might be offered a job, I should also apply to other places and see what the options might be. I came to the U.S. for a six-week visit and gave seminars at 11 institutions. My first visit was to Cornell University in Ithaca, N.Y. I was lucky to be offered a job while I was still there, just before I flew to Boston to visit Brandeis and MIT. This offer made my subsequent visits very relaxed. To my surprise, when I arrived at Brandeis I was told that although they wanted to meet me, no faculty position was currently available. Thus, I need not have started sending out job applications at all. Not long after my return to England I was contacted by Boris Magasanik, Chair of the MIT Department of Biology, and offered a faculty position. I accepted.  My laboratory at MIT I moved back to Boston in January, 1978, between the two huge snowstorms that blanketed the northeastern U.S. that month. My friends Fred Ausubel and Stephanie Bird kindly offered me a spare room in their home on Irving St. in Cambridge, near the Harvard Bio Labs. They also let me use their cross country skies to get to and from MIT, skiing over barely detectable mounds of snow that had cars beneath them. Pat joined me in April, and we rented an apartment in north Cambridge.  Setting up the new laboratory was a busy time. I had arrived with more than 500 strains of *C. elegans*, the transport of which had proved slightly problematic: to import nematodes, I needed permission from the U.S. Department of Agriculture. However, the Department of Agriculture gave import approval only for parasitic nematodes, and *C. elegans* was not a parasite. Therefore, they could not grant my request. It took a number of letters back and forth before they finally agreed that they could not be sure that *C. elegans* was not a parasite and thus could approve my importing a potential parasite. I also had arranged to avoid having to subject the living animals to X-rays at Heathrow Airport in London. The airline noted that this permission had been granted in my reservation information in their computer system. When I checked in, the woman behind the counter became wide-eyed as she looked at the computer screen, and said, “The computer says you have worms. Can I see them?” I explained that they were too small to be seen and that they were packaged in sealed boxes in any event. She let the opportunity pass.  Every day in my new laboratory I transferred worms, establishing and then freezing each of my many mutant strains. In April I was joined by Nancy Tsung, whom I hired as a technician. Nancy could not get over the fact that a professor could be so young, and for some years referred to me as her young boss. Nancy stayed in the laboratory for over 21 years, and she provided crucial technical and emotional support for projects and people, respectively. Soon thereafter, my first two graduate students joined the laboratory, Iva Greenwald and Chip Ferguson. Each proved to have a deep interest in biology and a natural flare for genetics, and the new lab was off to a very strong start in the areas of the genetic analysis of *C. elegans* development and behavior. Chip focused on the genetics of intercellular signaling, while Iva studied a muscle mutant with what then appeared to be unusual genetic and behavioral properties. Iva discovered that although this mutant had a severe muscular disorder, the inactivation of the gene responsible had no discernable effect whatsoever. This finding led to my first publication as a mentor, a paper with Iva in the journal Genetics in 1980.  Next, graduate students Paul Sternberg, Bill Fixsen and Carol Trent and postdoc [Victor Ambros](https://www.nobelprize.org/prizes/medicine/2024/ambros/facts/) entered the lab. Paul started by studying the cell lineage of another nematodes species, *Panagrellus redivivus*, with an eye toward an analysis of the genetic basis of evolutionary change at the level of cell lineage. Bill studied the genetic control of cell migration. Carol analyzed the genetic basis of the behavior of egg laying. Victor pioneered studies of genes that control developmental timing.  The diversity of problems – intercellular signaling, muscle, the genetics of evolution, egg laying and developmental timing – seems unusual and perhaps dangerous for a beginning faculty member. “No focus,” would be the criticism made by some today. However, these projects were highly coherent, in history, in philosophy and in experimentation. Each had derived directly from the studies of cell lineage and cell lineage genetics I had begun in collaboration with John Sulston in England. Most of my time examining the *C. elegans* cell lineage was spent observing the development of the musculature, including the muscles used for egg laying, and of the vulva, also used for egg laying. In large part for this reason, in seeking cell lineage mutants, I primarily sought those abnormal in egg laying. Amongst those mutants were all of those to be analyzed in our initial explorations into intercellular signaling, muscle, developmental timing and the behavior of egg laying. The comparative evolutionary project had a similar rationale – unlike *C. elegans*, *Panagrellus* does not lay eggs but rather releases hatched larvae; furthermore, the vulva of *Pangrellus* is displaced posteriorly compared to that of *C. elegans*. The cell lineages of the egg-laying systems of the two species seemed very likely to be different.  In addition, intellectually and experimentally, there was a single driving theme behind almost every project: use analytic genetics to define the genes and genetic pathways responsible for each biological phenomenon. How you design a mutant hunt, isolate additional mutations in a known gene, define a null phenotype, and order genes into a pathway is the same, whatever the problem being addressed. Each member of the laboratory could help each other member in thinking about such issues. There were two other factors that drove me to initiate so many distinct projects. First, given my experiences at Harvard and the LMB, I believed that one of the most important aspects of training a young scientist is to give that person the freedom to pursue his or her discoveries. Discovery leads to excitement, commitment, and fun. Elbow room is crucial. Training has always been one of my major goals, with the belief that training outstanding scientists will of necessity generate outstanding science. (The converse statement – that generating outstanding science will necessarily train outstanding scientists – in my view, is not necessarily the case.) In addition, the training environment is enhanced by exposure to a breadth of biological problems. A second factor that drove me to initiate so many distinct projects was, as I noted above, the fact that I am fascinated by the biology of the organism. The diversity of problems helped satisfy my personal curiosity.  My philosophy for the lab, then as now, was that we should be a community of scientists, with each graduate student and postdoctoral researcher focused on a biological problem of interest. Lab members should be independent, but highly interactive. Postdocs should be free to continue their projects independently after leaving the laboratory.  The next two young scientists to join my laboratory were graduate students Eun-chung (Joan) Park and Hilary Ellis. Again, I advised each to begin projects descended from but also distinct from projects already underway. Joan took a genetic approach that derived from the studies of Iva Greenwald to estimate the number of genes in *C. elegans*. Joan found that animals have a large number of genes that when inactivated have no obvious consequence to the organism. This finding was not broadly known and when rediscovered some years later in the field of mammalian genetics, as a consequence of the study of the first mouse “knock-out” mutants, was generally regarded as a great surprise. Hilary Ellis embarked on the study of the genetics of programmed cell death.  Postdoctoral researcher [Gary Ruvkun](https://www.nobelprize.org/prizes/medicine/2024/ruvkun/facts/) entered the laboratory slightly later. Gary and I shared a driving desire to find a way to clone the many genes our laboratory was defining by methods of classical genetics. We devised more than a dozen distinct possible approaches, involving a variety of molecular techniques. Gary was a Junior Fellow at Harvard University and his Harvard sponsor was Wally Gilbert. Gary was able to do many more molecular experiments using Wally’s funds than could have been supported by my rather limited budget. Gary, Wally and I published one paper together, my only publication with my official Ph.D. advisor. Gary introduced current methods of molecular biology to the laboratory. He succeeded in cloning one of the genes that Victor Ambros had shown to be key in the control of developmental timing.  The MIT lab grew in number, but not in physical size. Our only laboratory room, with seven lab benches, soon housed 11 scientists, three of whom worked at small desks where previously there had been a single -70°C freezer and one of whom sat at the end of a high bench with a cabinet door open so he would have some place to put his legs. I asked the Department Chair, Gene Brown, for more space, and he instantly provided it, moving his own laboratory, which was across the hall from mine, to do so. David Botstein, whose laboratory was located one floor upstairs, proved to be my major mentor on issues of science and non-science both. Lunches were a special treat, as varying groups of faculty would assemble in the faculty lounge at precisely noon (when Gene Brown began his lunch) and sit and talk. Collected wisdom concerning science and life was shared by all, and I had the good fortune to be able to learn from many of my senior colleagues, including [Salvador Luria](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1969/index.html). Salva was a humanist, an independent thinker and a scholar, and I was struck by the fact that he offered the first-year graduate students the opportunity to get together with him once a week to discuss literature, primary fiction, because he believed that a single-minded focus on science was intellectually stifling.  Other professional activities My scientific pursuits have led to many opportunities and responsibilities beyond those of simply doing research. For example, as a beginning graduate student it never occurred to me that the life of a scientist could involve so much travel, something that I have always loved. In the course of presenting lectures, attending meetings, serving on advisory committees and teaching courses, I have visited Alaska, most European countries, Russia, Israel, Egypt, India, Japan, Korea, China and Tibet. (Out of interest, and without scientific excuse, I have also traveled to Peru and Senegal.) I have been an advisor to many national and international organizations, including the U.S. National Cancer Institute; the National Human Genome Research Institute (the U.S. sponsor of the Human Genome Project); the Sanger Centre (the British arm of the Human Genome Project); and the Tropical Disease Program of the World Health Organization, which amongst other interests is concerned with diseases caused by parasitic nematodes, relatives of *C. elegans*.  I have also been very involved with scientific societies. I served as the President of the Genetics Society of America in 1995 and have been a member of the Public Policy Committee of the American Society for Cell Biology and of the Joint Steering Committee for Public Policy, an organization that advocates for biomedical research funding from the U.S. government. I feel strongly that the support of biomedical research is an important investment for society as a whole and that both the Congress and the public have the right to know what is being done with their funds. We, as scientists, have a responsibility both to advocate and to educate. Toward this end, in 1997 I presented a briefing of the Congressional Biomedical Research Caucus. I was hosted by Massachusetts Representative Joe Kennedy, and my lecture was entitled “All Creatures Great and Small: The Universality of Genes.” My theme, based in part upon findings of my research group, was that studies of simple non-human organisms – such as a yeast used for baking bread or making beer, a tiny fruit fly or a microscopic worm – can provide crucial breakthroughs important for the understanding, prevention and cure of human disease.  My laboratory and our studies of *C. elegans* have progressed in new directions and new dimensions. Our current interests include cell lineage and cell fate; programmed cell death; signal transduction; morphogenesis, micro RNAs; nervous system development; behavior; and the modulation of behavior by the environment and by experience. This last topic is essentially the one that drew me to *C. elegans* and was the interest that I wrote about when I first contacted Sydney Brenner – the genetic analysis of memory and learning. In addition, I have become increasingly interested in aspects of human disease. Much of the reason is that I have been repeatedly intrigued by the striking molecular genetic conservation between processes we have analyzed in *C. elegans* and those involved in human biology and human disease. The basic science has driven me toward human disease. My active involvement started in 1979, when Ed Kravitz, from the Department of Neurobiology at Harvard Medical School, invited me to a meeting about cell death. The meeting was sponsored by the Hereditary Disease Foundation, which is focused on Huntington’s Disease, and was until very recently run by Nancy Wexler and Allan Tobin, both of whom became good friends. This meeting opened my eyes to the possibility that our studies of programmed cell death in *C. elegans* might prove relevant to a variety of human neurological disorders and also indicated that discussions of some of the basic principles of analytic genetics used to study simple organisms like *C. elegans* might be helpful to those working on human genetic diseases. My involvement with the Hereditary Disease Foundation continues to this day.  In 1986, when my father was diagnosed as having amyotrophic lateral sclerosis, or ALS, he came to Boston and was seen by MGH neurologist Bob Brown. Bob proved to be a highly supportive and sympathetic physician. Bob and I talked and soon agreed to establish a collaboration to try to better understand ALS though genetics. This collaboration has involved my having a small group of people working in Bob Brown’s laboratory at MGH. This effort, in conjunction with the work of many others from around the world, led to the discovery in 1993 that one gene responsible for familial ALS encodes the enzyme copper-zinc superoxide dismutase.  During this period I began thinking that I might want to deepen my knowledge of medicine by attending medical school, but another friend, Mark Fishman, who later became Chief of Cardiology at MGH and is now the Global Head of Research for the pharmaceutical company Novartis, persuaded me not to do so. He told me that what I would learn in medical school I could more efficiently learn by reading text books, and that to understand medicine I should simply follow him while he did rounds in the clinic. So for brief periods during two summers, I did so.  I have also been introduced to aspects of clinical medicine through my involvement with biotechnology companies. Although for some time I was adamant about being “pure,” a conversation with friend and co-*C. elegans* researcher Jonathan Hodgkin changed my mind. When I told him I was about to turn down an invitation to become a company consultant, he said to me, “Don’t you ever want to do anything useful?” I thought about his comment, and accepted the consultancy. I now feel that my three hats, under which I supervise basic research concerning *C. elegans* at MIT, help with medical research concerning ALS at MGH and advise companies how to apply basic knowledge of biology and medicine to drug development, together both foster my continuing education and synergistically enhance my efforts in all three arenas.  My personal life and family My scientific life would be empty were it not complemented by my personal life. Since becoming a research scientist, I have enjoyed the companionship and support of a small number of women with whom I have had close, intense long-term relationships. All have been dedicated scientists, strongly independent and understanding of the demands of my professional obligations while working similar hours themselves to fulfill their own professional goals. They have provided me with enormous support and helped me to grow emotionally and intellectually.  Since 1991, I have shared my life with Martha Constantine Paton, now my wife. Martha studies the development of the nervous system. I first met Martha soon after we had both begun jobs as assistant professors – she was my host when I visited Princeton University to present a seminar in 1979. However, it was only years later, in 1991, that we became romantically involved. We have interests that are shared and interests that are complementary – all in all, a good match. In 1991, Martha was a professor at Yale University, and she had two sons, Joe and Chris, ages 13 and 17, respectively. Martha and I married, and I suddenly acquired a family, complete with a station wagon, two dogs, two teenage stepsons, and before long, a house in the suburbs. Joe and Chris are wonderful, and being close to them as they have grown into independent, intelligent and interesting adults has been a special pleasure for me. At present, Joe is immersed in neurobiology and is currently a graduate student at Columbia University, while Chris has had no interest in science whatsoever and spent some years working in the music industry before recently entering law school at St. John’s University in New York City.  Our marriage is a partnership with love. While I do most of the cooking and laundry, Martha is responsible for preventing the house and garden from degenerating into chaos and for maintaining our extensive indoor foliage, including our growing collection of orchids. Shopping we do together, which may not be efficient but preserves time with each other. We very much wanted to have a child together. Given our ages, we were very lucky. On September 2, 1993, when Martha and I both were 46 years old, our daughter was born. We had discussed extensively what to call her. We agreed that the last name of Horvitz was appropriate. Martha wanted her father’s name, Constantine, to be continued, so we had a Constantine Horvitz. But what should her first name be? We needed something substantial – a one syllable name would not suffice if followed by Constantine Horvitz. I desired a name in memory of my father Oscar, whose Hebrew name was Asher. So we focused on the A’s and O’s and decided upon Alexandra: Alexandra Constantine Horvitz.  Alex’s birth had a direct but little known consequence on the MIT Department of Biology. The Department was planning a new building, and I was chair of the building committee. The day we were selecting color schemes for the reading rooms, I was called out of the meeting for a phone call from Martha, who had just learned that she was pregnant with a healthy baby girl. I was elated! The reading rooms ended up with rather exuberant purple couches. Later, I telephoned my mother to tell her the news. “Mother,” I said, “How would you like to be a grandmother?” After an exceedingly long pause, in which my mother was no doubt thinking about Martha and me, both 46, she replied, “How would that happen?” I could think of no answer other than the obvious, “In the usual way.”  Alex has given me an unprecedented excitement and joy. Nothing delights me more than to spend time with her and to see her happy. She is a wonderful, loving, intelligent, engaging and strong-willed nine year-old girl. Alex enjoys math, puzzles, games and piano, like me (we play piano about equally well), and, like Martha, arts and crafts, swimming and animals. Alex also has talents that are not obviously derived from either of us, such as in music. Alex’s and Martha’s combined love for animals seems boundless, and were it not for my allergies our home would no doubt resemble a zoo. As it is, we have two dogs, a bearded dragon and two aquaria with tropical fish. Our family lived a hectic two-city life for six years, commuting between Boston and New Haven. I listened to and became a fan of books-on-tape. Our marriage and Alex’s birth have completely changed my life, which is now much more chaotic, much more interesting and much more fulfilling. In September, 1999, Martha moved from Yale to MIT, and we now all live in the lovely Victorian house in Auburndale, Massachusetts, we had purchased in 1994 and then renovated in 1999 in preparation for new lives together.  Thoughts and dreams It is easy to look back over the years that have brought me to writing this autobiography. I have been very lucky, both professionally and personally. I have had a fantastic family, wonderful friends and the opportunity to explore and experience much of the world. I have had the pleasure of running a successful research laboratory and the greater pleasure of having helped train a large number of young scientists, many of whom will contribute to the discoveries of the future. I hope that I have helped them develop not only the technical and intellectual abilities to do research and the confidence to persevere but also an approach to research that will make their efforts fun. Messages that emerge from my life’s experiences so far are less obvious. One, which I believe strongly, is that one should not be afraid to try something new: becoming an undergraduate at MIT instead of staying in the Midwest; studying biology as a graduate student after having earned degrees in mathematics and economics; and embarking upon the study of *C. elegans* at a point when nothing was published about the organism and many of the techniques of modern biology could not be applied to its analysis – all of these decisions proved to be good. What comes next for me I cannot know. I have three dreams. The first and most important is to be as good a father as I possibly can for Alexandra. The second is that some of the discoveries for which I can claim some credit, or perhaps my discoveries yet to come, will lead to applications in medicine that will alleviate human suffering. My third dream is that I will be able to use my new label of Nobel Laureate to contribute to the world in ways that will benefit society and mankind. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview |  |
| Interview |  |
| Q49 | “Man is but a worm,” that was the satirical, ironic comment that was given to Charles Darwin when he presented his theory of evolution. The same quotation was used in the [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2002/horvitz/lecture/) by Robert Horvitz, and I suppose, Robert Horvitz, that there was a hidden meaning in you showing that picture and doing that quotation. |
|  | Robert Horvitz: I don’t know that the meaning was specifically hidden but the point was that it reflects in fact the findings of the three of us combined. Because as we have learned more and more about biology, we find that the biological principles, the biological mechanisms, the precise genes and proteins that one sees in a worm of the sort that we’ve studied, or probably in any other organism, are remarkably similar to those that are present in human beings. |
| Q49 | “Science is at a crossroad,” is another quotation from the [Nobel Lectures](https://www.nobelprize.org/prizes/medicine/2002/sulston/lecture/). ”Either you decide to do science by press releases or you do science by publication.” That quotation came from the lecture given by John Sulston, what was the meaning of that quotation? |
|  | John E. Sulston: I think to be honest probably it’s more biology at the moment. It’s an old issue with science I think, whether one is going to simply make claims. In a previous discussion we were saying how the alchemist practiced science by press release, and he didn’t do very well. The point about press releases is you don’t check the facts behind and what you should do with press releases is to say: Show me your data. Biology is now finding itself in this position because suddenly biology is of commercial value and there’s a great temptation to try to gain financial advantage by issuing statements but not publishing them properly. We’ve had some experience of this with genome work and so that’s why I made a particular point of this, that we must publish openly, show the data and that’s the way science proceeds properly. |
| Q49 | “We’re drowning in an ocean, or a sea of data but we are starved from knowledge.” That is a quotation from Sydney Brenner’s [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2002/brenner/lecture/). Sydney Brenner, could you expand a little on that? |
|  | Sydney Brenner: Yes, I think we now have unprecedented ability to collect data about nature. Generated of course by our ability to sequence the genomes of complex organisms. You might say that we could in principle make an atom-by-atom description of what there is in nature, but there is now a crisis developing in biology that that completely unstructured information does not enhance understanding. What people want is to understand, which means you must have a theoretical framework in which to embed this. It is interesting that the word science and the word knowledge actually is the same word, so that people who just collect data are not doing science in that sense. I think that this problem will occupy our attention for certainly the next coming decades. Because we need it not only for understanding, but to communicate it and teach it. |
| Q34 | By this you have introduced yourselves, all the three Nobel Laureates in Physiology and Medicine. And welcome to the Nobel e-Museum and this interview on your prizes and the science around it. Let’s go back to this issue about differences between knowledge and data, Sydney Brenner. What are the great challenges that lie ahead of bioscience now when the human genome is almost, because it would always be almost completed? |
|  | Sydney Brenner: It was originally said that sequencing the human genome would be like sending a man to the moon, and if you reflect on it, it’s exactly the same. Because sending a man to the moon is very easy, it’s getting him back that’s the problem. I think the metaphor now extends, which is how can we get the human genome back from the moon, because we’ve done the first half. I think everybody knew that the major task would be to find the meaning of the genome, to interpret it. And I think that for more of the more sober people in this field, they’ve realised that the major part of the task still lies ahead. I think that that is going to be absolutely essential. Now there is a tendency in our science to say that everything could be done by this type of factory organisation, that was necessary to sequence the human genome and the other genomes. And there is now an idea afoot that we could just set up all of this to study proteins, to study cells, to study everything. But I’m a great believer in the fact that factories are not necessarily intelligent. And I think that what we’re going to need is human intelligence. I think the belief that we will put all this data into a computer and it will tell us the answer, this is ill-founded.John E. Sulston: I think it’s a minority who really feel that. I think what you have to guard against is this tendency that people put “-omics” on the end of everything and feel that it’s a new field and it really isn’t. Truth to say, although much drama was made of it and this was really because of the issue of the data release, there was never a very large fraction of science funding spent on the sequencing and I think that’s probably the rule. I think one should continue with large scale projects which have to be highly justified, but always with regard to the problems that they’re going to address. I think it should always be the case that by far the larger part of the funding should be spent on individual problem-solving efforts. If we can keep that balance, then I think we’re alright.Robert Horvitz: I would absolutely agree with that. One of the comments that echoes in my mind is the comment “don’t forget the biology”. The sea of information indeed does sometimes mask, and the excitement of the acquisition of such amounts of data, sometimes masks the fact that this is simply the foundation. To understand, we do need the basic inquiry. I think that what is really vital is to keep in mind creativity as being much of the source of future progress. Creativity is not the product of either a factory or a committee, the creativity really comes from an individual or sometimes a very small group of individuals, and we must make sure in all contexts that we keep those paths to creativity as open and as supported as we possibly can.John E. Sulston: I’m particularly pleased that we made a clear expression of this, since we’re here on behalf of the worm, the way the worm DNA sequence was published, it was entitled “A platform for investigating biology”. And there was a rather short paper about the genome itself surrounded by many other papers which were making the first steps towards the analysis that Sydney was speaking of. I’m very pleased that we did that because I think it expresses our feelings very well. |
| Q23 | Does that mean that we are focusing in a way too much on the genes? There might be much more interesting knowledge to be gained from complexity and the interaction between all the other things that are around the gene. Who is deciding over the genes? |
|  | Sydney Brenner: I think the complexity problem is the problem. It’s going to be even more enhanced in later years as we begin to tackle such questions as how does the brain work? I think that we need to, and biological systems are unique in that they can encode their own complexity within themselves, so biological systems will be the ones where this new science can be investigated in an objective manner and will form a bridge between the complex systems we ourselves invent, in economic systems and the law governed systems that you find in physics and chemistry. I think biology will occupy intellectually a pivotal role.Robert Horvitz: I think genes are very important but as we talk about biology, we are of necessity talking about biological complexity, and there are different levels of complexity. We have complexity at the level of genes; we have complexity at the level of cells; we have complexity at the level of networks of cells. As we talk for example about the nervous system, certainly genes provide the framework and the foundation for all that goes on, but some of the problems of the nervous system are probably best addressed not at the level of genes, but rather at the level of cell networks and neural networks. It’s only part of the problem, the genes, and we certainly want to understand at that level but my statement again is don’t forget the biology. The biology is much broader than genes. And some of the studies absolutely have to be carried at these higher levels. |
| Q23 | But the exciting thing is that it sounds as if there were some general knowledge to be harvested from this theory of complexity that could be applied even to economics and to associated questions or to other complex systems. What is your idea on that, John Sulston? |
|  | John E. Sulston: I’m not sure. People talk a lot about complexity theory. There’s a web thing that keeps being sent to me and I’m not sure that I believe in this abstraction. But of course people should try, if they think they can produce generalisable rules that may be right. One other point, I think the construction of devices is immensely important. I must say, when we come to talk about the human brain, I am one of those who regard it as least as important, the attempt to make intelligent devices. At the moment the words are being misused because none of our devices are intelligent. But nevertheless, as soon as you begin to make machines that learn and indeed evolve in some fashion, then I think we are beginning to use messages from life. In that sense you might be saying that we are using some similar ideas. But whether or not some real understanding of complexity will emerge, or it will be rather the case as Sydney has often said, that you cannot make a description which is shorter than the thing itself. I think we have to find out. But I think we have to explore. I do emphasise, it’s so important that we should use our creativity in this way. I think it’s actually particularly important, it came to light in a comment the other day that maybe Mozart had a completely different sort of creativity from scientists because without Mozart the music wouldn’t have existed, whereas with science we only discover and it’s there. I don’t think that’s true as we go forward in the areas we’re talking about now, because I think our creation will be as important as our discovery.Sydney Brenner: The answer to the Mozart thing is that the sounds exist in nature and he found the language to put them together in an interesting way. We could take exactly the same view which is that the objects exist in nature and it is the language that we use, whether it’s mathematics or scientific theory, to put them together. I don’t necessarily believe that there is a fundamental difference between them. I think the important thing is that it seems to me, that there are still enormous puzzles in this that are quite difficult to grasp. Because we have now systems of enormous complexity, like the human brain, which has arisen by an evolutionary process from the systems and shows continuity with *C-elegans*, that something came from *C-elegans* to reach this level of complexity by a process of mutation, accretion, but not by a process of design, which is the difference between this and man-made objects. And I think that that says to me that there must be some architecture within this that permits that flexibility because for many other systems, we know that if you change them, the most probable consequence is you break them. Whereas through this evolutionary process, nature has achieved something and to comprehend that I think is really a big challenge.John E. Sulston: The major thing of course is the rearrangement of the parts. I think we now understand that that’s the most likely key role of sexual reproduction. It’s an old puzzle for the geneticists, how organisms are inconveniently diploid, they have two copies of everything. The reason is probably that every generation can get a great rearrangement. Although the process is blind, in fact evolution is indeed arranging the parts. This is more likely to be productive than mutation which is usually destructive or merely adding new bits, and where do you get the new bits from? But if you rearrange old parts which work together in slightly new combinations, you can make much more rapid progress. And I think it’s right to say that’s how evolution has proceeded.Robert Horvitz: I think evolution is also a key word in the context of the question you raised a few moments ago about complexity. And the question is biological complexity likely to provide models for complexity of other systems? I think the answer is that evolution has done the work of generating a number of solutions and that if we understand those solutions, we can then see at least some cases in which complexity has been defined and we can then ask whether we can apply that knowledge, that framework, in other spheres. My guess is actually that we will be able to do so but probably not in ways that we’ll anticipate until we see what the answers really are. I think in part about devices that have been made in bioengineering, where people have made a variety of prosthetics and other devices, always with the notion that they’re copying biological systems but by and large, what is done before the knowledge of the biology is actually very unlike the biology. But the knowledge of the biology can then change what one can do in the future. I’m perhaps a little bit more optimistic than John of the general principles emerging, but we don’t know ahead of time what they are. Evolution has solved problems.John E. Sulston: The reason I speak about it negatively, I do feel that complexity is now a buzz word just as chaos was about 10 years ago and it annoys me. It’s like “-omics” over again. Let’s just find out how it works |
| Q34 | Along the path you understand more and more about how life works, but what would you say would be the most serious challenge to our ethics? What is the most controvert ethical question that will arise out of the science that you are a part of? |
|  | John E. Sulston: I think the challenge to the ethics is ourselves and our social systems actually. I don’t think inherently we are creating worse ethical problems with biology than we did by, for example, inventing nuclear weapons. But in both cases, if we don’t apply the democratic process properly, and of course we do have to bear in mind all the time, as [Winston Churchill](https://www.nobelprize.org/prizes/literature/1953/churchill/facts/) said that “Democracy is most awful way of governing ourselves until you think about the alternatives.” I think it’s very true that we don’t have any alternative to democracy and unless we apply it properly, and that means a rather full democracy, not a microsecond response referendum but a full democracy in which everybody has a chance to learn and to participate, then I think we might be in some trouble through discrimination of various kinds, and people have painted various horror stories of how we might actually specie-ate ourselves, if the rich ought to start breeding themselves in some clever way. I believe that properly applied social democracy will be a sufficient check on excesses of that kind.Robert Horvitz: One comment that was made really can be seen in a book written some years ago by [Jacques Monod](https://www.nobelprize.org/prizes/medicine/1965/monod/facts/), which he entitled *Chance and Necessity*. In that he took this topic that Sydney has alluded to, and that is the knowledge that essentially biological organisms have not been designed, they have evolved by chance. And what we see before us just is the consequence of a large number of random events and the selection of those that happened to work better than others. That may, as Monod very well discussed, interface with the issue of ethics because we have to begin to think of ourselves in different ways than perhaps much of human society has thought in the past. Particularly in the context of religion and ethics that are driven by religion. I think what we’re going to need is basically an ethical foundation that is humanity driven as some of these concepts really change with time. But I think those ethics inherently shouldn’t be altered by knowledge, but it’s the responsibility of all of us to make sure that the ethics are very much front and centre stage. |
| Q50 | Given that reproductive cloning could be done as safely as IVF and IXa today without any risk for the child or for the mother. Would reproductive cloning fit into that ethical framework in the future? Sydney Brenner? |
|  | Sydney Brenner: I think your assumption has to be questioned, whether it could be done. No, because I think that I can imagine a society that would accept that. There was a tremendous row over the case of *in-vitro* fertilisation and many people thought that it was unethical. Of course the argument was that this was of great benefit to a certain group of individuals. In that way now the machinery exists for those people to benefit from it and it’s a safe procedure. What worries me more is that the objectives of human beings in different countries differ, and we have to sit and ponder not so much on the ethics of any procedure, but the ethics of spending large resources say on cardiac transplantation, just to keep away from the genetics, and very little on famine. And I mean it’s that that worries me more, that the world is not a uniform place with a uniform set of standards. I think we have to be careful when we are thinking which leaf is higher than another leaf to be sure which branch we are standing on.John E. Sulston: In fact I think I would go a little further than that, I would say that the world is in danger of being pushed towards a uniform standard. The standard of the unadulterated marketplace, where indeed the money will continue to be spent on cardiac transplants and drugs that are used mainly by the rich countries, because that’s where the markets are, and the others are neglected. I think in a sense we have a uniform principle and I think it’s wrong. I think we’ve got to have a new principle where we deliberately try and spread the healthcare more evenly and I think this is something we desperately need today. |
| Q50 | And you have a recipe or any road ahead for that? |
|  | John E. Sulston: The road ahead? I’m afraid I have to say democracy again, because in the end if it’s not a democratic voice then it won’t work. But I think what’s happening is that our great world organisations, the World Trade Organisation and also the World Health Organisation, are much more nearly one vote, one dollar than one vote, one person or one country as they should be. I think it’s up to us. I think we actually share a rather higher platform than we did a couple of months ago for speaking about these matters, so it’s important that we do think about them. I think that we should press for this.Robert Horvitz: I think democracy is a key word, but I think what we need is an enlightened democracy, because in a democracy there is always the risk of the rule of the majority to the detriment of the minority. In this case we’re talking about the rule of the minority to the detriment of the majority, so it’s more extreme. But I think even in the case where it’s a majority we have to make sure that the rights and privileges of the minority are very well maintained and supported. I think that we need education. I think we need leadership to really inform and perhaps even persuade the majority of people who are making decisions that it is in their interest as well as in the interest of humanity in general to follow the kinds of paths that have just been described. |
| Q49 | When the genome project was almost finished, President Clinton and the British Prime Minister met at a press conference announcing this completion of the genome. Then President Clinton said: “Now, maybe we have seen the language in which God created Man”, and Sydney Brenner, you wrote a comment on that. |
|  | Sydney Brenner: I think that what I wrote on that is in the same way we could view the Bible as the language which man used to create God. That was just a comment like that. I think that that’s a very, how shall I say, exaggerated way of putting it.Your saying or Clinton’s saying?Sydney Brenner: Clinton’s saying. Because I think it has to pay respects to certain views in society and it’s not the language which anybody used to create man.Because you have said very clearly that the architecture is inside the structure.Sydney Brenner: The architecture is inside and I still think that that is the question of how this … This is why I think ordinary people don’t believe in evolution because we’re telling them by random changes that we can change a black and white television set into a colour television set. And everybody says there’s no way that can happen because if I try and change a television set, I’ll break it. That’s what will happen. And that is why a lot of questions about the internal architecture become important. That mutation happens but certain mutations carry a greater value than others. And we need to understand, so clearly mutations which affect the language of gene regulation are going to be more profoundly important than ones which just might affect the function of a protein. |
| Q51 | Maybe Robert Horvitz, couldn’t Sydney Brenner’s statement about the Bible be interpreted seriously? Given the mutations work finally gives us consciousness and awareness and we have created God or made him. The Bible was the language in which we describe what we think is the higher meaning for life. |
|  | Sydney Brenner: Exactly, yes, it’s a deeper thought than is done in terms of what it was alluding to. It was double edged, and one edge was what you said, the other edge was to say, it’s a more comic way of looking at the human genome.John E. Sulston: I think that there is a serious point there. But incidentally, what I would like just to replace the President’s remark with is that what we’ve done is to read the language of evolution. As Sydney emphasises, and he’s absolutely right, we don’t understand it. But nevertheless, we have the hieroglyph, we know how we brush the sand off the hieroglyph and now we’re working on its interpretation, I think. But to the other point, I think we do have, and that’s why I agree so much with what Bob said about trying to develop a real humanist basis for ethics. Because after all it’s not just the Bible, it’s the Koran, it’s a zillion other writings, all of which are more or less contradictory, all of which incidentally are very capable of leading people to physical combat and really serious warfare over points which were written in these books. I think we can develop serious humanism, but we do only have a limited amount of time because I do think we are going to understand the workings of our brain in much greater detail. I do think that we’re going to come much closer maybe to have a full understanding of what we really mean by self-consciousness and free will. By understanding what I mean is, and it is going to be complex, that in some fashion we’ll be able to write down all the components. Now the question is what will that mean? How can one comprehend oneself? It’s like trying to understand the Klein bottle. It’s a real paradox.I suspect the way we shall do it is to actually understand all the pieces but nevertheless not be able to hold an image of how it works all at once in our own heads. You can sort of trace around the pathway and do each bit at a time. I think most of us actually feel like that thinking about relativity, I certainly do. I can do the bits but just getting the whole thing, it just won’t gel for me. Now the reason I say it’s urgent is that I think we are going to, at the same time, be increasing our physical power, our power of the biological world and we have got to come to a way of making responsible decisions about how to use these things, and to come to the point where we’re going to do it in the knowledge where we really cannot sustain the idea reasonably of us being driven all the time by some higher thing, but rather seriously regard ourselves as products of the evolution. I think we are going to have to have that sort of social ethical revolution. It’s going to be needed over the next 50 years or so. I think it’s a very, very urgent matter and one that’s very worth paying attention to, to try and contribute. |
| ID | 0554 |
| Biographical | On my mother’s side I come from Midlands engineers and on my father’s from tenant farmers near Oxford. As far back as I remember, and earlier, I was an artisan, a maker and doer. Mechanically minded, my parents said.Ted, my father, was an Anglican priest; after serving as an army chaplain in the second world war he joined the missionary society SPG (later USPG) and spent his life as an administrator, though he was active in the local parish at weekends. He had a great interest in the natural world, and was a keen gardener. When young I was mainly interested in the physical world, especially anything to do with electricity, but I think something of his love for living things may have rubbed off on me. He brought me up as a Christian, and it was a source of distress to him that I lost my faith, as they say, during my adolescence. That was a hard struggle, one of the hardest I’ve had. When I tried to talk to my fellow students about it at Cambridge I found them uncomprehending, not seeing it as very important in the scheme of things: but I had had to choose between my judgement and my father. It was a slight worry to me that our children were raised faithless – not prohibited, just not encouraged – in case the religious upbringing was essential to their moral development. Great relief that they’ve got on fine! Daphne said don’t be silly, and of course she was right.Muriel, my mother, was my main confidant. She was a teacher of English at Watford grammar school, but took a break while my sister Madeleine and I were children. She held court in the kitchen, and we talked about everything. Questions, help with homework. She was more subtle than my father, and it was only after her death that I opened a letter from her and realised that she too desperately wanted me to have continued in the Christian faith.From them both I gained a sense that there is not, or need not be, any clear distinction between work and play, and that one has a duty both to serve others and to do the best one can in everything.They believed in private education, and at five I was sent to the local preparatory school. It was just round the corner. The classroom work was easy enough and I got on well with that, but I absolutely loathed games at which I was hopeless. Whether it was eyesight, reflexes or just daydreaming I don’t know, but it just didn’t turn out well. Cricket was the worst because it went on so long, on beautiful summer afternoons when there were so many better things to do. Once we had catching practice and the ball hit me in the forehead because I was thinking about something else to pass the time. It knocked me over and there was some concern about safety – rather embarrassing for my teacher.From there I got a scholarship to Merchant Taylors at Northwood, which was a financial relief for my parents, who were not particularly well off. I could have gone to a grammar school like Madeleine, but I’m ashamed to say that there was the sense that the boy had to have the “best”. One can’t blame them too much – that was the tenor of the age. School gradually became more interesting because I was able to specialise in science. Games continued to be a nightmare for a while, but that gradually faded as I realised that one didn’t have to take them seriously and began to discover the joy of hill walking on my own.When it came to choice of subjects, science was obvious – since I was uninterested in anything else – but a decision that caused consternation in some eyes was my demand to take biology for A-level. I was told that this was not sensible at all and would lower my chances, upon which what had initially been more or less a whim on my part hardened into determination. So biology, physics and chemistry it was, with maths abandoned. Not sensible at all, but I had tremendous fun dissecting animals and sectioning plants and wondering about their workings. This was the late 50’s, and the molecular biology revolution was getting under way with reports from the front starting to trickle back to us. And we had great support: my enthusiastic zoology teacher, Richard Stokes, wrote to me regularly until his death last year.In 1960 I arrived in Cambridge, with a scholarship to read Natural Sciences at Pembroke College. The first year was easy because those of us with scholarships had a head start, but the second year was a grind. I wasn’t enjoying my course work much, because biology wasn’t fulfilling its promise, and anyway I’m not a books person but a hands person, but mainly because by then I had become distracted by other activities, especially theatre lighting at the ADC. Meredith Dewey, my tutor, warned me that those who went into the theatre seldom did well at anything else, but of course that was of no great concern to me. I also became fairly depressed at my lack of social graces and everything seemed pretty pointless. It culminated in a night of drunken disorder that ended in the police station, and poor Meredith was hauled out to retrieve me. Covered in shame, I felt nobody would ever speak to me again. Of course my misdemeanour was hardly noticed, but it did have the effect of motivating me to make some sort of effort in my final year. I plumped for organic chemistry, reasoning that at least I could get a job with it, found it interesting because of my sparky supervisor Ian Fleming, and ended up with a 2.1, though without tremendous enthusiasm.My only attempt at job-seeking had been an application to VSO, and I was actually expecting to join a scheme that summer. However it fell through at the last moment, and so with my 2.1 in hand I went along to see [Alexander Todd](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1957/index.html) at the chemistry department in Lensfield Road, on the off chance of being taken on as a research student. To my amazement I was taken on immediately and handed over to Colin Reese, who put me to work on his research into oligonucleotide synthesis.And that was the beginning of my scientific career, if you can call it that. No more text books, just my own lab books, and the toys, the lovely toys, to play with. I was put in a large lab, sharing a long bench with Mike Tanner, swarthy and amiable. Life was simple, revolving largely around the lab and the Panton Arms where Iris Ambrose dispensed beer, egg on toast with beans (or sometimes as a variant beans on toast with egg), sympathy, and cashed our cheques.That first year my lodging was in a bedsit on the other side of town. For the second year I arranged with another research student Henry Chan to share a flat. We advertised for a third, and a geophysicist Bob Grasty replied. Most Tuesdays we shared a meal, to which Bob brought two women from his group – Monica Dirac and Daphne Bate. We were all very cheerful together, and when the year ended we seemed to disperse.But that autumn we went to London for Bob’s wedding to his long standing girl friend Jenny. I sat behind Daphne, and she turned and smiled at me. I asked her if she wanted a lift home, and we haven’t really been apart since. And Mike, Henry and Bob are our lifelong friends.Meanwhile, thanks to Colin’s efficient organisation and my love of playing with the toys, my labwork was trundling along nicely, and already it was time to be writing up and moving on. Colin suggested that I should take a post-doc position with Leslie Orgel at the Salk Institute, and Daphne agreed to get married. And so we whooshed away to California, where Daphne intended to get a job too but then found she was pregnant. So Ingrid was born there, and though at first we feared destitution it turned out to be idyllic. The lab was a great place, and we spent holidays travelling around the western states; shores, deserts, forests and mountains – an earthly utopia.With Leslie’s prebiotic chemistry I felt I was beginning to get back towards biology. It was through the discussions there that I really grasped the power of evolution for the first time. And Leslie spoiled me terribly, frequently inviting us to dinner when he had visitors, and making me feel pretty important. I fear that I became rather obnoxious as a result. In my second year there Leslie introduced me to [Francis Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html), who interviewed me on behalf of [Sydney Brenner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/index.html). All I really knew at the time was that Sydney had picked a small animal to study neurobiology. There were lots of jokes about Sydney’s worm, and general scepticism about its chances of coming to anything. This seemed a pretty good recommendation to me: there’s little point in doing what everybody else is doing. In fact, Leslie suggested that I could just go away for a year and then apply for a junior fellowship at the Salk Institute. The buzz word was neurobiology, and the place was full of meetings and discussion about this next step in molecular biology. One of the events was a summer programme run by Steve Kuffler and Ed Furshpan from Harvard Medical School, and I was invited to join in. They put me on to studying the formaldehyde-induced- fluorescence of catecholamines, a method for revealing these neurotransmitters in sections of frozen tissue. Although I was not deeply involved in their objectives, learning this technique was to make a difference in my life. In the spring of 1969 the three of us took our last holiday, swinging around Mexico and then departed on an extended break, travelling overland to the east coast via Florida and Canada. After the open spaces of America, southern England felt pretty cramped, but in no time we were settled again in Cambridge, I joined Sydney’s group, and Adrian was born.The group was housed in the Cell Biology Division of the Medical Research Council’s Laboratory of Molecular Biology in Cambridge, where so many of the basic mechanisms of molecular biology had been worked out: a rather awe-inspiring place to arrive as a junior staff member. Space was at a premium, as it is in any successful institute, and I ended up in the “big lab”. Hugh Robertson, [Sidney Altman](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1989/index.html) and Mary Osborn were all there. Next door was Mike Wilcox working on *Anabaena*, later switching to *Drosophila*. Our families became great friends, and we often shared weekend trips as the children grew up. His death from cancer in 1992 was a great loss.My first years there were devoted to exploring all manner of things to do with the worm: it was a largely virgin field, and so one didn’t have to know much in advance. I worked on neurotransmitters, and, because of my background, I spent some time on the DNA using the global methods of hybridisation that were all we had available at the time.But as a side project I tried out the FIF method, and got it to work on the tiny cells of the worm. The neurons I discovered have not proved especially important in themselves, but they led me to start looking at the cellular anatomy as a whole. And so, quite by chance, I was the one who began to watch the cell divisions unfold. For a decade I became essentially a pure zoologist, and with several colleagues worked out the entire cell lineage of the animal. My key colleagues at this time were [Bob Horvitz](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/index.html) and John White, and after Bob returned to the US for a tenure track post at MIT I felt distinctly bereft. But there was Judith Kimble as my first post-doc, and [Marty Chalfie](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2008/) with Sydney, and Jonathan Hodgkin as Sydney’s research student, so we continued as a vigorous little group. It suited me very well not to be in charge, so that I was free to go on playing. The LMB gave me a junior staff position, for which I am immensely grateful. To set up a formal research programme would have been impossible for me then.The last and most difficult stage of the cell lineage to be completed, that of the embryo, was an important accomplishment for me. It quickly secured my election to the Royal Society, proposed by Sydney, and is now a factor in bringing me to Stockholm. Later, better methods of observation were devised, which to some extent are superseding direct observation. Of course one has to begin somehow, and that beginning then stimulates the development of new approaches, so that what had been difficult becomes routine. I was lucky to have the chance to start it off.Another feature of the community that was instigated by Bob Edgar was the series of international worm meetings. The first was at Woods Hole in 1977, then it moved to Cold Spring Harbor, then to Madison. The meetings played a vital role in holding together and nurturing the growing *C. elegans* community, and for me they were particularly important when I moved on in 1982 to map and eventually sequence the worm’s DNA. This was no longer to be a solitary endeavour for me. It began with new partnerships – Alan Coulson and Bob Waterston – and continued with an increasingly large group.The worm genome work was funded throughout by the Medical Research Council, but in 1992 the Wellcome Trust accepted a proposal for tackling the human genome and under Michael Morgan’s management built a new laboratory, the Sanger Centre, to house worm, human and other projects. From then until I stepped down in 2000 I found myself to my astonishment being an actual director. Thanks to a close knit group of colleagues (Alan Coulson, Jane Rogers, Richard Durbin, David Bentley, Bart Barrell and Murray Cairns) we succeeded in our aims, and it all seems to have worked out well enough, but it was a strange time.The human sequence is being brought to completion this year through the international consortium of the human genome project. More than half the effort is in the US; the central management is there – initially under [Jim Watson](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html), then under Francis Collins from1992 – as are other leading figures including Bob Waterston, Eric Lander, Maynard Olson and Phil Green. Outside the US are several groups, including Jean Weissenbach in France, and others in Germany, Japan and China. Michael Morgan is a key organiser of the international aspects.It all took a lot of work, organisation, and of course money. Despite helping to set up the UK side of it, I didn’t expect to be playing a visible role myself. But in 1999 we were drawn into defending our position against a vigorous bid, by Celera Genomics, to take over the project for profit, and it fell to me to be a major UK spokesman.Having to deal with this extraordinary dispute, at what turned out to be a moderately unpleasant level of public acrimony, was quite a shock. It seemed to me self-evident that on both moral and practical grounds the human genome itself (as opposed to inventions that may be made from a knowledge of it) is an inappropriate subject for commercial investment and ownership. It was not just the commercial bid itself that shocked, what was worse was that it gained support from all sorts of people for whom I’d previously had respect. I still don’t exactly know why, but part of the reason seems to be a business-style way in science nowadays of following bandwagons and avoiding controversy in case things turn out politically against you.During these events, I thought all the time that I would return to my lab bench once we’d got the episode over with. It had never been my ambition to run a large enterprise, and the thought of returning to play with the toys buoyed me along. Well, get over it we did – Celera collapsed, and the human, mouse and other genomes are firmly in the public domain. It’s immensely exciting to reflect that the plan has worked out, and that all these sequences are quietly providing a new and firm foundation for biological research. But I found myself impelled further away from practical science rather than returning.First, I felt it important to write an account of what had happened. Other books had already been published, and more were to come, but all were written by journalists who drew on the press accounts, largely from the US where for no solid reason the balance of opinion had been in favour of the private effort. So I thought someone should provide an accurate record of events. Bob Waterston and I discussed writing something, but we were neither expert nor free enough to get it done in a reasonable time. So at Daphne’s suggestion I got together with Georgina Ferry, a very accomplished science writer. I found it an enormously rewarding undertaking, and a wholly novel experience. Georgina drew on my email records, interviewed many people, and did the greater part of the actual writing, but I wrote some parts and we finished it off jointly, merging our ideas as we went (Sulston and Ferry, 2002).The exercise had a great influence on me, because it forced me to examine some of the premises under which I had been working all my life. Like many scientists I had felt that my job was to get on with my work, and leave the world to be run by politicians who have the skills and experience to do it properly. Indeed while writing these words I’ve had a conversation with a colleague who argued exactly that. She feels that to stray from one’s expertise is to become second rate.However, it’s become apparent to me that the problems that we encountered over the human genome are much more widespread than I had realised. The researchers at Oxfam, in particular, have educated me in the global consequences of ignoring common goods in the quest for short term profit. These issues are not simple, but I do think we would benefit from a greater and genuine involvement by us non-professionals in deciding the sort of world we want. Many people say: “Yes, I agree with you, but what can I do?”. For me, it’s been like climbing up from a valley and reaching a col: suddenly you can see new territories, stretching away into the distance, and you wonder.At present, of course, I’m indeed second-rate in these matters – an amateur. But one should not be afraid of being an amateur if one is willing also to be a student. Has my head been turned by the Nobel prize? No, this happened to me two years ago. But getting the prize provides us all with a higher platform from which (if we don’t fall off through excessive gesticulation) we can have more influence than we did before. So it changes our lives.It remains for me to say thank you to my family for putting up with me, and for all the talking. Daphne retires this year from her duties as librarian at DAMTP. Through her I’ve had a lot of interaction with the staff there, and shall miss seeing them at parties. After taking her PhD at Berkeley Ingrid went into interactive museums. She lives in New York with her husband Paul Pavlidis, and son Micah. Adrian is in Edinburgh, and works in software. Madeleine worked for many years in the Gray Lab at Mount Vernon Hospital; now retired, she lives with her husband John Harvey near Lewes. We all met in Stockholm on 7 December, and had a marvellous week together. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0554 |
| Interview |  |
| Q49 | “Man is but a worm,” that was the satirical, ironic comment that was given to Charles Darwin when he presented his theory of evolution. The same quotation was used in the [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2002/horvitz/lecture/) by Robert Horvitz, and I suppose, Robert Horvitz, that there was a hidden meaning in you showing that picture and doing that quotation. |
|  | Robert Horvitz: I don’t know that the meaning was specifically hidden but the point was that it reflects in fact the findings of the three of us combined. Because as we have learned more and more about biology, we find that the biological principles, the biological mechanisms, the precise genes and proteins that one sees in a worm of the sort that we’ve studied, or probably in any other organism, are remarkably similar to those that are present in human beings. |
| Q49 | “Science is at a crossroad,” is another quotation from the [Nobel Lectures](https://www.nobelprize.org/prizes/medicine/2002/sulston/lecture/). ”Either you decide to do science by press releases or you do science by publication.” That quotation came from the lecture given by John Sulston, what was the meaning of that quotation? |
|  | John E. Sulston: I think to be honest probably it’s more biology at the moment. It’s an old issue with science I think, whether one is going to simply make claims. In a previous discussion we were saying how the alchemist practiced science by press release, and he didn’t do very well. The point about press releases is you don’t check the facts behind and what you should do with press releases is to say: Show me your data. Biology is now finding itself in this position because suddenly biology is of commercial value and there’s a great temptation to try to gain financial advantage by issuing statements but not publishing them properly. We’ve had some experience of this with genome work and so that’s why I made a particular point of this, that we must publish openly, show the data and that’s the way science proceeds properly. |
| Q49 | “We’re drowning in an ocean, or a sea of data but we are starved from knowledge.” That is a quotation from Sydney Brenner’s [Nobel Lecture](https://www.nobelprize.org/prizes/medicine/2002/brenner/lecture/). Sydney Brenner, could you expand a little on that? |
|  | Sydney Brenner: Yes, I think we now have unprecedented ability to collect data about nature. Generated of course by our ability to sequence the genomes of complex organisms. You might say that we could in principle make an atom-by-atom description of what there is in nature, but there is now a crisis developing in biology that that completely unstructured information does not enhance understanding. What people want is to understand, which means you must have a theoretical framework in which to embed this. It is interesting that the word science and the word knowledge actually is the same word, so that people who just collect data are not doing science in that sense. I think that this problem will occupy our attention for certainly the next coming decades. Because we need it not only for understanding, but to communicate it and teach it. |
| Q34 | By this you have introduced yourselves, all the three Nobel Laureates in Physiology and Medicine. And welcome to the Nobel e-Museum and this interview on your prizes and the science around it. Let’s go back to this issue about differences between knowledge and data, Sydney Brenner. What are the great challenges that lie ahead of bioscience now when the human genome is almost, because it would always be almost completed? |
|  | Sydney Brenner: It was originally said that sequencing the human genome would be like sending a man to the moon, and if you reflect on it, it’s exactly the same. Because sending a man to the moon is very easy, it’s getting him back that’s the problem. I think the metaphor now extends, which is how can we get the human genome back from the moon, because we’ve done the first half. I think everybody knew that the major task would be to find the meaning of the genome, to interpret it. And I think that for more of the more sober people in this field, they’ve realised that the major part of the task still lies ahead. I think that that is going to be absolutely essential. Now there is a tendency in our science to say that everything could be done by this type of factory organisation, that was necessary to sequence the human genome and the other genomes. And there is now an idea afoot that we could just set up all of this to study proteins, to study cells, to study everything. But I’m a great believer in the fact that factories are not necessarily intelligent. And I think that what we’re going to need is human intelligence. I think the belief that we will put all this data into a computer and it will tell us the answer, this is ill-founded.John E. Sulston: I think it’s a minority who really feel that. I think what you have to guard against is this tendency that people put “-omics” on the end of everything and feel that it’s a new field and it really isn’t. Truth to say, although much drama was made of it and this was really because of the issue of the data release, there was never a very large fraction of science funding spent on the sequencing and I think that’s probably the rule. I think one should continue with large scale projects which have to be highly justified, but always with regard to the problems that they’re going to address. I think it should always be the case that by far the larger part of the funding should be spent on individual problem-solving efforts. If we can keep that balance, then I think we’re alright.Robert Horvitz: I would absolutely agree with that. One of the comments that echoes in my mind is the comment “don’t forget the biology”. The sea of information indeed does sometimes mask, and the excitement of the acquisition of such amounts of data, sometimes masks the fact that this is simply the foundation. To understand, we do need the basic inquiry. I think that what is really vital is to keep in mind creativity as being much of the source of future progress. Creativity is not the product of either a factory or a committee, the creativity really comes from an individual or sometimes a very small group of individuals, and we must make sure in all contexts that we keep those paths to creativity as open and as supported as we possibly can.John E. Sulston: I’m particularly pleased that we made a clear expression of this, since we’re here on behalf of the worm, the way the worm DNA sequence was published, it was entitled “A platform for investigating biology”. And there was a rather short paper about the genome itself surrounded by many other papers which were making the first steps towards the analysis that Sydney was speaking of. I’m very pleased that we did that because I think it expresses our feelings very well. |
| Q23 | Does that mean that we are focusing in a way too much on the genes? There might be much more interesting knowledge to be gained from complexity and the interaction between all the other things that are around the gene. Who is deciding over the genes? |
|  | Sydney Brenner: I think the complexity problem is the problem. It’s going to be even more enhanced in later years as we begin to tackle such questions as how does the brain work? I think that we need to, and biological systems are unique in that they can encode their own complexity within themselves, so biological systems will be the ones where this new science can be investigated in an objective manner and will form a bridge between the complex systems we ourselves invent, in economic systems and the law governed systems that you find in physics and chemistry. I think biology will occupy intellectually a pivotal role.Robert Horvitz: I think genes are very important but as we talk about biology, we are of necessity talking about biological complexity, and there are different levels of complexity. We have complexity at the level of genes; we have complexity at the level of cells; we have complexity at the level of networks of cells. As we talk for example about the nervous system, certainly genes provide the framework and the foundation for all that goes on, but some of the problems of the nervous system are probably best addressed not at the level of genes, but rather at the level of cell networks and neural networks. It’s only part of the problem, the genes, and we certainly want to understand at that level but my statement again is don’t forget the biology. The biology is much broader than genes. And some of the studies absolutely have to be carried at these higher levels. |
| Q23 | But the exciting thing is that it sounds as if there were some general knowledge to be harvested from this theory of complexity that could be applied even to economics and to associated questions or to other complex systems. What is your idea on that, John Sulston? |
|  | John E. Sulston: I’m not sure. People talk a lot about complexity theory. There’s a web thing that keeps being sent to me and I’m not sure that I believe in this abstraction. But of course people should try, if they think they can produce generalisable rules that may be right. One other point, I think the construction of devices is immensely important. I must say, when we come to talk about the human brain, I am one of those who regard it as least as important, the attempt to make intelligent devices. At the moment the words are being misused because none of our devices are intelligent. But nevertheless, as soon as you begin to make machines that learn and indeed evolve in some fashion, then I think we are beginning to use messages from life. In that sense you might be saying that we are using some similar ideas. But whether or not some real understanding of complexity will emerge, or it will be rather the case as Sydney has often said, that you cannot make a description which is shorter than the thing itself. I think we have to find out. But I think we have to explore. I do emphasise, it’s so important that we should use our creativity in this way. I think it’s actually particularly important, it came to light in a comment the other day that maybe Mozart had a completely different sort of creativity from scientists because without Mozart the music wouldn’t have existed, whereas with science we only discover and it’s there. I don’t think that’s true as we go forward in the areas we’re talking about now, because I think our creation will be as important as our discovery.Sydney Brenner: The answer to the Mozart thing is that the sounds exist in nature and he found the language to put them together in an interesting way. We could take exactly the same view which is that the objects exist in nature and it is the language that we use, whether it’s mathematics or scientific theory, to put them together. I don’t necessarily believe that there is a fundamental difference between them. I think the important thing is that it seems to me, that there are still enormous puzzles in this that are quite difficult to grasp. Because we have now systems of enormous complexity, like the human brain, which has arisen by an evolutionary process from the systems and shows continuity with *C-elegans*, that something came from *C-elegans* to reach this level of complexity by a process of mutation, accretion, but not by a process of design, which is the difference between this and man-made objects. And I think that that says to me that there must be some architecture within this that permits that flexibility because for many other systems, we know that if you change them, the most probable consequence is you break them. Whereas through this evolutionary process, nature has achieved something and to comprehend that I think is really a big challenge.John E. Sulston: The major thing of course is the rearrangement of the parts. I think we now understand that that’s the most likely key role of sexual reproduction. It’s an old puzzle for the geneticists, how organisms are inconveniently diploid, they have two copies of everything. The reason is probably that every generation can get a great rearrangement. Although the process is blind, in fact evolution is indeed arranging the parts. This is more likely to be productive than mutation which is usually destructive or merely adding new bits, and where do you get the new bits from? But if you rearrange old parts which work together in slightly new combinations, you can make much more rapid progress. And I think it’s right to say that’s how evolution has proceeded.Robert Horvitz: I think evolution is also a key word in the context of the question you raised a few moments ago about complexity. And the question is biological complexity likely to provide models for complexity of other systems? I think the answer is that evolution has done the work of generating a number of solutions and that if we understand those solutions, we can then see at least some cases in which complexity has been defined and we can then ask whether we can apply that knowledge, that framework, in other spheres. My guess is actually that we will be able to do so but probably not in ways that we’ll anticipate until we see what the answers really are. I think in part about devices that have been made in bioengineering, where people have made a variety of prosthetics and other devices, always with the notion that they’re copying biological systems but by and large, what is done before the knowledge of the biology is actually very unlike the biology. But the knowledge of the biology can then change what one can do in the future. I’m perhaps a little bit more optimistic than John of the general principles emerging, but we don’t know ahead of time what they are. Evolution has solved problems.John E. Sulston: The reason I speak about it negatively, I do feel that complexity is now a buzz word just as chaos was about 10 years ago and it annoys me. It’s like “-omics” over again. Let’s just find out how it works |
| Q34 | Along the path you understand more and more about how life works, but what would you say would be the most serious challenge to our ethics? What is the most controvert ethical question that will arise out of the science that you are a part of? |
|  | John E. Sulston: I think the challenge to the ethics is ourselves and our social systems actually. I don’t think inherently we are creating worse ethical problems with biology than we did by, for example, inventing nuclear weapons. But in both cases, if we don’t apply the democratic process properly, and of course we do have to bear in mind all the time, as [Winston Churchill](https://www.nobelprize.org/prizes/literature/1953/churchill/facts/) said that “Democracy is most awful way of governing ourselves until you think about the alternatives.” I think it’s very true that we don’t have any alternative to democracy and unless we apply it properly, and that means a rather full democracy, not a microsecond response referendum but a full democracy in which everybody has a chance to learn and to participate, then I think we might be in some trouble through discrimination of various kinds, and people have painted various horror stories of how we might actually specie-ate ourselves, if the rich ought to start breeding themselves in some clever way. I believe that properly applied social democracy will be a sufficient check on excesses of that kind.Robert Horvitz: One comment that was made really can be seen in a book written some years ago by [Jacques Monod](https://www.nobelprize.org/prizes/medicine/1965/monod/facts/), which he entitled *Chance and Necessity*. In that he took this topic that Sydney has alluded to, and that is the knowledge that essentially biological organisms have not been designed, they have evolved by chance. And what we see before us just is the consequence of a large number of random events and the selection of those that happened to work better than others. That may, as Monod very well discussed, interface with the issue of ethics because we have to begin to think of ourselves in different ways than perhaps much of human society has thought in the past. Particularly in the context of religion and ethics that are driven by religion. I think what we’re going to need is basically an ethical foundation that is humanity driven as some of these concepts really change with time. But I think those ethics inherently shouldn’t be altered by knowledge, but it’s the responsibility of all of us to make sure that the ethics are very much front and centre stage. |
| Q50 | Given that reproductive cloning could be done as safely as IVF and IXa today without any risk for the child or for the mother. Would reproductive cloning fit into that ethical framework in the future? Sydney Brenner? |
|  | Sydney Brenner: I think your assumption has to be questioned, whether it could be done. No, because I think that I can imagine a society that would accept that. There was a tremendous row over the case of *in-vitro* fertilisation and many people thought that it was unethical. Of course the argument was that this was of great benefit to a certain group of individuals. In that way now the machinery exists for those people to benefit from it and it’s a safe procedure. What worries me more is that the objectives of human beings in different countries differ, and we have to sit and ponder not so much on the ethics of any procedure, but the ethics of spending large resources say on cardiac transplantation, just to keep away from the genetics, and very little on famine. And I mean it’s that that worries me more, that the world is not a uniform place with a uniform set of standards. I think we have to be careful when we are thinking which leaf is higher than another leaf to be sure which branch we are standing on.John E. Sulston: In fact I think I would go a little further than that, I would say that the world is in danger of being pushed towards a uniform standard. The standard of the unadulterated marketplace, where indeed the money will continue to be spent on cardiac transplants and drugs that are used mainly by the rich countries, because that’s where the markets are, and the others are neglected. I think in a sense we have a uniform principle and I think it’s wrong. I think we’ve got to have a new principle where we deliberately try and spread the healthcare more evenly and I think this is something we desperately need today. |
| Q50 | And you have a recipe or any road ahead for that? |
|  | John E. Sulston: The road ahead? I’m afraid I have to say democracy again, because in the end if it’s not a democratic voice then it won’t work. But I think what’s happening is that our great world organisations, the World Trade Organisation and also the World Health Organisation, are much more nearly one vote, one dollar than one vote, one person or one country as they should be. I think it’s up to us. I think we actually share a rather higher platform than we did a couple of months ago for speaking about these matters, so it’s important that we do think about them. I think that we should press for this.Robert Horvitz: I think democracy is a key word, but I think what we need is an enlightened democracy, because in a democracy there is always the risk of the rule of the majority to the detriment of the minority. In this case we’re talking about the rule of the minority to the detriment of the majority, so it’s more extreme. But I think even in the case where it’s a majority we have to make sure that the rights and privileges of the minority are very well maintained and supported. I think that we need education. I think we need leadership to really inform and perhaps even persuade the majority of people who are making decisions that it is in their interest as well as in the interest of humanity in general to follow the kinds of paths that have just been described. |
| Q49 | When the genome project was almost finished, President Clinton and the British Prime Minister met at a press conference announcing this completion of the genome. Then President Clinton said: “Now, maybe we have seen the language in which God created Man”, and Sydney Brenner, you wrote a comment on that. |
|  | Sydney Brenner: I think that what I wrote on that is in the same way we could view the Bible as the language which man used to create God. That was just a comment like that. I think that that’s a very, how shall I say, exaggerated way of putting it.Your saying or Clinton’s saying?Sydney Brenner: Clinton’s saying. Because I think it has to pay respects to certain views in society and it’s not the language which anybody used to create man.Because you have said very clearly that the architecture is inside the structure.Sydney Brenner: The architecture is inside and I still think that that is the question of how this … This is why I think ordinary people don’t believe in evolution because we’re telling them by random changes that we can change a black and white television set into a colour television set. And everybody says there’s no way that can happen because if I try and change a television set, I’ll break it. That’s what will happen. And that is why a lot of questions about the internal architecture become important. That mutation happens but certain mutations carry a greater value than others. And we need to understand, so clearly mutations which affect the language of gene regulation are going to be more profoundly important than ones which just might affect the function of a protein. |
| Q51 | Maybe Robert Horvitz, couldn’t Sydney Brenner’s statement about the Bible be interpreted seriously? Given the mutations work finally gives us consciousness and awareness and we have created God or made him. The Bible was the language in which we describe what we think is the higher meaning for life. |
|  | Sydney Brenner: Exactly, yes, it’s a deeper thought than is done in terms of what it was alluding to. It was double edged, and one edge was what you said, the other edge was to say, it’s a more comic way of looking at the human genome.John E. Sulston: I think that there is a serious point there. But incidentally, what I would like just to replace the President’s remark with is that what we’ve done is to read the language of evolution. As Sydney emphasises, and he’s absolutely right, we don’t understand it. But nevertheless, we have the hieroglyph, we know how we brush the sand off the hieroglyph and now we’re working on its interpretation, I think. But to the other point, I think we do have, and that’s why I agree so much with what Bob said about trying to develop a real humanist basis for ethics. Because after all it’s not just the Bible, it’s the Koran, it’s a zillion other writings, all of which are more or less contradictory, all of which incidentally are very capable of leading people to physical combat and really serious warfare over points which were written in these books. I think we can develop serious humanism, but we do only have a limited amount of time because I do think we are going to understand the workings of our brain in much greater detail. I do think that we’re going to come much closer maybe to have a full understanding of what we really mean by self-consciousness and free will. By understanding what I mean is, and it is going to be complex, that in some fashion we’ll be able to write down all the components. Now the question is what will that mean? How can one comprehend oneself? It’s like trying to understand the Klein bottle. It’s a real paradox.I suspect the way we shall do it is to actually understand all the pieces but nevertheless not be able to hold an image of how it works all at once in our own heads. You can sort of trace around the pathway and do each bit at a time. I think most of us actually feel like that thinking about relativity, I certainly do. I can do the bits but just getting the whole thing, it just won’t gel for me. Now the reason I say it’s urgent is that I think we are going to, at the same time, be increasing our physical power, our power of the biological world and we have got to come to a way of making responsible decisions about how to use these things, and to come to the point where we’re going to do it in the knowledge where we really cannot sustain the idea reasonably of us being driven all the time by some higher thing, but rather seriously regard ourselves as products of the evolution. I think we are going to have to have that sort of social ethical revolution. It’s going to be needed over the next 50 years or so. I think it’s a very, very urgent matter and one that’s very worth paying attention to, to try and contribute. |
| ID | 0555 |
| Biographical | I don’t remember much about my early childhood. I am told that before I began school, my older cousin would return from her school and teach me what she had learned. By the time I was 10 or so, I was displaying a curiosity that might have suggested an academic bent. I was an avid collector of bugs, butterflies, lizards, snakes, and spiders. I remember on one of these adventures learning to be skeptical of everything one reads in books. I had read that lizards do not have teeth. I had grabbed a very big lizard and stared in disbelief as it turned its head, displayed a fine set of teeth and sank them into my thumb. From age 13 to 17 I was preoccupied with sports, girls and cars. But midway through high school a fortunate event happened. I became unhappy with the football coach and bored of carousing with my car club friends. A close friend of mine suggested we transfer to the cross town high school and my accommodating mother moved apartments so I could do so. At the new school I was fortunate to find some teachers that challenged me, particularly a physics teacher and my grades improved dramatically. Since no one in my family had ever been to college, I had little in the way of career guidance. However, I was good at math and physics and I liked mechanical drawing, so I thought I might become an engineer. I went for one year to a two-year junior college, Glendale Junior College, in preparation, taking math, chemistry and physics. I did well, and my counselor encouraged me to meet with a recruiter from the California Institute of Technology. This was my next major break. I took the entrance exams and was admitted into the sophomore class.For the first time, I was in an environment of real science and it was magical. In hindsight, I can see that I was destined for science. I have always been curious and wanted to understand things at a fundamental level. For example, I used to get annoyed at my father, a neon sign man, because he would not explain to me, how neon signs work. I only realized later, that I wanted to know about electricity and atomic emissions, topics that he knew nothing about. At Cal Tech, I enrolled as a physics major. During my sophomore year, I took a lecture course in Biology, taught by James Bonner. He was incredibly enthusiastic. This must have been around 1958, only five years after the discovery of the DNA structure, and the course was all about DNA, RNA and protein. The clincher for me was an optional evening laboratory in bacteriophage genetics taught by Bob Edgar and Charlie Steinberg. Here, I learned that biology could be quantitative and it was little time before I changed my major to biology. At Cal Tech I was able to do research nearly every quarter and summer, in chemistry, biochemistry, and genetics. I worked with Hildegard Lamfrom, [Howard Temin](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1975/index.html) and Bob Edgar. Another feature of the Cal Tech undergraduate education was the opportunity to take credits as reading which I did most quarters, reading the original literature in phage genetics and gene regulation.I graduated in 1961 and went to MIT for graduate school. I had decided that I wanted to work on gene regulation and I knew of only two prominent labs in the US, Arthur Pardee at Berkeley, and Boris Magasanik, at MIT. I visited Arthur Pardee at Berkeley and he was not encouraging so I went to MIT. Being a graduate student at MIT was great fun and very intense. Boris Magasanik would come through the lab each afternoon and stop at each desk to discuss the previous day’s results. I wanted a new result each day so that set quite a pace! I was there only about two and a half years when Boris came to me and said that I had essentially finished my thesis but since no one could leave that soon I would have to stay another year.By this time [François Jacob and Jacques Monod](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1965/index.html) had published their famous work on the lac operon and I figured that gene regulation was pretty well understood. I thought it appropriate to do my postdoctoral work on something much less well understood and I decided to work on the control of cell growth. Going to the literature again, I was most impressed with the work coming out of [Renato Dulbecco](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1975/index.html)‘s laboratory, so I applied to Renato and he accepted me. My timing was excellent because Renato was moving to the Salk Institute but the buildings had not been built. We were quartered in temporary buildings that kept the lab groups very small. Most of the original fellows at the Salk had only one or two postdocs so it was very intimate. I spent a lot of time talking with Marguerite Vogt, Renato’s long time collaborator. Marguerite’s enthusiasm for cancer research and her adeptness at cell culture were a joy to behold and try to learn from. During that period I spent about half my time working on polyoma virus infected cells, the main research program of the laboratory, and about half the time trying to get something of my own started. The polyoma work went very well. DNA hybridization was a relatively new technique and Nada Ledinko had come to Renato’s lab with experience with this technique. We used it to show that polyoma infected cells induced cellular DNA synthesis and a complement of cellular DNA replication enzymes. This seemed like it might be fundamentally interesting to the cancer problem. However, none of the three projects that I worked on as possible starting points for my own entry into research worked. I left the lab after only about 18 months as a postdoc, taking a position as assistant professor at the new University of California, Irvine in 1965.I had applied for and gotten a grant to study the control of cellular DNA synthesis but I was not enthusiastic about the prospects for reaching fundamental insights with mammalian cells. It was again a fortunate circumstance. While I was waiting for my newly ordered equipment to arrive, I spent considerable time in the library trying to figure out what to do. Dan Wulff, another new recruit, suggested that I find a model eukaryotic cell that could be used for genetic studies of cell growth. I thought this a great idea and went to the library to discover that *Saccharomyces cerevisiae*, baker’s yeast was one of the only singled celled eukaryotic organisms with facile genetics. I visited Bob Mortimer at Berkeley and Herschel Roman and Don Hawthorne at Seattle to find out how one worked with yeast. They were both incredibly kind and generous. Hersch and Don loaned me a micromanipulator to start my work.I began by isolating temperature-sensitive mutants and analyzing them for macromolecule synthesis and cell division at the restrictive temperature. This approach came directly from my earlier experience with Bob Edgar at Cal Tech where I had seen the power of conditional mutants to analyze phage morphogenesis. Three years later, Herschel Roman invited me to join the faculty at the genetics department in Seattle which I did. Soon after that move, we discovered the power of time-lapse photomicroscopy to study the cell cycle.Looking back over my life, I feel in some sense destined because of my native interest in understanding things at a fundamental level. And I also feel extremely fortunate for a great number of people who intervened or mentored me on my path. I sought a rigorous approach to mysterious problems and found people at each step that pointed the way. I feel very fortunate to have become a biologist at a time when curiosity was paramount and to have been trained by people who had high standards. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0555 |
| Interview |  |
| Q6 | But is it true you are the royalties is of a scientific community for one year now or for the rest of your life? |
|  | Leland Hartwell: Certainly feel it during this celebration here.Sir Paul Nurse: But of course, science moves on so in fact the Kings get changed very quickly. |
| Q14 | Oh yes, those days, no scientist is happier as the one which can prove that the professor was wrong. |
|  | Sir Paul Nurse: Correct. That’s one of the beauties of science that it does move on and there isn’t a received wisdom that just stays in one place with one person.Tim Hunt: But at the same time there were giants present here, this week, I’m thinking people like [Jim Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/), I’m thinking of people like [François Jacob](https://www.nobelprize.org/prizes/medicine/1965/jacob/facts/), thinking of people like [Günter Blobel](https://www.nobelprize.org/prizes/medicine/1999/blobel/facts/), they haven’t been disapproved, they put a new big step on our constant stairway of knowledge. |
| Q22 | But does that mean that science actually really is coming closer and closer to reality? There are some truths that remain truths even throughout the centuries. |
|  | Sir Paul Nurse: This is quite complex philosophically because we tend to work in certain paradigms and for a while in fact we put these bricks in the wall as Tim was alluding to within that paradigm, but then you can get a real shift which takes you into a sort of different area altogether. That’s certainly been the case in physics at the beginning of the last century with quantum mechanics and relativity there was a real shift from Newtonian paradigms of the previous two and a half centuries. In biology it’s sometimes a little bit more difficult to see that.Tim Hunt: That’s really happened in biology, you know, the establishment of the cell theory and then Pasteur proves that there’s no such thing as spontaneous creation, these are sort of universal truths. |
| Q23 | But what differentiation that everyone thought that higher animals could never be cloned and then all of a sudden there’s a Dolly. Isn’t that a major shift in how you perceived DNA? |
|  | Sir Paul Nurse: I think that not sure so much in the sense that was a technical achievement but it had been achieved with frogs actually that particular …But not with high animals.Leland Hartwell: Frogs are very high animals …Tim Hunt: The frog is a high animal. What do you mean, were you trying to despise the poor frog?Sir Paul Nurse: You’re talking to a …Tim Hunt: You’re talking to the wrong people of course, we love frogs. They are called low organisms, but we love them.Sir Paul Nurse: You’re talking to a CO and two /- – -/ here and frogs are something up there, very complex to us.Leland Hartwell: But in terms of paradigms we are in an era now, from about the last 30 or 40 years, where we are sort of enumerating the molecular pieces, we’re making catalogues of who the players are in different processes and we’re already beginning to see the end of that era and a new era of you know, what are the properties of assemblies and modules and circuits of these groups.Tim Hunt: Emergent properties ensemble of all of those subunits, sorry sub-assemblies. |
| Q23 | But anyway, if you excuse me, in one way you have solved the easy problem and now you come to the real difficult problem. |
|  | Sir Paul Nurse: I think Lee, I mean this is why I was referring to paradigm shifts with physics which is clear, because I have a feeling there will be a paradigm shift in biology. I like to think of it a little bit like this a metaphor is that we’ve been identifying the actors in a play and we now have to write the script, and we’ve been identifying a lot of the molecules, the elements but actually putting it all together is in the symphony analogy or the play analogy requires maybe different sorts of thinking I actually am beginning to wonder.Leland Hartwell: What’s easy and what’s hard depends on the era, I think when we began our careers and were interested in dissecting some of the complexity of cell biology that was considered very mysterious and difficult and impossible but we’re moving beyond that era now and now people see that as relatively straight forward but how all things work together now appears to be a big mystery.Tim Hunt: I think one of the curious things … I mean I never really seriously thought in my lifetime to see so much progress and developmental biology. I think [Eric Wieschaus](https://www.nobelprize.org/prizes/medicine/1995/wieschaus/facts/) and [Christiane Nüsslein-Volhard](https://www.nobelprize.org/prizes/medicine/1995/nusslein-volhard/facts/) – this was extraordinary what they did – that was one of my favourite prizes of recent years actually, because the deep deep mystery and suddenly it’s all plain. |
| Q23 | But nevertheless do you think there is need for a total new concept? Because you made a wonderful metaphor at your banquet speech about the cell being a symphony orchestra. You could maybe add that life was the music and you could have included the audience and even if you can analyse the conductor, could you then explain the symphony orchestra by looking at the details? |
|  | Leland Hartwell: I think that’s a metaphor of the transition that’s taking place is that as we learn more and more of the individual musicians, if you will, and what it is that they do as individuals we don’t yet understand how the whole assembly creates something that is as beautiful and mysterious as a cell dividing or just a cell metabolising or any of the wonderful things that cells do. That’s the era that I think most biologists, molecular biologists would say we’re moving into now, is how does the properties emerge.Tim Hunt: It’s becoming much more … I’m so pleased that we have a prize for physiology because I think that’s exactly where we’re going, it’s molecular physiology from now on by which I mean that how things work together, right. It’s all very well having … we’ve sort of come out of a chemical phase almost and I think we’re entering a real physiological phase. |
| Q23 | But I mean science is per definition reductionistic. How you look at structures, you look at details, and life is time- and spacedependent and dynamics and interactive. You have looked at frozen moments of details, can you ever understand system … |
|  | Tim Hunt: Oh sure, look at the way that muscles and nerves work for example, was done a long time ago. It’s funny, sometimes things are done from the top down and sometimes done from the bottom up.Sir Paul Nurse: I often think too much is made of this reductionism holism difference. Of course science has to explain in terms of basic components or elements or sub systems but nearly all of us working at a holistic framework looking at the overall system. The challenge we have now is in particularly in the life sciences is that these systems are actually quite complicated, in fact very complicated and unlike for example in chemistry and physics where you have lots of objects behaving identically like atoms, what we have is lots of objects which don’t behave identicallyTim Hunt: Which interact and each feedback positively and negatively with each other. It’s very complicated and the trick of doing successful science is from isolating the simplicity out of that complexity otherwise you’re lost. It’s all very well to look at a dividing cell and going, ‘Gosh, this is marvellous’! but it doesn’t help you understand what’s going on behind the scenes.Sir Paul Nurse: I think that’s absolutely right, but now we’ve got to start thinking. We have all this individual components, behaving in different ways, interact in different ways and we’ve got to somehow extract the general principles from that behaviour and try and get … You can use these words like emerge and properties or whatever, they often raise more heat than light when you use these terms, it must be said, but I think there is a challenge there and describing the dynamics of this in real space and real time. which we’re just beginning to do in cell biology. I think a brave new world is going to come from this, I’m an optimist I must say, but I think that it’s very exciting times.Leland Hartwell: I think there’s another thing too to say about reductionism is that you take some global property and you try to explain it at the next level down and the next level down may just be cell society. We’re now very concentrated on the molecular level but as we start asking how cells behave the right description may not be in molecules, the right description may be in circuits or modules or certain properties, so creating the right concepts to go the next level down is sort of the nature of reductionism and the creative part. |
| Q52 | Which means that you can find some very precise detail in hierarchy that is really governing the next level |
|  | Tim Hunt: Yes, the clue to the whole thing.Sir Paul Nurse: I think there’s two ways actually to answer that: One is, which is perhaps what we’ve done, which is to focus on certain components and elements which are crucial and critical and I think that that falls naturally out of our analysis. I think a second way of viewing this, which I think is what Lee was hinting at, is could we describe general properties of these systems, are there rules that would govern general properties which don’t require going down to specific behaviours of individual components but when in a certain assemblage give rise to behaviours that are interesting. I think that’s perhaps what you were getting at.Leland Hartwell: Exactly, we have our signalling system, cells respond to signals for example and they may respond over a certain concentration range, they may respond by flipping states or by a gradual transition. These are sort of dynamic concepts that don’t necessary require molecular explanation but require some kind of probably creative conceptualisation that may be different than anything we think of right now.Tim Hunt: I know there’s an economist might describe an economy, sort of abstractable principles.Leland Hartwell: Exactly, yes |
| Q13 | Does that also mean that you are looking for inspiration from other areas of science, like scientists who are dealing with the mathematics, the complex system, dealing with the scientists from economy are trying to do mathematics for complex systems. |
|  | Leland Hartwell: Yes, very much. I think one important area that we can learn a lot about molecular circuits from, or from electronic circuits in order to understand a complex circuit, what you’d really like to have is a very detailed description of the input/output characteristics, as you perturb the system how does it respond. We don’t usually have that for many of our biological circuits, we know what the components are but we don’t know how the input/output are related in any quantitative terms.Sir Paul Nurse: Because I’d like to push that metaphor even further. It may be by knowing the sorts of components that you have and by knowing that they can be connected in certain ways. In fact all the huge variety that is possible may not actually be occurring because it may be that the only linking certain components that behave in certain ways in particular ways that may only generate certain stable operating systems and that we’re not actually faced with immense complexity we’re faced with a few solutions. If we can identify the rules for getting those solutions, we’ll simplify the problem. |
| Q50 | But given that you’re right, what will the implications be? Finding the simple rules that govern complex systems, you said ‘brave new world’, it really sounds something in that direction, Tim? |
|  | Sir Paul Nurse: He’s more sceptical of …Tim Hunt: I think, it’s very interesting. Paul likes theoretical biology and he has some good friends who are rather good theoretical biologists but my own view is that these approaches so far have not been very successful. Partly because we don’t even know the parts, secondly because it’s very difficult to measure accurately the properties of those parts. There are certain kinetic constants about how fast things happen and the values of those parameters are rather critical when it comes to building a model and so far the modellers have been quite good at describing what they know is the right answer because they knew that to start with. They’ve not been so good, in my view, about saying well you know about this component a, b, c, d, e, f and g, but without factor x it won’t have the behaviour that we know that it does have and it would be very helpful if they came in and said you’re missing the x factor and we said oh my goodness we can go and look for that. Actually that’s not the way it works and in fact, what happens is that the geneticists start having a kind of lucky dip and then some biochemists come along and analyse it and we keep on finding the various components, the key components of these systems completely by luck, well not completely by luck, but I mean going and looking for them, never by predicting sort of …Leland Hartwell: I think we ought to look at history here. For example take gene regulation. This is an area where it might have been simple in Paul’s terms where it makes good sense to control a gene by turning on or off its message. But in fact, nature has used every single step of information transformation from turning on the gene, from getting the message part way started, the stopping it, from once it’s made degrading it, from starting the translation of a protein. You could every single step of information transfer from the gene to the protein and the activity of the programme is utilised by itself.Tim Hunt: If you conceive a bit controlled somewhere, it will be controlled somewhere.Leland Hartwell: Yes, and I have a feeling that that’s the level of complexity we’re going to be faced with and everything as anything that could happen will have been used somewhere.Sir Paul Nurse: But it may be that it doesn’t matter where it’s regulated, in the sense that one can get an explanation by just understanding that this module if you like, will lead to regulation and it may be that when you’re trying to describe the higher order phenomena you do not need the detailed understanding of exactly where that regulation occurs. |
| Q35 | But given that your optimism is real and you are getting some correct on the system, what would you like to explain by this, what are the really hard questions in bioscience today that you want to get to. |
|  | Sir Paul Nurse: Can I jump in there because there’s a new problem that really is interesting me which is how biological systems generate form, spatial order, because I think this is an interesting issue because, knowing within three-dimensional space, the positions of different objects and components within that is not a trivial problemTim Hunt: Theoretical everything should be spherical and they’re not.Sir Paul Nurse: And that’s what I …Tim Hunt: /- – -/ was wrong.Sir Paul Nurse: I’m really fascinated by this because I’m thinking about it in terms of a single cell just because it’s such a simple system to approach. It may be the rules that are important, there are not the same rules that generate the shape of my nose for example, but simply understanding spatial order in any system I think is an interesting challenge. |
| Q54 | Bioscience today is generating a lot of fear, so what is your role in this perspective, what is /- – -/ science |
|  | Tim Hunt: Trying to explain clearly, for example take genetically modified food for example. I just simply don’t understand why this bothers people, but it turned out on interrogation a lot of people don’t realise that with every mouthful of every food whether it’s a plate of fish and chips or a big fat steak they take in billions of DNA molecules. People really thought that only the genetically modified corn contained DNA and that was dangerous somehow, I mean it’s just absurd ignorance on the part of the public.Leland Hartwell: I think there’s another side to this which is as explores basic discoverers bring back knowledge that illuminates mystery in the world and I think everybody enjoys that. That’s an experience of awe over nature and astronomy is a terrific science in a sense because it is almost all that level of appreciation, but the other aspect that scientific knowledge brings in is the possibility to apply it in some way. It’s the application phase, particularly with respective biology and medicine and human life that fear is created and I think we are all afraid. For example just the transition from being not knowing what the sex of a child was until it’s born to being able to determine at an early stage and decide whether or not you want a child of that sex, that really changes human culture and make life in a very profound way. |
| Q54 | Paul Nurse, in this debate on science and society there has been much talk about public understanding of science but maybe there is a reverse of that question, science understanding of public, do you think that is crucial? |
|  | Sir Paul Nurse: I think there is a bridge that we have to construct between scientists and society and it has two sides to that bridge and one is the public understanding, the point Tim emphasised, we have to explain these things so that society has a proper sense. Quite often, just to expand on that briefly, quite often the real debates are not actually about science but they’re about politics and in fact the GM foods debate is as much to do with large corporations controlling the crops and having economic control over issues as much as the gene transfer issue and it all gets mixed together and that’s why it creates so much fire and I think we …Tim Hunt: It’s sort of eased a demonise some giant corporation …Sir Paul Nurse: We need to separate those debates so that there’s a clear scientific issue and a political one because you may find people are on one side of that debate with one issue and on the other with the other. But back to this bridge between science and society, I think there it is also important for the scientists to be listening to the public and to be aware of what their issues are and to be aware of the sorts of questions they want answered and the sorts of approaches that should be taken. Sometimes we may get divorced from what the ordinary person or the politician’s thinking, and that I think is truly potentially dangerous because we can become a priesthood and separate it off as some sort of witch doctor class and I think that is a real danger for us.Tim Hunt: It’s so important that the public should really trust us as far as we’re trustworthy, otherwise everything will break down. |
| Q13 | But somehow you are advisors to the companies and some of you work inside the companies, and you are funded by money from the company. How do you look upon your credibility when it comes to funding in this respect. |
|  | Sir Paul Nurse: This is another huge area of course.About ten minutes left.Sir Paul Nurse: This is a huge area about funding and accountability and these issues. I think that there are a number of misconceptions and I think that often many of the general public think that many scientists are funded simply by private capital and they have this sense that we’re in the pockets of a big industry. That is very often not the case. We have received most of our support from Government funded work, mostly at the front end of work which is available to everybody and indeed one of the nice aspects of science is making that information, that knowledge available for all the societies in the world to make use of, so I think we do have a role here in explaining how work is funded and our accountability within that.Leland Hartwell: But there also is a conflict of interest thing that we need to be very cautious of and within our Institutions we have rules for dealing with conflict of interest, for example if you have an interest in a company, you cannot be involved in clinical trials in a direct way that are testing products that you have a financial interest in and when we make pronouncements to the public about some area of knowledge if we have a financial interest in it we should disclose that. |
| Q13 | I mean have an interest in thing is not only financial interest. Today I think almost every research is interest driven, you have strategic interests, you have environmental interests, you have commercial interests, you have carrier interests, so what about the credibility of a scientist when they are all driven by interests. |
|  | Leland Hartwell: Everybody’s driven by interests. If you don’t limit it to a financial conflict of interest, then of course we’re all interested in all sorts of /- – -/. |
| Q14 | Why do we always distrust the science that are commercial driven interests and not suspicious about the idealistic interests? |
|  | Leland Hartwell: I don’t distrust scientists who have a commercial interest, I just want to know what their biases are, I want to know, that’s all.Tim Hunt: There’s no reason to distrust companies. After all drug companies, the best thing you can do is produce a highly successful drug and the more people it cures the better, so I must say I think their interests and the public interests are one in the same. Where it comes bad is if they try and foist some imperfect product and exaggerate it’s properties, that’s a different matter.Sir Paul Nurse: But you touch upon something which is not quite what you were getting at, but I’d like to draw attention to, which is actually a problem to do with managing good science, because in fact good science is carried out by creative individuals working within the scientific society because it’s very socially interactive but still with lots of freedom to follow their own ideas. Then sitting on top of that is some sort of scientific management that provides money and support which has certain strategic objectives and because we’re not paid as scientists simply to play in our laboratories, we like to think that we are, but in fact society supports us and we’re very expensive to support, because they expect something back. They expect something to increase the health or wealth of the nation and balancing this is actually a very difficult task and I don’t think anybody gets it quite right and it’s very very difficult to explain that to our political masters who would really be much happier sometimes with a very heavy strong strategic top /- – -/.Tim Hunt: They would love to be able to say just solve this problem. In Britain for example BSE is a problem, we really don’t know whether sheep have it, we really don’t know whether humans eating this stuff are going to get it and they would love to be able to direct scientists to solve these problems and the trouble is that people like us are really not very good at behaving under those circumstances.Leland Hartwell: There are a full range of possibilities though. It’s ok to have to fund areas of strategic direction that where you want problems solved and at that point they almost become engineering problems but if you don’t have a foundation of undirected investigation, it’s going to draw you up. |
| Q12 | But given the path, the experience of the path of science you know that when you’re looking for one thing you always pop up with something else, so those who are going to finance you with a specific goal will probably find themselves financing some totally different knowledge not that they really knew they were looking for. |
|  | Sir Paul Nurse: That’s certainly the case, but there is, you know, science is a complex activity and there are roles of different sorts of people at different stages in that process. At the front end you need the explorers, a little later the explorers are no good at turning into practical benefit some of those, or not necessarily good at it.Tim Hunt: And explorers maybe very good exploring mountains but rotten at the seabed.Leland Hartwell: In one place you see this happening is in start-up companies. Very often start-up company starts up with a very specific idea and they get venture capital to go out and six months later they’re doing something entirely different because the first idea didn’t work and they’ve still got to be profitable and that’s an arena in which you see a lot of shifting around. |
| Q55 | But that turns us into what might be the gist of science, the serendipity I mean you are always seeking for something else what you really found. What is the role of serendipity in science? |
|  | Sir Paul Nurse: I’ll kick off with this but I think we’ve all had our own experiences. I think that serendipity does play an important role but in a very particular context. We’re biologists, we’re trying to understand nature and we have to pay real attention to what nature gives us. If we try and impose too much our own thoughts on such complex system, we will either miss things or simply try and force it into a box that is not good for it. I think you have to be very aware of all the possibilities, you have to be very observant and then you can pick up on the serendipitous event, which has certainly happened to me on many occasions in my career and the way I like to think of it, is that nature is giving us the clue that we try and follow.Leland Hartwell: I think there are actually two forms of approaches to science, both of which lend themselves to serendipity. One is Tim’s example which maybe he can amplify, where all of a sudden nature presents you with some observations say, My gosh that’s interesting, I wasn’t looking for that, let’s see what’s there. The other is more /- – -/ approach where we knew what we looking for, but we didn’t know quite how to find it and all of a sudden something popped up that said, Look over here and you might find what you’re looking for.Tim Hunt: In my case it really was complete serendipity and I was really studying one problem but interestingly in a system where actually cell division was very much a part of the system, that’s what it was specialised for, but that aspect of it was just fun for me. It was fun to look at these things down a microscope, I never seriously thought I would make any advance, it was much too difficult a problem. Then suddenly I saw this protein go away and because I’d been sort of half thinking about the nature of the problem, worrying about things, it immediately announced to me what was going on. It was something that nobody for a century had even sort of remotely considered possible but once you see it, bang, it’s obvious. Then you go chasing after it because it leads you in that direction. But nobody would ever have even gone looking for the damn thing in the first place because, precisely, because theoretical biology hadn’t said we should be looking for this so, when nature sort of presents itself to you on a plate then you’re …The secret is to really be open minded …Tim Hunt: You’ve got to be terribly open minded and have …… to the unexpected.Tim Hunt: Yes, absolutely, and all my career I’ve had things like that, you know, suddenly, it’s like walking down the street and seeing something shiny and kneel down and have a look and see whether it’s gold or not.Let’s finish off then with some really easy questions.Sir Paul Nurse: I suspect not. |
| Q55 | It seems as if bioscience is getting into realms that before has been totally occupied by philosophers and theologians. We’re starting to ask those questions about when does a human become human and when do we finish being human. Take for example this stem cell debate and the debate of embryology. How do you look on your own science when you were really going into this field that raises so many existential questions? |
|  | Sir Paul Nurse: First of all you’re right, and this is why biomedical research is now becoming increasingly contentious because we now are addressing really critical problems about the nature of a human being, about the nature of identity when a human being begins and finishes, and this moves us really into the realm of religious thoughts and brings in fact scientists increasingly into a challenging position with well established religious thoughts. Not unlike I would suggest, the Copernican revolution in the 16th century with physics and the heliocentric, the sun centred world, and I have a feeling that biology and biomedicine is really going to take us into that realm which is one reason why I think this two way process of listening to the society and listening to what really bothers people is so important so that we can make a better go at this transition in the brave new world than maybe happened with astronomy and physics in the 16th century.With the big difference that there is no death sentence for scientists these days.Tim Hunt: I find these kind of ethical issues very difficult to deal with and I’m not really used to thinking about them, and I’m not even particularly well informed on the details for example of the stem cell debate which I’ve been asked about a lot. I myself don’t think there’s much wrong with it, I have to say, after all you know things like blood transfusions have been going on for a very long time, that doesn’t seem to bother anybody. I’m slightly confused, I don’t really understand, maybe again it’s a case of what Paul said I should be listening more to the public and finding out what’s really bothering them at the bottom because, scientifically, it seems to be only a good thing. If your leg drops off and you can make a new one from stem cells – who could possibly say that was a bad thing, I just don’t … am I missing something?Leland Hartwell: It’s a moving target, I feel like the ethics and religious and things come up around areas of mystery where we try to develop some concepts about what’s going on and as knowledge accumulates and enlightens these areas, the sort of ethical questions have to move with them and that’s sort of hard. It’s always a difficult transition and as I look forward, one of the things that I see that looks scary to me, I don’t think I’ll live to see it, is the sort of combination of much more integration of machines with people. Now we wear glasses for example to correct eyesight, I don’t think it will be long before we have all sorts of little computer chips in us and you know …Tim Hunt: Yes, you can get false ears that really say work like ears if you are deaf …Leland Hartwell: … and that sort of bothers me you know, it’s going to happen, it’s inevitable.Tim Hunt: Yes, and completely synthetic hearts. |
| Q34 | Finally, many people are really getting scared about what is going to happen. One of the questions thar raises is when you really have managed to find the mechanisms of life, we feel, many of us, that life is also going to be instrumentalised as you decrease the respect for life. What is going on in your own mind when you see the details on how intricate the system is in biology. Are you getting more or less a miracle when you’re looking at it? |
|  | Sir Paul Nurse: I think the more you understand about this beautiful thing we call life the more wonderful it is. Again, it’s easier to look to history because it’s less contentious. Darwin’s theory of evolution by natural selection was such a beautiful idea that you could still have a sense of god who created such a beautiful process and still see it as a wonderful solution to that particular problem. I think if we look at today’s new understanding you can have nothing but a great sense of wonder that comes with that, I think it deepens, in a sense a spiritual understanding beyond simply ignorance and total mystery.Leland Hartwell: I agree in a little bit difference sense. I don’t think we really ever understand anything. I think we only describe it. That we look and look at greater detail and we develop words and concepts to describe it and we’re all just describing the beauty of nature and it doesn’t become any less beautiful just because we describe it.Tim Hunt: Yes exactly, as you walk through a forest, knowing what the trees are growing it doesn’t make it any less the more beautiful forest exactly as Lee says. Inside the cell you find almost every day more wonderful things and say, Oh, that’s how it works, it’s beautiful it’s really beautiful. |
| ID | 0556 |
| Biographical | I was born in 1943 at Neston in the Wirral, not far from Liverpool where my father, Richard William Hunt was a lecturer in paleography, the study of mediaeval manuscripts. Richard’s father was a doctor, and there is still a chemist’s shop (i.e. pharmacy) in Winchester that bears the family name. My mother’s father, Harry Rowland was a businessman, a timber merchant who imported wood from South America. Actually, as I discovered from letters to my mother, Kit, which I found after they were both dead, Richard was working in London at Bush House, presumably in some kind of intelligence role although he never spoke of it, and I was always afraid to ask. He was the kind of man who, having signed the Official Secrets Act, would have felt bound by it to the grave. Immediately the war was over, Richard accepted a position as Keeper of the Western Manuscripts in the Bodleian Library in Oxford, a post he held for the next 32 years. My earliest memories are of the winter of 1947-8, pushing a pram down to the coal depot about a mile away near the railway station as the delivery trucks having been stuck in snow drifts. Food rationing also made a deep impression on me, and the habit of breaking eggs separately into a cup lest one should be bad and the week’s omelette be spoiled persisted for many years. Kind American mediaevalists would send food parcels, which prejudiced me strongly in favour of the USA at an early age.My education started with latin taught at home by a governess, I can’t imagine why, and for some reason I attended the Infants Department of the Oxford High School for Girls before moving to the Dragon School at the dangerous age of 8 or so. All I can remember of the girls is their bossy mothers, who liked to organise parties that I detested because of the competitive spirit that I detected in games like musical chairs. There was also knitting squares for the refugees’ blankets, at which I was hopeless – the girls produced neat squares, myself ragged trapezoids. And there was the matter of the garden. My small patch was so barren that I was told to describe an imaginary garden when it came time to write Nature notes. The Dragon was much better, much less regimented, at the same time much more playful and more serious. Woe betide you for grammatical errors. Although mornings were largely devoted to latin and greek, at which I got worse and worse as time went by, there was a science lesson every week conducted by a young German called Gerd Sommerhoff. It was he who showed me that biology was an easy subject, and from then on I really never had to make any more career decisions. I also liked English, was bad at maths and hopeless at history, and fanatical about cricket, though not terribly good. My hero was Denis Compton.At the age of 14, I moved across town to Magdalen College School, Oxford, where science played a much larger role in the curriculum. I loved Chemistry in particular, largely because the teacher, Colonel Simmons was much more concerned with principles than facts, although a thoroughly practical man himself. We were allowed considerable freedom, and on more than one occasion started fires from distilling volatile flammable solvents. One became adept at avoiding injury. Later on, biology again came to the fore when a young teacher called Terence Doherty took just three of us for Zoology. We dissected my brother’s pet rabbit when it died, which was a treat after all the formalin-fixed dogfish. Terence wanted to be a painter, really, and later worked as an assistant with the sculptor, Michael Ayrton. I was also introduced by Terence to the Craftsman Potters’ Shop in London, where I still love to browse. Very important during these years were Extramural Lectures given by the University of Oxford and the Christmas lectures in the Oxford Museum. For me, the University appeared to be largely devoted to the classics and history, and our house had a steady flow of mediaevalists of various stripes, but here in corners were revealed real treasures: the shrunken heads of the Pitt Rivers Collection, the dinosaur skeletons, lectures on the Theory of Evolution (on the occasion of the centenary of the publication of the Origin of Species) and on the Krebs Cycle. We also used to visit local factories and research institutes; at Alcan Aluminum they were trying to develop a Coca-Cola resistant lining for the cans, and somewhere we watched the zone refinement of an enormous silicon crystal. Balances that could weigh a human hair were pretty impressive, and even the telephone exchange was fascinating behind the scenes. [George Beadle](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1958/index.html) spent a year as Eastman Professor and came to give a lecture to the Scientific Society (his son Redmond attended the school), and I remember asking him to explain the work that led him to win the Nobel Prize.In the fall of 1961 I went up to Clare College, Cambridge to read Natural Sciences, with the intention of becoming a biochemist in the end. The courses were mostly excellent, and I did much better in the practical exams than in the theory. We were worked extremely hard, with certain practical classes falling on Saturday afternoons. Sydney Brenner organised seminars in his college rooms, and gave lectures that were officially off-limits to biochemists. It was all tremendously exciting, and we were very conscious, I think, of being surrounded by Very Great Men as well as very much in awe of the weight of the history of scientific discovery, especially in physics.I started my scientific career in 1964 in the Department of Biochemistry at Cambridge, under the supervision of Asher Korner, who encouraged a great deal of freedom among his students to work on any aspect they chose of DNA, RNA or protein synthesis! Very early on, I decided that I wanted to work on the control of translation of mRNA, and thanks to Louis Reichardt (who spent a year in Cambridge in the same bay as me before going to Stanford to do his Ph.D. with Dale Kaiser) I learned about the use of rabbit reticulocytes for studies of haemoglobin synthesis, and began to appreciate the advantages of simple model systems. Together with Tony Hunter, a fellow student, I became interested in the question of when the haem was inserted into globin to make haemoglobin, and the question of whether ribosomes had to queue up under conditions where iron (and hence haem) was limiting. This was inspired by a talk we hear in 1965 by Vernon Ingram at a meeting in Cambridge on the subject of haemoglobin, at which I also listened to Henry Borsook’s talk comparing protein synthesis in sea urchin eggs with protein synthesis in red cells. I thought very little about this at the time, but it planted an important seed. Tony and I found that the ribosomes were evenly spaced along the mRNA, and never formed a queue unless we forced them by other means. In 1966, I went to another meeting about haemoglobin, this time in Thessaloniki in northern Greece, where I met Irving London. I persuaded him that it would be fun to come and work in his lab during the summer, and by the time I was back in Cambridge (the train through Yugoslavia went very slowly), tickets to New York awaited me. I spent July through October 1966 living in a very hot dormitory out in the far east Bronx, and thoroughly enjoyed myself. The lab was the coolest place to be.When I finished my Ph.D. in 1968, I went to New York to work with Irving, who had long been interested in the haem question. These were turbulent times, but I was fortunate in having a number of collaborators at the Albert Einstein College of Medicine. In particular, with Nechama Kosower and her husband Ed, we discovered that tiny amounts of oxidized glutathione were extremely inhibitory to protein synthesis in reticulocytes, and with Ellie Ehrenfeld that even tinier amounts of double-stranded RNA killed protein synthesis. Most striking was the finding that depletion of haem, and addition of GSSG or dsRNA all seemed to have similar effects on cell-free protein synthesis in the reticulocyte lysate, as though these disparate agents all acted in a similar manner. I also discovered that simple gel-filtration of the lysate caused a drastic fall in its activity. All these effects needed several more years to work out. One other thing I learned about during the studies on the inhibition of protein synthesis by dsRNA was that micrococcal nuclease, which requires Ca2+ for activity, did not inhibit protein synthesis in the reticulocyte lysate provided no Ca2+ was present.On my return to Cambridge, I found myself reunited with two friends from the Korner laboratory, Richard Jackson and Tony Hunter. They had recently made the important discovery that Met-tRNAf was used to initiate haemoglobin synthesis, and this enabled us to probe the process of initiation in much more detail, leading to a set of very surprising results: that the initiator tRNA bound to ribosomes before the mRNA, and that all the inhibitory effects I had been studying in New York blocked the very first step, the binding of Met-tRNAf to 40S ribosomal subunits. It took three or four years to realise that this inhibition was due to the action of at least two inhibitors of the process, one activated by the absence of haem, the other by the presence of dsRNA, and that these inhibitors were protein kinases, which phosphorylated eIF-2, the key initiation factor that catalysed the binding of Met-tRNAf to ribosomes. Actually, it turned out to be rather complicated, because phosphorylation did not block the reaction the first time round, but rather prevented nucleotide recycling on the initiation factor, so that its re-use was inhibited.By 1977, the outlines of all this were pretty clear, and we had a very good understanding of the reticulocyte lysate and its properties. The cause of the gel-filtration problem proved to be loss of polyamines, and the GSSG inhibition was a problem with thioredoxin and thioredoxin reductase which were needed to keep something in the reduced state. The micrococcal nuclease calcium dependence was put to good use by Hugh Pelham, a graduate student in the lab, who developed the use of nuclease treatment of the lysate to assay heterologous mRNAs. An important factor in this development was a ready source of messenger RNA, for which we used tobacco mosaic virus. Working with David Zimmern, a student of [Aaron Klug](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1982/index.html)‘s, and John Knowland, who was in [John Gurdon](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2012/)‘s laboratory, it became clear that the RNA in the virions did not direct the synthesis of coat protein. Tony Hunter and I therefore ground up som TMV-infected tobacco leaves in liquid nitrogen and found to our great joy that a small mRNA was present that efficiently directed the synthesis of authentic TMV coat protein.I therefore turned to new systems for studying translational control, and took the opportunity of teaching summer courses at the Marine Biological Laboratory, Woods Hole, to look at changes in protein synthesis in sea urchin and clam eggs after fertilization. This opened new horizons, not only in learning to deal with new systems, but in the breadth of approaches and interests of the scientists who passed through Woods Hole during the summers. I learned a tremendous amount of developmental and cell biology over the years. In 1979, Joan Ruderman and her student Eric Rosenthal were teaching the embryology course, and I helped them with experiments on the translational control of maternal mRNA; the major mRNAs concerned later turned out to be the A and B-type cyclins and the small subunit of ribonucleotide reductase. We carried out quite a lot of work together on the translational control, and Nancy Standart worked as a postdoc first with Joan and then with me in Cambridge. I believe that these clam mRNAs were the first really well-authenticated case of specific translational control. Together with Nancy, we later identified the key regulatory regions in the 3′ untranslated region of ribonucleotide reductase and cyclin A mRNAs that are necessary for translational masking.By 1982, work on the control of protein synthesis in sea urchin eggs had almost ground to a halt; every idea that my students and I tested proved to be false, and the very basis of the system was essentially flawed in that we were studying a system in which the ribosomes changed from having almost no activity to one in which about 2% of them were active, leaving the 98% majority of them still inert. The one question we did not ask up to that point, because the answer was supposed to be known already, was as to why an increase in protein synthesis occurred at fertilization, although it had been shown many years earlier that inhibiting protein synthesis inhibited cell division. One day in July 1982, with teaching over, I did a very simple experiment that was actually designed to answer the question of whether the proteins made after fertilisation were the same as the proteins made after parthenogenetic activation of the eggs. The eggs were divided into two batches, one of which was fertilized, the other treated with calcium ionophore, A23187. Radiolabelled methionine was added to both, and samples taken until after the fertilized eggs had divided into two-cell embryos. When the autoradiograph of the 1-dimensional SDS slab gel was developed, I noticed a very strange thing in the fertilized samples, which was a labelled band that went away, unlike all the others which, as expected, got stronger with time. Scarcely was the film dry when I ran into John Gerhart at the traditional Friday night lecture wine and cheese party, who told me about experiments he and Marc Kirschner had been doing on the oscillations in frog MPF activity during meiotic maturation of *Xenopus* oocytes. They found that MPF activity went away transiently between meiosis I and meiosis II, but if protein synthesis was inhibited, the MPF never returned. The behaviour of the band I had just seen fitted in beautifully with their physiological findings, and I was sure that this band, which we called cyclin, must have something to do with MPF. The rest of that summer was spent looking for cyclins in other species, and describing the basic behaviour of the strange disappearance, which turned out to occur about 10 minutes before each cell division. The oscillations went on for several hours after fertilization. Clam eggs did the same thing, except that two bands showed this behaviour. It is very surprising that nobody had spotted this before; it could have been done any time after the invention of the slab SDS polyacrylamide gel in about 1970.It was impossible to work on cyclins back in Cambridge, because there were no clams or sea urchins, and by the time the next summer arrived I thought perhaps the suddenly-disappearing proteins had been a complete fantasy. Fortunately, on return to Woods Hole next summer the results proved quite reproducible, but it was clearly going to be an uphill struggle to find out what was going on, and whether it had any general application. Progress was slow for various accidental reasons, like the fact that Tom Evans who spent the summer of 1982 as my undergraduate assistant had already signed up with David Secher at the MRC Molecular Biology Laboratory as his Ph.D. supervisor and it did not seem right to alter the arrangements. Jon Pines joined me a year later, but his first year was a terrible one for sea urchin eggs, delaying library construction by a whole year! Not until Christmas 1986 did we succeed in cloning and sequencing sea urchin cyclin B. After that, the pace began to accelerate, and it did not take long to isolate clones for *Xenopus* cyclins A and B, which was very exciting, because it made it clear that these proteins were not restricted to marine invertebrates. We developed the use of oligodeoxynucleotides in conjunction with RNase H as a way of specifically cutting particular mRNAs, and were able to show thereby that B-type cyclin synthesis was necessary for *Xenopus* extracts to enter mitosis, and that *Xenopus* MPF contained B-type cyclins as well as p34cdc2.Today, cyclins and cyclin-dependent protein kinases are recognised as key elements in the regulation of cell cycle transitions, and the family of proteins has grown considerably, thanks to work in many laboratories. I well recall the scepticism in the early days, however, when most people did not believe things could be so simple as making an enzyme to catalyse mitosis, and then destroying the enzyme to leave mitosis. Moreover, in retrospect, we were very slow to realise that cyclins were regulatory and activating subunits of Cdc2 and its relatives. I do not know why this penny took so long to drop.Moving to ICRF allowed better access to *Xenopus* than had been possible in Cambridge, and important achievements have been the identification of c-*mos* as the activator of MAP kinase with Angel Nebreda, which also led to the discovery of a new member of the MAP kinase family called p38; the identification of John Shuttleworth’s MO15 kinase as the CDK activating kinase with Randy Poon, and the purification of soluble and active fragments of cyclin A that allowed Jane Endicott, Martin Noble and Nick Brown to solve its crystal structure. We have defined a very large family of cyclins in *Xenopus*, and tested the importance of different members of the cyclin B family by making “knockout” mice. Right now, major interests of the laboratory lie in understanding how cyclins are targeted for proteolysis by their “destruction boxes”, and in seeking substrates for cyclin dependent kinases. This is no easy matter, and our successes in the past, finding the salient substrates for c-*mos* and MO15 owed more to luck, and keeping our eyes open while doing other things, than any rational approach.Postscript Of the many letters of congratulation that arrived after the announcement of the Nobel Prize, the one that gave me the purest pleasure was from a Swedish woman called Kerstin Westin in Uppsala, enquiring if I was, by any chance, the Tim Hunt she had known in Oxford in 1950 when she worked as an au pair girl with my family – and I was. Unlike my brother Sandy, who was only 5 at the time, I could clearly recall the young girl who looked after us all those years ago, and we had a happy reunion 51 years later in Stockholm. Apparently, nothing about the 7-year old boy gave any hint of his future. I would say that I was lucky to grow up in a loving family with wonderful teachers. Later, as a young scientist, I had the further good fortune to witness many of the founders of molecular biology at close hand. They set the standards of what was and could be expected. For my generation, [Francis Crick](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1962/index.html) was probably the most obviously influential presence. He was often at lunch in the canteen of the Laboratory of Molecular Biology where he liked to explain what he was thinking about, and he was always careful to make sure that everyone round the table really understood. He was a frequent presence at talks in and around Cambridge, where he liked to ask questions. Sometimes, I remember thinking, they seemed slightly ignorant questions to which a man of his extraordinary range and ability ought to have known the answers. Only slowly did it dawn on me that he only and always asked questions when he was unclear or unsure, a great lesson.For many years, I used to supervise students in Cambridge, preferring either to teach the introductory course in Cell Biology or third year students in their biochemistry laboratory projects. Here again, I had the good fortune to meet a succession of clever people, many much cleverer than I. Supervisions worked best when the group (typically of two or three students and myself) was engaged on a mutual course of discovery, for at the time, not so much was known about how cells worked and one could profitably muse on how things might work. Very different, as a friend pointed out, from teaching, say, crystallography where the principles had been worked out years and years before and your job was to clarify them for the newcomer. As more and more became known, I found teaching became less fun, whereas learning became more pleasurable. In particular, I learned a tremendous amount at the Marine Biological Laboratory during the summers I taught and researched there, and when that phase of my life was over, I started working with John Wilson on the problems book that accompanies *Molecular Biology of the Cell* by Alberts *et al*. The ferreting around trying to make sense of unfamiliar territory and the discussions with the other authors provided an even more intense pleasure of learning new things.But none of these pleasures, great and satisfying though they are, match the joy of discovery. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0556 |
| Interview |  |
| Q6 | But is it true you are the royalties is of a scientific community for one year now or for the rest of your life? |
|  | Leland Hartwell: Certainly feel it during this celebration here.Sir Paul Nurse: But of course, science moves on so in fact the Kings get changed very quickly. |
| Q14 | Oh yes, those days, no scientist is happier as the one which can prove that the professor was wrong. |
|  | Sir Paul Nurse: Correct. That’s one of the beauties of science that it does move on and there isn’t a received wisdom that just stays in one place with one person.Tim Hunt: But at the same time there were giants present here, this week, I’m thinking people like [Jim Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/), I’m thinking of people like [François Jacob](https://www.nobelprize.org/prizes/medicine/1965/jacob/facts/), thinking of people like [Günter Blobel](https://www.nobelprize.org/prizes/medicine/1999/blobel/facts/), they haven’t been disapproved, they put a new big step on our constant stairway of knowledge. |
| Q22 | But does that mean that science actually really is coming closer and closer to reality? There are some truths that remain truths even throughout the centuries. |
|  | Sir Paul Nurse: This is quite complex philosophically because we tend to work in certain paradigms and for a while in fact we put these bricks in the wall as Tim was alluding to within that paradigm, but then you can get a real shift which takes you into a sort of different area altogether. That’s certainly been the case in physics at the beginning of the last century with quantum mechanics and relativity there was a real shift from Newtonian paradigms of the previous two and a half centuries. In biology it’s sometimes a little bit more difficult to see that.Tim Hunt: That’s really happened in biology, you know, the establishment of the cell theory and then Pasteur proves that there’s no such thing as spontaneous creation, these are sort of universal truths. |
| Q23 | But what differentiation that everyone thought that higher animals could never be cloned and then all of a sudden there’s a Dolly. Isn’t that a major shift in how you perceived DNA? |
|  | Sir Paul Nurse: I think that not sure so much in the sense that was a technical achievement but it had been achieved with frogs actually that particular …But not with high animals.Leland Hartwell: Frogs are very high animals …Tim Hunt: The frog is a high animal. What do you mean, were you trying to despise the poor frog?Sir Paul Nurse: You’re talking to a …Tim Hunt: You’re talking to the wrong people of course, we love frogs. They are called low organisms, but we love them.Sir Paul Nurse: You’re talking to a CO and two /- – -/ here and frogs are something up there, very complex to us.Leland Hartwell: But in terms of paradigms we are in an era now, from about the last 30 or 40 years, where we are sort of enumerating the molecular pieces, we’re making catalogues of who the players are in different processes and we’re already beginning to see the end of that era and a new era of you know, what are the properties of assemblies and modules and circuits of these groups.Tim Hunt: Emergent properties ensemble of all of those subunits, sorry sub-assemblies. |
| Q23 | But anyway, if you excuse me, in one way you have solved the easy problem and now you come to the real difficult problem. |
|  | Sir Paul Nurse: I think Lee, I mean this is why I was referring to paradigm shifts with physics which is clear, because I have a feeling there will be a paradigm shift in biology. I like to think of it a little bit like this a metaphor is that we’ve been identifying the actors in a play and we now have to write the script, and we’ve been identifying a lot of the molecules, the elements but actually putting it all together is in the symphony analogy or the play analogy requires maybe different sorts of thinking I actually am beginning to wonder.Leland Hartwell: What’s easy and what’s hard depends on the era, I think when we began our careers and were interested in dissecting some of the complexity of cell biology that was considered very mysterious and difficult and impossible but we’re moving beyond that era now and now people see that as relatively straight forward but how all things work together now appears to be a big mystery.Tim Hunt: I think one of the curious things … I mean I never really seriously thought in my lifetime to see so much progress and developmental biology. I think [Eric Wieschaus](https://www.nobelprize.org/prizes/medicine/1995/wieschaus/facts/) and [Christiane Nüsslein-Volhard](https://www.nobelprize.org/prizes/medicine/1995/nusslein-volhard/facts/) – this was extraordinary what they did – that was one of my favourite prizes of recent years actually, because the deep deep mystery and suddenly it’s all plain. |
| Q23 | But nevertheless do you think there is need for a total new concept? Because you made a wonderful metaphor at your banquet speech about the cell being a symphony orchestra. You could maybe add that life was the music and you could have included the audience and even if you can analyse the conductor, could you then explain the symphony orchestra by looking at the details? |
|  | Leland Hartwell: I think that’s a metaphor of the transition that’s taking place is that as we learn more and more of the individual musicians, if you will, and what it is that they do as individuals we don’t yet understand how the whole assembly creates something that is as beautiful and mysterious as a cell dividing or just a cell metabolising or any of the wonderful things that cells do. That’s the era that I think most biologists, molecular biologists would say we’re moving into now, is how does the properties emerge.Tim Hunt: It’s becoming much more … I’m so pleased that we have a prize for physiology because I think that’s exactly where we’re going, it’s molecular physiology from now on by which I mean that how things work together, right. It’s all very well having … we’ve sort of come out of a chemical phase almost and I think we’re entering a real physiological phase. |
| Q23 | But I mean science is per definition reductionistic. How you look at structures, you look at details, and life is time- and spacedependent and dynamics and interactive. You have looked at frozen moments of details, can you ever understand system … |
|  | Tim Hunt: Oh sure, look at the way that muscles and nerves work for example, was done a long time ago. It’s funny, sometimes things are done from the top down and sometimes done from the bottom up.Sir Paul Nurse: I often think too much is made of this reductionism holism difference. Of course science has to explain in terms of basic components or elements or sub systems but nearly all of us working at a holistic framework looking at the overall system. The challenge we have now is in particularly in the life sciences is that these systems are actually quite complicated, in fact very complicated and unlike for example in chemistry and physics where you have lots of objects behaving identically like atoms, what we have is lots of objects which don’t behave identicallyTim Hunt: Which interact and each feedback positively and negatively with each other. It’s very complicated and the trick of doing successful science is from isolating the simplicity out of that complexity otherwise you’re lost. It’s all very well to look at a dividing cell and going, ‘Gosh, this is marvellous’! but it doesn’t help you understand what’s going on behind the scenes.Sir Paul Nurse: I think that’s absolutely right, but now we’ve got to start thinking. We have all this individual components, behaving in different ways, interact in different ways and we’ve got to somehow extract the general principles from that behaviour and try and get … You can use these words like emerge and properties or whatever, they often raise more heat than light when you use these terms, it must be said, but I think there is a challenge there and describing the dynamics of this in real space and real time. which we’re just beginning to do in cell biology. I think a brave new world is going to come from this, I’m an optimist I must say, but I think that it’s very exciting times.Leland Hartwell: I think there’s another thing too to say about reductionism is that you take some global property and you try to explain it at the next level down and the next level down may just be cell society. We’re now very concentrated on the molecular level but as we start asking how cells behave the right description may not be in molecules, the right description may be in circuits or modules or certain properties, so creating the right concepts to go the next level down is sort of the nature of reductionism and the creative part. |
| Q52 | Which means that you can find some very precise detail in hierarchy that is really governing the next level |
|  | Tim Hunt: Yes, the clue to the whole thing.Sir Paul Nurse: I think there’s two ways actually to answer that: One is, which is perhaps what we’ve done, which is to focus on certain components and elements which are crucial and critical and I think that that falls naturally out of our analysis. I think a second way of viewing this, which I think is what Lee was hinting at, is could we describe general properties of these systems, are there rules that would govern general properties which don’t require going down to specific behaviours of individual components but when in a certain assemblage give rise to behaviours that are interesting. I think that’s perhaps what you were getting at.Leland Hartwell: Exactly, we have our signalling system, cells respond to signals for example and they may respond over a certain concentration range, they may respond by flipping states or by a gradual transition. These are sort of dynamic concepts that don’t necessary require molecular explanation but require some kind of probably creative conceptualisation that may be different than anything we think of right now.Tim Hunt: I know there’s an economist might describe an economy, sort of abstractable principles.Leland Hartwell: Exactly, yes |
| Q13 | Does that also mean that you are looking for inspiration from other areas of science, like scientists who are dealing with the mathematics, the complex system, dealing with the scientists from economy are trying to do mathematics for complex systems. |
|  | Leland Hartwell: Yes, very much. I think one important area that we can learn a lot about molecular circuits from, or from electronic circuits in order to understand a complex circuit, what you’d really like to have is a very detailed description of the input/output characteristics, as you perturb the system how does it respond. We don’t usually have that for many of our biological circuits, we know what the components are but we don’t know how the input/output are related in any quantitative terms.Sir Paul Nurse: Because I’d like to push that metaphor even further. It may be by knowing the sorts of components that you have and by knowing that they can be connected in certain ways. In fact all the huge variety that is possible may not actually be occurring because it may be that the only linking certain components that behave in certain ways in particular ways that may only generate certain stable operating systems and that we’re not actually faced with immense complexity we’re faced with a few solutions. If we can identify the rules for getting those solutions, we’ll simplify the problem. |
| Q50 | But given that you’re right, what will the implications be? Finding the simple rules that govern complex systems, you said ‘brave new world’, it really sounds something in that direction, Tim? |
|  | Sir Paul Nurse: He’s more sceptical of …Tim Hunt: I think, it’s very interesting. Paul likes theoretical biology and he has some good friends who are rather good theoretical biologists but my own view is that these approaches so far have not been very successful. Partly because we don’t even know the parts, secondly because it’s very difficult to measure accurately the properties of those parts. There are certain kinetic constants about how fast things happen and the values of those parameters are rather critical when it comes to building a model and so far the modellers have been quite good at describing what they know is the right answer because they knew that to start with. They’ve not been so good, in my view, about saying well you know about this component a, b, c, d, e, f and g, but without factor x it won’t have the behaviour that we know that it does have and it would be very helpful if they came in and said you’re missing the x factor and we said oh my goodness we can go and look for that. Actually that’s not the way it works and in fact, what happens is that the geneticists start having a kind of lucky dip and then some biochemists come along and analyse it and we keep on finding the various components, the key components of these systems completely by luck, well not completely by luck, but I mean going and looking for them, never by predicting sort of …Leland Hartwell: I think we ought to look at history here. For example take gene regulation. This is an area where it might have been simple in Paul’s terms where it makes good sense to control a gene by turning on or off its message. But in fact, nature has used every single step of information transformation from turning on the gene, from getting the message part way started, the stopping it, from once it’s made degrading it, from starting the translation of a protein. You could every single step of information transfer from the gene to the protein and the activity of the programme is utilised by itself.Tim Hunt: If you conceive a bit controlled somewhere, it will be controlled somewhere.Leland Hartwell: Yes, and I have a feeling that that’s the level of complexity we’re going to be faced with and everything as anything that could happen will have been used somewhere.Sir Paul Nurse: But it may be that it doesn’t matter where it’s regulated, in the sense that one can get an explanation by just understanding that this module if you like, will lead to regulation and it may be that when you’re trying to describe the higher order phenomena you do not need the detailed understanding of exactly where that regulation occurs. |
| Q35 | But given that your optimism is real and you are getting some correct on the system, what would you like to explain by this, what are the really hard questions in bioscience today that you want to get to. |
|  | Sir Paul Nurse: Can I jump in there because there’s a new problem that really is interesting me which is how biological systems generate form, spatial order, because I think this is an interesting issue because, knowing within three-dimensional space, the positions of different objects and components within that is not a trivial problemTim Hunt: Theoretical everything should be spherical and they’re not.Sir Paul Nurse: And that’s what I …Tim Hunt: /- – -/ was wrong.Sir Paul Nurse: I’m really fascinated by this because I’m thinking about it in terms of a single cell just because it’s such a simple system to approach. It may be the rules that are important, there are not the same rules that generate the shape of my nose for example, but simply understanding spatial order in any system I think is an interesting challenge. |
| Q54 | Bioscience today is generating a lot of fear, so what is your role in this perspective, what is /- – -/ science |
|  | Tim Hunt: Trying to explain clearly, for example take genetically modified food for example. I just simply don’t understand why this bothers people, but it turned out on interrogation a lot of people don’t realise that with every mouthful of every food whether it’s a plate of fish and chips or a big fat steak they take in billions of DNA molecules. People really thought that only the genetically modified corn contained DNA and that was dangerous somehow, I mean it’s just absurd ignorance on the part of the public.Leland Hartwell: I think there’s another side to this which is as explores basic discoverers bring back knowledge that illuminates mystery in the world and I think everybody enjoys that. That’s an experience of awe over nature and astronomy is a terrific science in a sense because it is almost all that level of appreciation, but the other aspect that scientific knowledge brings in is the possibility to apply it in some way. It’s the application phase, particularly with respective biology and medicine and human life that fear is created and I think we are all afraid. For example just the transition from being not knowing what the sex of a child was until it’s born to being able to determine at an early stage and decide whether or not you want a child of that sex, that really changes human culture and make life in a very profound way. |
| Q54 | Paul Nurse, in this debate on science and society there has been much talk about public understanding of science but maybe there is a reverse of that question, science understanding of public, do you think that is crucial? |
|  | Sir Paul Nurse: I think there is a bridge that we have to construct between scientists and society and it has two sides to that bridge and one is the public understanding, the point Tim emphasised, we have to explain these things so that society has a proper sense. Quite often, just to expand on that briefly, quite often the real debates are not actually about science but they’re about politics and in fact the GM foods debate is as much to do with large corporations controlling the crops and having economic control over issues as much as the gene transfer issue and it all gets mixed together and that’s why it creates so much fire and I think we …Tim Hunt: It’s sort of eased a demonise some giant corporation …Sir Paul Nurse: We need to separate those debates so that there’s a clear scientific issue and a political one because you may find people are on one side of that debate with one issue and on the other with the other. But back to this bridge between science and society, I think there it is also important for the scientists to be listening to the public and to be aware of what their issues are and to be aware of the sorts of questions they want answered and the sorts of approaches that should be taken. Sometimes we may get divorced from what the ordinary person or the politician’s thinking, and that I think is truly potentially dangerous because we can become a priesthood and separate it off as some sort of witch doctor class and I think that is a real danger for us.Tim Hunt: It’s so important that the public should really trust us as far as we’re trustworthy, otherwise everything will break down. |
| Q13 | But somehow you are advisors to the companies and some of you work inside the companies, and you are funded by money from the company. How do you look upon your credibility when it comes to funding in this respect. |
|  | Sir Paul Nurse: This is another huge area of course.About ten minutes left.Sir Paul Nurse: This is a huge area about funding and accountability and these issues. I think that there are a number of misconceptions and I think that often many of the general public think that many scientists are funded simply by private capital and they have this sense that we’re in the pockets of a big industry. That is very often not the case. We have received most of our support from Government funded work, mostly at the front end of work which is available to everybody and indeed one of the nice aspects of science is making that information, that knowledge available for all the societies in the world to make use of, so I think we do have a role here in explaining how work is funded and our accountability within that.Leland Hartwell: But there also is a conflict of interest thing that we need to be very cautious of and within our Institutions we have rules for dealing with conflict of interest, for example if you have an interest in a company, you cannot be involved in clinical trials in a direct way that are testing products that you have a financial interest in and when we make pronouncements to the public about some area of knowledge if we have a financial interest in it we should disclose that. |
| Q13 | I mean have an interest in thing is not only financial interest. Today I think almost every research is interest driven, you have strategic interests, you have environmental interests, you have commercial interests, you have carrier interests, so what about the credibility of a scientist when they are all driven by interests. |
|  | Leland Hartwell: Everybody’s driven by interests. If you don’t limit it to a financial conflict of interest, then of course we’re all interested in all sorts of /- – -/. |
| Q11 | Why do we always distrust the science that are commercial driven interests and not suspicious about the idealistic interests? |
|  | Leland Hartwell: I don’t distrust scientists who have a commercial interest, I just want to know what their biases are, I want to know, that’s all.Tim Hunt: There’s no reason to distrust companies. After all drug companies, the best thing you can do is produce a highly successful drug and the more people it cures the better, so I must say I think their interests and the public interests are one in the same. Where it comes bad is if they try and foist some imperfect product and exaggerate it’s properties, that’s a different matter.Sir Paul Nurse: But you touch upon something which is not quite what you were getting at, but I’d like to draw attention to, which is actually a problem to do with managing good science, because in fact good science is carried out by creative individuals working within the scientific society because it’s very socially interactive but still with lots of freedom to follow their own ideas. Then sitting on top of that is some sort of scientific management that provides money and support which has certain strategic objectives and because we’re not paid as scientists simply to play in our laboratories, we like to think that we are, but in fact society supports us and we’re very expensive to support, because they expect something back. They expect something to increase the health or wealth of the nation and balancing this is actually a very difficult task and I don’t think anybody gets it quite right and it’s very very difficult to explain that to our political masters who would really be much happier sometimes with a very heavy strong strategic top /- – -/.Tim Hunt: They would love to be able to say just solve this problem. In Britain for example BSE is a problem, we really don’t know whether sheep have it, we really don’t know whether humans eating this stuff are going to get it and they would love to be able to direct scientists to solve these problems and the trouble is that people like us are really not very good at behaving under those circumstances.Leland Hartwell: There are a full range of possibilities though. It’s ok to have to fund areas of strategic direction that where you want problems solved and at that point they almost become engineering problems but if you don’t have a foundation of undirected investigation, it’s going to draw you up. |
| Q12 | But given the path, the experience of the path of science you know that when you’re looking for one thing you always pop up with something else, so those who are going to finance you with a specific goal will probably find themselves financing some totally different knowledge not that they really knew they were looking for. |
|  | Sir Paul Nurse: That’s certainly the case, but there is, you know, science is a complex activity and there are roles of different sorts of people at different stages in that process. At the front end you need the explorers, a little later the explorers are no good at turning into practical benefit some of those, or not necessarily good at it.Tim Hunt: And explorers maybe very good exploring mountains but rotten at the seabed.Leland Hartwell: In one place you see this happening is in start-up companies. Very often start-up company starts up with a very specific idea and they get venture capital to go out and six months later they’re doing something entirely different because the first idea didn’t work and they’ve still got to be profitable and that’s an arena in which you see a lot of shifting around. |
| Q55 | But that turns us into what might be the gist of science, the serendipity I mean you are always seeking for something else what you really found. What is the role of serendipity in science? |
|  | Sir Paul Nurse: I’ll kick off with this but I think we’ve all had our own experiences. I think that serendipity does play an important role but in a very particular context. We’re biologists, we’re trying to understand nature and we have to pay real attention to what nature gives us. If we try and impose too much our own thoughts on such complex system, we will either miss things or simply try and force it into a box that is not good for it. I think you have to be very aware of all the possibilities, you have to be very observant and then you can pick up on the serendipitous event, which has certainly happened to me on many occasions in my career and the way I like to think of it, is that nature is giving us the clue that we try and follow.Leland Hartwell: I think there are actually two forms of approaches to science, both of which lend themselves to serendipity. One is Tim’s example which maybe he can amplify, where all of a sudden nature presents you with some observations say, My gosh that’s interesting, I wasn’t looking for that, let’s see what’s there. The other is more /- – -/ approach where we knew what we looking for, but we didn’t know quite how to find it and all of a sudden something popped up that said, Look over here and you might find what you’re looking for.Tim Hunt: In my case it really was complete serendipity and I was really studying one problem but interestingly in a system where actually cell division was very much a part of the system, that’s what it was specialised for, but that aspect of it was just fun for me. It was fun to look at these things down a microscope, I never seriously thought I would make any advance, it was much too difficult a problem. Then suddenly I saw this protein go away and because I’d been sort of half thinking about the nature of the problem, worrying about things, it immediately announced to me what was going on. It was something that nobody for a century had even sort of remotely considered possible but once you see it, bang, it’s obvious. Then you go chasing after it because it leads you in that direction. But nobody would ever have even gone looking for the damn thing in the first place because, precisely, because theoretical biology hadn’t said we should be looking for this so, when nature sort of presents itself to you on a plate then you’re …The secret is to really be open minded …Tim Hunt: You’ve got to be terribly open minded and have …… to the unexpected.Tim Hunt: Yes, absolutely, and all my career I’ve had things like that, you know, suddenly, it’s like walking down the street and seeing something shiny and kneel down and have a look and see whether it’s gold or not.Let’s finish off then with some really easy questions.Sir Paul Nurse: I suspect not. |
| Q55 | It seems as if bioscience is getting into realms that before has been totally occupied by philosophers and theologians. We’re starting to ask those questions about when does a human become human and when do we finish being human. Take for example this stem cell debate and the debate of embryology. How do you look on your own science when you were really going into this field that raises so many existential questions? |
|  | Sir Paul Nurse: First of all you’re right, and this is why biomedical research is now becoming increasingly contentious because we now are addressing really critical problems about the nature of a human being, about the nature of identity when a human being begins and finishes, and this moves us really into the realm of religious thoughts and brings in fact scientists increasingly into a challenging position with well established religious thoughts. Not unlike I would suggest, the Copernican revolution in the 16th century with physics and the heliocentric, the sun centred world, and I have a feeling that biology and biomedicine is really going to take us into that realm which is one reason why I think this two way process of listening to the society and listening to what really bothers people is so important so that we can make a better go at this transition in the brave new world than maybe happened with astronomy and physics in the 16th century.With the big difference that there is no death sentence for scientists these days.Tim Hunt: I find these kind of ethical issues very difficult to deal with and I’m not really used to thinking about them, and I’m not even particularly well informed on the details for example of the stem cell debate which I’ve been asked about a lot. I myself don’t think there’s much wrong with it, I have to say, after all you know things like blood transfusions have been going on for a very long time, that doesn’t seem to bother anybody. I’m slightly confused, I don’t really understand, maybe again it’s a case of what Paul said I should be listening more to the public and finding out what’s really bothering them at the bottom because, scientifically, it seems to be only a good thing. If your leg drops off and you can make a new one from stem cells – who could possibly say that was a bad thing, I just don’t … am I missing something?Leland Hartwell: It’s a moving target, I feel like the ethics and religious and things come up around areas of mystery where we try to develop some concepts about what’s going on and as knowledge accumulates and enlightens these areas, the sort of ethical questions have to move with them and that’s sort of hard. It’s always a difficult transition and as I look forward, one of the things that I see that looks scary to me, I don’t think I’ll live to see it, is the sort of combination of much more integration of machines with people. Now we wear glasses for example to correct eyesight, I don’t think it will be long before we have all sorts of little computer chips in us and you know …Tim Hunt: Yes, you can get false ears that really say work like ears if you are deaf …Leland Hartwell: … and that sort of bothers me you know, it’s going to happen, it’s inevitable.Tim Hunt: Yes, and completely synthetic hearts. |
| Q34 | Finally, many people are really getting scared about what is going to happen. One of the questions thar raises is when you really have managed to find the mechanisms of life, we feel, many of us, that life is also going to be instrumentalised as you decrease the respect for life. What is going on in your own mind when you see the details on how intricate the system is in biology. Are you getting more or less a miracle when you’re looking at it? |
|  | Sir Paul Nurse: I think the more you understand about this beautiful thing we call life the more wonderful it is. Again, it’s easier to look to history because it’s less contentious. Darwin’s theory of evolution by natural selection was such a beautiful idea that you could still have a sense of god who created such a beautiful process and still see it as a wonderful solution to that particular problem. I think if we look at today’s new understanding you can have nothing but a great sense of wonder that comes with that, I think it deepens, in a sense a spiritual understanding beyond simply ignorance and total mystery.Leland Hartwell: I agree in a little bit difference sense. I don’t think we really ever understand anything. I think we only describe it. That we look and look at greater detail and we develop words and concepts to describe it and we’re all just describing the beauty of nature and it doesn’t become any less beautiful just because we describe it.Tim Hunt: Yes exactly, as you walk through a forest, knowing what the trees are growing it doesn’t make it any less the more beautiful forest exactly as Lee says. Inside the cell you find almost every day more wonderful things and say, Oh, that’s how it works, it’s beautiful it’s really beautiful. |
| ID | 0557 |
| Biographical | My parents were born in Norfolk and spent their early years working in the big houses of that rural English county, my mother as a cook and my father as a handyman and chauffeur. After the 1930s recession they moved to Wembley, North-West London, where my father worked as a mechanic in the local H.J. Heinz food processing factory, and my mother brought up their four children and was a part-time cleaner. I was by far the youngest of the family, and at times it was like being an only child. My parents were neither wealthy nor academic, but we lived comfortably and they were always extremely supportive of my academic efforts and aspirations, both at school and university.My primary school was a considerable distance from where we lived and so I had long walks, often alone, to and from school. This walk took me through a park and some rough land where I could not fail to notice the animals, insects and plants there and how they changed during the seasons. During the winter my attention was attracted to the changes in the stars and planets in the sky. I think it was this curiosity about the natural world which awoke my early interest in science. Two incidents from this time that I remember, were, wondering why leaves were larger on plants growing in the shade compared with the same plants growing in sunlight, and watching Sputnik 2, the second ever artificial satellite and the first with a living cargo (a dog called Laika), as it sped across the skies of London. My life-long interest in astronomy started then and I still regularly use a telescope for astronomical observations, although very much as an amateur.I enjoyed my time at primary school because my teachers made the world seem such an interesting place and encouraged my innate curiosity. At age 11 in 1960, I moved to an academic state secondary school, Harrow County Grammar School for Boys. This was a mixed experience for me. It was a good, well-resourced school, but was very exam oriented and most of the other boys came from wealthier and more academic families which sometimes made me feel like a fish out of water. I was never very good at exams, having a poor memory and finding the examination process rather artificial, and there never seemed to be enough time to follow up things that really interested me. But there were good things about the school. I had an excellent Biology teacher, Keith Neal, who encouraged his pupils to study natural history and to do real experiments. I had a great time investigating the pigments of different mutant fruit flies by following experimental protocols published in Scientific American, and I also remember making my own beetle collection when it was still acceptable to make such collections. There were also good extra-curricular activities, particularly hill and mountain walking and more surprisingly, learning to fly. I am still a keen mountain walker and an enthusiastic glider pilot. I also made some very good friends who remained important to me into adulthood. It was during my time at secondary school that I abandoned religion. My mother was a Baptist, and as a young teenager I was also a committed believer. But I had real difficulties reconciling a literal belief in Genesis with evolution, and my attempts to accommodate the biblical account of creation by viewing it as a poetic metaphor suitable for an unsophisticated nomadic people was completely rejected by my church. I gradually slipped away from religion over several years and became an atheist or to be more philosophically correct, a sceptical agnostic.By the end of my time at school I had achieved examination grades which allowed me to go to University, but did not have a basic foreign language qualification which was compulsory for all University entrants. This meant that when I left school I had to work as a technician in a microbiological laboratory associated with the local Guinness brewery. This was a great experience for me because I had a very sympathetic lab head Vic Knivett, who rapidly realised that I could complete the routine requirements of my job in a couple of days each week, and encouraged me to carry out research experiments for the rest of my time. Unfortunately I continued to fail my French Exam and it was only the intervention of Professor Jinks at Birmingham that got me into a University. He had noticed my application for entry and asked me to visit his Genetics Department. After an extensive interview he arranged for my weaknesses in foreign languages to be over-looked and so I started a Biology degree at Birmingham in 1967.My time as an undergraduate at Birmingham was extremely stimulating both as a biologist and also for my more general intellectual development. It was the heady times of the sixties when everything could be challenged and everything seemed possible. I met my wife Anne who was a sociology student, and her influence together with activities associated with the student movement of the time opened up my interests amongst other things into the theatre, art, music, politics and philosophy. For the first time I fully recognised the excitement of intellectual endeavour and realised that this was what I wanted to do with my life.The lecturers on my courses were generally enthusiastic about their subjects and encouraged my interest in the biological world. At first my inclinations turned towards the subject of ecology with its then new theoretical models of ecological systems, but a field course collecting marine specimens in freezing cold weather taught me that I was too soft for practical ecology, and I realised that I had a preference for the more controlled and warmer environment of the laboratory. Gradually my interests settled on developmental biology with an emphasis on plants and a molecular approach to the problem. I had an eccentric zoology tutor Jack Cohen who was hugely stimulating and entertaining, and although frequently wrong was always wrong in an interesting way. He taught me the value of the alternative view and also was the first to introduce me to the cell cycle with a project on the respiration rate of dividing fish eggs, a project which ended in complete disaster. This time at Birmingham turned me into a general biologist, and ever since then I have always tried to take a biological approach to any research project that I have undertaken.A key issue in developmental biology at that time was the problem of how cells underwent differentiation, with most workers concentrating on explanations in terms of changes in enzyme and gene regulation. To me the cell cycle seemed to be a good and simple model for such problems, because the cell underwent molecular changes as it proceeded through its cell cycle. So when my thoughts turned towards a PhD I looked for a laboratory where I could study molecular changes during the cell cycle. Tony Sims at the University of East Anglia (UEA) in Norfolk was just beginning such studies by looking at the enzymes of amino acid metabolism during the cell cycle of the fungus *Candida utilis*. I went to his lab as a graduate student because I was joining a project at its inception and thought that I would be able to make a more important contribution to the work. Tony was a great experimentalist and I rapidly learnt the need for good experiments to make any progress at all in a research project. Like many students, I found the drudgery of real experiments and the slowness of progress a complete shock, and at my low points I contemplated other alternative careers including study of the philosophy or sociology of science. However, the atmosphere at UEA was very supportive and my colleagues made me feel I was making a useful contribution so I survived the difficulties of carrying out real research. In fact I am very much an experimentalist and an empiricist, so it would have been a major mistake for me to have abandoned this type of work. But this experience did teach me the need for sympathetic support of scientific colleagues, because at the forefront of research there are so many difficulties that depression and low motivation are a constant danger.The next step was what to do as a post-doctoral worker and this question exercised me greatly in my final year as a graduate student. I felt strongly that since the pursuit of good science was so difficult it was essential that the problem being studied was an important one to justify the effort expanded. Rather grandly I argued to myself that the process of reproduction was a central property of life, and that this was seen in its simplest form with the reproduction of cells. Therefore, I reasoned that study of the cell cycle responsible for the reproduction of cells was important and might even be illuminating about the nature of life. In particular the control of these processes would be crucial, just like control of flux through a pathway was important for amino acid metabolism. But how could such processes be investigated given so little was known about them? The answer came to me in 1972 when I read two papers from Lee Hartwell who showed how genetics could be used to study the budding yeast cell cycle. I thought this was a beautiful approach to the problem, one I wanted to use as well. The difficulty was that Anne was by now a teacher and neither of us wanted to move to the USA, and so I needed to find a UK laboratory for this work. Murdoch Mitchison in Edinburgh was the UK authority on the cell cycle and worked on fission yeast but he was not a geneticist. I. went to Edinburgh on a wonderful blue day with the city under snow to discuss my aspirations, and was immediately attracted both to Murdoch’s laboratory and to this beautiful city. He suggested that I spent a couple of months in Bern Switzerland with Urs Leupold, the father of fission yeast genetics, so that I could gain experience that would allow me to begin a genetic analysis of the fission yeast cell cycle. Urs was a careful but inspirational teacher and within six months I was able to introduce genetics into Murdoch’s cell cycle laboratory.My 6 years with Murdoch were pivotal for my entire research career. He gave me both complete support and total freedom, spending hours each week talking with me but never instructing me what to do. An astonishingly generous supervisor, he never once was a co-author on any of the papers I produced during my time in Edinburgh. He considered, quite wrongly of course, that he had not made a sufficient contribution to justify inclusion! His laboratory was an exciting environment where I had many interesting colleagues. During my first year, two new recruits came, Peter Fantes as a postdoc and Kim Nasmyth as a graduate student. Peter was of a mathematical and theoretical bent and it was through discussions and joint work with him that the importance of cell mass in regulating progression through the fission yeast cell cycle first became clear to me. Murdoch asked me to look after Kim who was extra-ordinarily bright, and he extended the cell cycle mutant collections during his thesis work. My main efforts focussed on trying to identify the rate controlling steps during the cell cycle. Crucial for this analysis were wee mutants that were advanced prematurely through the cell cycle and so divided at a reduced cell size. I would like to claim that I reasoned abstractly that such mutants would be useful and then tried to find them, but in reality I noticed them only by accident whilst searching for completely different mutants. As is often the case it was nature that provided the best lead to be followed. A third new recruit was a friend of mine from Bern, Pierre Thuriaux who worked with me on showing that *cdc2* was a rate limiting factor controlling the onset of mitosis. A second key advance was showing that *cdc2* was also required for the onset of S-phase. This emerged from work with Yvonne Bissett while we were trying to identify a G1 control start similar to the one de- fined by Lee Hartwell in budding yeast. As a negative control for this experiment we used *cdc2* mutants which we thought would block cell cycle progression in G2. In fact the results we obtained were ambiguous with the negative controls always giving a small but significant positive response. For some time we thought the experiment flawed and then in desperation hypothesised that *cdc2* was required twice in the cell cycle explaining the mixed results. This turned out to be correct establishing that *cdc2* was a controlling factor for the onset of both S-phase and mitosis.It was now 1980 and Anne and myself had two little children Sarah and Emily, and we were wondering whether to stay permanently in Edinburgh. This possibility bothered me as I thought it was not advisable to remain in one academic environment, and the long dark winters in Edinburgh could be rather dismal. I also thought that the next stage in cell cycle analysis required molecular genetics, and fission yeast was not developed for these types of experiments, and so I looked for an environment which would make this possible. In the end I decided that the University of Sussex in Brighton was a good place for this work because it had a strong tradition in bacterial molecular genetics and an excellent reputation in biology. It was also almost as far south as it was possible to go in the UK and so had a reasonable chance of having decent summers! I set up my first laboratory there with a technician and myself and began working on fission yeast molecular genetic manipulation. In this project I had great assistance from an excellent post-doc from the next door lab, David Beach, who was already skilled in DNA cloning procedures. There followed a very fruitful collaboration that led to the cloning of the more important cell cycle genes. This allowed me to recruit more workers, in particular my first graduate student Jacky Hayles, who went on to contribute immeasurably to many subsequent projects in my laboratory and still is a stimulating and imaginative colleague with me today. Another very important recruit was Paul Russell who cloned the more important regulators of *cdc2*.This progress in the molecular analysis of the cell cycle led to more interest being taken in my work and as a consequence to greater competition. My job was not secure in Sussex as I only had a time limited position and the financial support for my lab was limited. I had failed to secure a permanent appointment at Sussex or the major MRC research institutes in Cambridge and London, and was on the verge of moving to the EMBL in Heidelberg where the Director Lennart Philipson had offered me a post. However, we wanted to stay in the UK and just in time Walter Bodmer, Scientific Director of the Imperial Cancer Research Fund (ICRF) offered me a permanent lab head position at his main laboratories in Lincoln’s Inn Fields and I moved there in 1984. For the first time I found myself in a very well funded laboratory and a hot-house scientific environment. There were pros and cons to this; the financial support meant we could do any experiment we wished but there was not the same collegiate support that I was used to in the Universities. Perhaps, not unreasonably, some wondered what a yeast researcher was doing in a cancer research institute. Despite this I was now able to set up an effective laboratory which could take on many of the problems that I could not have addressed before. Lincoln’s Inn was a wonderful scientific institute with nearly every molecular biology procedure being carried out by someone within its walls. I quickly built up a laboratory of excellent post-docs who brought in expertise that I did not have, expertise which was essential for a proper molecular analysis of the cell cycle control genes. These included Viesturs Simanis, Sergio Moreno and Kathy Gould, who between them worked out that *cdc2* encoded a protein kinase that was regulated during the cell cycle and was controlled by tyrosine phosphorylation. Another post-doc Melanie Lee cloned the human *CDC2* gene by rescue of a fission yeast *cdc2* mutant, and so established that the cell cycle in humans was likely to be regulated in the same way as yeasts. This was a major step forward, all the more so because she persevered with a project that many argued was highly unlikely to succeed.At the end of the 1980s as a complete surprise my old Edinburgh friend, Ed Southern offered me the Chair of Microbiology at the University of Oxford. It was a difficult decision to move to Oxford as things were going so well at Lincoln’s Inn, but when my daughters realised that they would be able to ride ponies almost daily the debate was over and we moved to Oxford in 1988. I had a lot more space and my lab grew in size probably beyond a level that I could properly supervise. Many of my lab colleagues moved with me to Oxford and others including Chris Norbury, Iain Hagan and Tamar Enoch joined me there. During this time the links of *cdc2* with cyclins and maturation promoting factor (MPF) were established, as well as its involvement with checkpoint controls. My administrative work load increased dramatically as the head of a University Department and also as President of the UK Genetical Society. This together with being the supervisor of a large laboratory meant that I failed to take sufficient advantage of the broader academic environment that a University has to offer. I had hoped to recreate my times at Sussex and Edinburgh but this was not to be. However, I did learn how to manage things and how to deal with finances which led to me being approached about returning to London as Scientific Director to ICRF. The temptation of the properly founded laboratory was too great to resist and I returned to Lincoln’s Inn Fields in 1993.This return to ICRF made me a colleague of Tim Hunt with whom I had had close contacts for the previous decade although we had never worked together. He was and is a most delightful companion and our very different backgrounds meant that our conversations, for me at least, were always stimulating and productive. We had the closeness and mutual respect which meant we could utterly disagree without the slightest risk of the other becoming upset. As a biochemist he was more grounded in reality, whilst as a geneticist I was more abstract in my thought. This meant I tended to lose contact with what was really possible within the constraints of the Laws of Thermodynamics as Tim was always ready to point out to me. We were also both natural performers on the lecture stage and not infrequently we entertained as a double act at conferences. There were many other scientists on the world stage that had great influence on the cell cycle field during the crucial times of the 1980s to the early 1990s. Important for me were those working on frog and marine invertebrate egg cell cycles, work started by Yoshio Masui. Marc Kirschner provided immense clarity to this sometimes murky field, whilst Jim Maller successfully achieved the very important task of purifying maturation promoting factor or MPF. My lab collaborated with the French Scientist Marcel Dorée who not only brought well needed biochemistry to my work but great gaiety as well. Closer to my own experimental system were the yeast geneticists, in particular Mitsuhiro Yanagida, a towering powerhouse of rigorous experimental activity, and Andrew Murray, a worker of great imaginative ability. My interactions with these and many others greatly shaped and corrected my thinking about the cell cycle and its control.The 1990s saw my children grow up and in their early 20s they left home. Sarah is an assistant producer for a major TV soccer programme in the UK, whilst Emily has just started a PhD in theoretical particle physics. My heavy responsibilities as Director General of ICRF have taken their toll on my experimental work. It is a constant worry to me that I have not supervised my graduate students and post-docs properly during this time. It has only been their excellent quality which has kept the work going reasonably well. Their main focus has been elucidating the controls regulating the onset of S-phase and ensuring that there is only one S-phase each cell cycle, a new set of projects dealing with the controls during the meiotic cell cycle, and genomic analysis of fission yeast. These problems all interest me and hopefully in the not too distant future I will be able to devote more of my time to their study. Two other projects are also being pursued. The first is a Science in Society Initiative of the Royal Society which I chair and has as its objective an improvement in dialogue between scientists and the public. Its agenda bears an uncanny similarity to that discussed in the late 1960s during student occupations at the University of Birmingham. The second is the merger of the ICRF with the CRC to generate a single organisation Cancer Research UK, which will form the largest cancer research organisation in the world outside of the USA.The award of this prize is a water-shed in my life, forcing me to look back over my past and to consider what I should do for the next 15-20 years. I have an idealistic view of science as a liberalising and progressive force for humanity. Better understanding of the natural world not only enhances all of us as human beings, but can also be harnessed for the better good, leading to improved health and quality of life. It is also a truly international activity which breaks down barriers between the peoples of world, an objective that always has been necessary and never more so than now. Scientific understanding is often beautiful, a profoundly aesthetic experience which gives pleasure not unlike the reading of a great poem. It has been a privilege to pursue knowledge for its own sake and to see how it might help mankind in more practical ways. I hope that the future will allow me to continue that pursuit for as long as I am able.From [*Les Prix Nobel*](https://www.nobelprize.org/nobel_organizations/nobelfoundation/publications/lesprix.html)*. The Nobel Prizes 2001*, Editor Tore Frängsmyr, [Nobel Foundation], Stockholm, 2002This autobiography/biography was written at the time of the award and later published in the book series [*Les Prix Nobel/*](https://www.nobelprize.org/nobel_organizations/nobelfoundation/publications/lesprix.html)[*Nobel Lectures*](https://www.nobelprize.org/nobel_organizations/nobelfoundation/publications/lectures/index.html)*/*[*The Nobel Prizes*](https://www.nobelprize.org/nobel_organizations/nobelfoundation/publications/nobel-prizes.html). The information is sometimes updated with an addendum submitted by the Laureate.Copyright © The Nobel Foundation 2001**Addendum, February 2008**It was six years after these words were written when I was 57 years of age, that I discovered my parents were not my parents. This revelation came about because of the US Department of Homeland Security rejecting my Green Card application on the grounds that the details given on my birth certificate were insufficient. In the UK there is both a short and a long birth certificate, and the former which I had did not record the names of parents. I applied to the UK Registry Office for a long certificate and went on holiday. On my return, I was greeted by my PA asking if “I had made a mistake with the name of my mother.” She handed me the new long birth certificate and the next few seconds of my life were both unexpected and transforming. The name of my mother given on the certificate was the name of the person I thought was my sister and the space for my father’s name was blank. I had been brought up by my grandparents thinking that they were my parents.Both my mother and grandparents died some years ago so I could not confirm with them what had happened. A more distant relative had been 12 years of age and lived in the house where I was born, and had been sworn to secrecy about my birth. She was able to tell me that my mother became pregnant at 18 years and was sent away to her aunt’s for the last months of pregnancy and my birth. My grandmother then came and pretended that she was the mother and returned to the family home with her “new son.” My grandparents then brought me up to protect their daughter. My mother got married when I was nearly three and there is a poignant photograph of the wedding with her holding her new husband with one hand and me with her other hand. Everyone kept the secret so even my two brothers (now my uncles) did not know the truth of my origins. And of course I still do not know who my father is beyond a rumour that he may have been a serviceman, perhaps even an American serviceman which would presumably please the US Department of Homeland Security.Does any of this change anything? Not really, I was brought up by loving grandparents and had a happy childhood. All my relations have changed of course, with parents becoming grandparents, brothers becoming uncles, nephews and nieces becoming half brothers and sisters. In fact, it was quite nice to acquire new half siblings at a late stage in life. Both my grandparents were also illegitimate so I inherited the name ‘Nurse’ twice through the maternal line in three generations: so apart from being somewhat unsettled, which I suppose is understandable, nothing really has changed, although I continue to wonder who my father is. Of course I regret not having had time with my real mother or the opportunity to discuss my origins with her later in life, and then there is the final irony that even though I am a geneticist my family managed to keep my genetic origins secret from me for over half a century. |
| Autobiographical |  |
| Podcast | **”When a politician gets up and says that we are following the science, the question needs to be what science? Because there are more than one scientific conclusion out there”**What is life? This is a question that has puzzled scientists for centuries, one of the most famous being [Erwin Schrödinger](https://www.nobelprize.org/prizes/physics/1933/schrodinger/facts/). In this podcast episode, conducted in December 2020, we meet Paul Nurse and hear his thoughts on the matter.The host of this podcast is nobelprize.org’s Adam Smith. |
| Telephone  interview |  |
| Interview |  |
| Q6 | But is it true you are the royalties is of a scientific community for one year now or for the rest of your life? |
|  | Leland Hartwell: Certainly feel it during this celebration here.Sir Paul Nurse: But of course, science moves on so in fact the Kings get changed very quickly. |
| Q14 | Oh yes, those days, no scientist is happier as the one which can prove that the professor was wrong. |
|  | Sir Paul Nurse: Correct. That’s one of the beauties of science that it does move on and there isn’t a received wisdom that just stays in one place with one person.Tim Hunt: But at the same time there were giants present here, this week, I’m thinking people like [Jim Watson](https://www.nobelprize.org/prizes/medicine/1962/watson/facts/), I’m thinking of people like [François Jacob](https://www.nobelprize.org/prizes/medicine/1965/jacob/facts/), thinking of people like [Günter Blobel](https://www.nobelprize.org/prizes/medicine/1999/blobel/facts/), they haven’t been disapproved, they put a new big step on our constant stairway of knowledge. |
| Q22 | But does that mean that science actually really is coming closer and closer to reality? There are some truths that remain truths even throughout the centuries. |
|  | Sir Paul Nurse: This is quite complex philosophically because we tend to work in certain paradigms and for a while in fact we put these bricks in the wall as Tim was alluding to within that paradigm, but then you can get a real shift which takes you into a sort of different area altogether. That’s certainly been the case in physics at the beginning of the last century with quantum mechanics and relativity there was a real shift from Newtonian paradigms of the previous two and a half centuries. In biology it’s sometimes a little bit more difficult to see that.Tim Hunt: That’s really happened in biology, you know, the establishment of the cell theory and then Pasteur proves that there’s no such thing as spontaneous creation, these are sort of universal truths. |
| Q23 | But what differentiation that everyone thought that higher animals could never be cloned and then all of a sudden there’s a Dolly. Isn’t that a major shift in how you perceived DNA? |
|  | Sir Paul Nurse: I think that not sure so much in the sense that was a technical achievement but it had been achieved with frogs actually that particular …But not with high animals.Leland Hartwell: Frogs are very high animals …Tim Hunt: The frog is a high animal. What do you mean, were you trying to despise the poor frog?Sir Paul Nurse: You’re talking to a …Tim Hunt: You’re talking to the wrong people of course, we love frogs. They are called low organisms, but we love them.Sir Paul Nurse: You’re talking to a CO and two /- – -/ here and frogs are something up there, very complex to us.Leland Hartwell: But in terms of paradigms we are in an era now, from about the last 30 or 40 years, where we are sort of enumerating the molecular pieces, we’re making catalogues of who the players are in different processes and we’re already beginning to see the end of that era and a new era of you know, what are the properties of assemblies and modules and circuits of these groups.Tim Hunt: Emergent properties ensemble of all of those subunits, sorry sub-assemblies. |
| Q23 | But anyway, if you excuse me, in one way you have solved the easy problem and now you come to the real difficult problem. |
|  | Sir Paul Nurse: I think Lee, I mean this is why I was referring to paradigm shifts with physics which is clear, because I have a feeling there will be a paradigm shift in biology. I like to think of it a little bit like this a metaphor is that we’ve been identifying the actors in a play and we now have to write the script, and we’ve been identifying a lot of the molecules, the elements but actually putting it all together is in the symphony analogy or the play analogy requires maybe different sorts of thinking I actually am beginning to wonder.Leland Hartwell: What’s easy and what’s hard depends on the era, I think when we began our careers and were interested in dissecting some of the complexity of cell biology that was considered very mysterious and difficult and impossible but we’re moving beyond that era now and now people see that as relatively straight forward but how all things work together now appears to be a big mystery.Tim Hunt: I think one of the curious things … I mean I never really seriously thought in my lifetime to see so much progress and developmental biology. I think [Eric Wieschaus](https://www.nobelprize.org/prizes/medicine/1995/wieschaus/facts/) and [Christiane Nüsslein-Volhard](https://www.nobelprize.org/prizes/medicine/1995/nusslein-volhard/facts/) – this was extraordinary what they did – that was one of my favourite prizes of recent years actually, because the deep deep mystery and suddenly it’s all plain. |
| Q23 | But nevertheless do you think there is need for a total new concept? Because you made a wonderful metaphor at your banquet speech about the cell being a symphony orchestra. You could maybe add that life was the music and you could have included the audience and even if you can analyse the conductor, could you then explain the symphony orchestra by looking at the details? |
|  | Leland Hartwell: I think that’s a metaphor of the transition that’s taking place is that as we learn more and more of the individual musicians, if you will, and what it is that they do as individuals we don’t yet understand how the whole assembly creates something that is as beautiful and mysterious as a cell dividing or just a cell metabolising or any of the wonderful things that cells do. That’s the era that I think most biologists, molecular biologists would say we’re moving into now, is how does the properties emerge.Tim Hunt: It’s becoming much more … I’m so pleased that we have a prize for physiology because I think that’s exactly where we’re going, it’s molecular physiology from now on by which I mean that how things work together, right. It’s all very well having … we’ve sort of come out of a chemical phase almost and I think we’re entering a real physiological phase. |
| Q23 | But I mean science is per definition reductionistic. How you look at structures, you look at details, and life is time- and spacedependent and dynamics and interactive. You have looked at frozen moments of details, can you ever understand system … |
|  | Tim Hunt: Oh sure, look at the way that muscles and nerves work for example, was done a long time ago. It’s funny, sometimes things are done from the top down and sometimes done from the bottom up.Sir Paul Nurse: I often think too much is made of this reductionism holism difference. Of course science has to explain in terms of basic components or elements or sub systems but nearly all of us working at a holistic framework looking at the overall system. The challenge we have now is in particularly in the life sciences is that these systems are actually quite complicated, in fact very complicated and unlike for example in chemistry and physics where you have lots of objects behaving identically like atoms, what we have is lots of objects which don’t behave identicallyTim Hunt: Which interact and each feedback positively and negatively with each other. It’s very complicated and the trick of doing successful science is from isolating the simplicity out of that complexity otherwise you’re lost. It’s all very well to look at a dividing cell and going, ‘Gosh, this is marvellous’! but it doesn’t help you understand what’s going on behind the scenes.Sir Paul Nurse: I think that’s absolutely right, but now we’ve got to start thinking. We have all this individual components, behaving in different ways, interact in different ways and we’ve got to somehow extract the general principles from that behaviour and try and get … You can use these words like emerge and properties or whatever, they often raise more heat than light when you use these terms, it must be said, but I think there is a challenge there and describing the dynamics of this in real space and real time. which we’re just beginning to do in cell biology. I think a brave new world is going to come from this, I’m an optimist I must say, but I think that it’s very exciting times.Leland Hartwell: I think there’s another thing too to say about reductionism is that you take some global property and you try to explain it at the next level down and the next level down may just be cell society. We’re now very concentrated on the molecular level but as we start asking how cells behave the right description may not be in molecules, the right description may be in circuits or modules or certain properties, so creating the right concepts to go the next level down is sort of the nature of reductionism and the creative part. |
| Q52 | Which means that you can find some very precise detail in hierarchy that is really governing the next level |
|  | Tim Hunt: Yes, the clue to the whole thing.Sir Paul Nurse: I think there’s two ways actually to answer that: One is, which is perhaps what we’ve done, which is to focus on certain components and elements which are crucial and critical and I think that that falls naturally out of our analysis. I think a second way of viewing this, which I think is what Lee was hinting at, is could we describe general properties of these systems, are there rules that would govern general properties which don’t require going down to specific behaviours of individual components but when in a certain assemblage give rise to behaviours that are interesting. I think that’s perhaps what you were getting at.Leland Hartwell: Exactly, we have our signalling system, cells respond to signals for example and they may respond over a certain concentration range, they may respond by flipping states or by a gradual transition. These are sort of dynamic concepts that don’t necessary require molecular explanation but require some kind of probably creative conceptualisation that may be different than anything we think of right now.Tim Hunt: I know there’s an economist might describe an economy, sort of abstractable principles.Leland Hartwell: Exactly, yes |
| Q13 | Does that also mean that you are looking for inspiration from other areas of science, like scientists who are dealing with the mathematics, the complex system, dealing with the scientists from economy are trying to do mathematics for complex systems. |
|  | Leland Hartwell: Yes, very much. I think one important area that we can learn a lot about molecular circuits from, or from electronic circuits in order to understand a complex circuit, what you’d really like to have is a very detailed description of the input/output characteristics, as you perturb the system how does it respond. We don’t usually have that for many of our biological circuits, we know what the components are but we don’t know how the input/output are related in any quantitative terms.Sir Paul Nurse: Because I’d like to push that metaphor even further. It may be by knowing the sorts of components that you have and by knowing that they can be connected in certain ways. In fact all the huge variety that is possible may not actually be occurring because it may be that the only linking certain components that behave in certain ways in particular ways that may only generate certain stable operating systems and that we’re not actually faced with immense complexity we’re faced with a few solutions. If we can identify the rules for getting those solutions, we’ll simplify the problem. |
| Q50 | But given that you’re right, what will the implications be? Finding the simple rules that govern complex systems, you said ‘brave new world’, it really sounds something in that direction, Tim? |
|  | Sir Paul Nurse: He’s more sceptical of …Tim Hunt: I think, it’s very interesting. Paul likes theoretical biology and he has some good friends who are rather good theoretical biologists but my own view is that these approaches so far have not been very successful. Partly because we don’t even know the parts, secondly because it’s very difficult to measure accurately the properties of those parts. There are certain kinetic constants about how fast things happen and the values of those parameters are rather critical when it comes to building a model and so far the modellers have been quite good at describing what they know is the right answer because they knew that to start with. They’ve not been so good, in my view, about saying well you know about this component a, b, c, d, e, f and g, but without factor x it won’t have the behaviour that we know that it does have and it would be very helpful if they came in and said you’re missing the x factor and we said oh my goodness we can go and look for that. Actually that’s not the way it works and in fact, what happens is that the geneticists start having a kind of lucky dip and then some biochemists come along and analyse it and we keep on finding the various components, the key components of these systems completely by luck, well not completely by luck, but I mean going and looking for them, never by predicting sort of …Leland Hartwell: I think we ought to look at history here. For example take gene regulation. This is an area where it might have been simple in Paul’s terms where it makes good sense to control a gene by turning on or off its message. But in fact, nature has used every single step of information transformation from turning on the gene, from getting the message part way started, the stopping it, from once it’s made degrading it, from starting the translation of a protein. You could every single step of information transfer from the gene to the protein and the activity of the programme is utilised by itself.Tim Hunt: If you conceive a bit controlled somewhere, it will be controlled somewhere.Leland Hartwell: Yes, and I have a feeling that that’s the level of complexity we’re going to be faced with and everything as anything that could happen will have been used somewhere.Sir Paul Nurse: But it may be that it doesn’t matter where it’s regulated, in the sense that one can get an explanation by just understanding that this module if you like, will lead to regulation and it may be that when you’re trying to describe the higher order phenomena you do not need the detailed understanding of exactly where that regulation occurs. |
| Q35 | But given that your optimism is real and you are getting some correct on the system, what would you like to explain by this, what are the really hard questions in bioscience today that you want to get to. |
|  | Sir Paul Nurse: Can I jump in there because there’s a new problem that really is interesting me which is how biological systems generate form, spatial order, because I think this is an interesting issue because, knowing within three-dimensional space, the positions of different objects and components within that is not a trivial problemTim Hunt: Theoretical everything should be spherical and they’re not.Sir Paul Nurse: And that’s what I …Tim Hunt: /- – -/ was wrong.Sir Paul Nurse: I’m really fascinated by this because I’m thinking about it in terms of a single cell just because it’s such a simple system to approach. It may be the rules that are important, there are not the same rules that generate the shape of my nose for example, but simply understanding spatial order in any system I think is an interesting challenge. |
| Q54 | Bioscience today is generating a lot of fear, so what is your role in this perspective, what is /- – -/ science |
|  | Tim Hunt: Trying to explain clearly, for example take genetically modified food for example. I just simply don’t understand why this bothers people, but it turned out on interrogation a lot of people don’t realise that with every mouthful of every food whether it’s a plate of fish and chips or a big fat steak they take in billions of DNA molecules. People really thought that only the genetically modified corn contained DNA and that was dangerous somehow, I mean it’s just absurd ignorance on the part of the public.Leland Hartwell: I think there’s another side to this which is as explores basic discoverers bring back knowledge that illuminates mystery in the world and I think everybody enjoys that. That’s an experience of awe over nature and astronomy is a terrific science in a sense because it is almost all that level of appreciation, but the other aspect that scientific knowledge brings in is the possibility to apply it in some way. It’s the application phase, particularly with respective biology and medicine and human life that fear is created and I think we are all afraid. For example just the transition from being not knowing what the sex of a child was until it’s born to being able to determine at an early stage and decide whether or not you want a child of that sex, that really changes human culture and make life in a very profound way. |
| Q54 | Paul Nurse, in this debate on science and society there has been much talk about public understanding of science but maybe there is a reverse of that question, science understanding of public, do you think that is crucial? |
|  | Sir Paul Nurse: I think there is a bridge that we have to construct between scientists and society and it has two sides to that bridge and one is the public understanding, the point Tim emphasised, we have to explain these things so that society has a proper sense. Quite often, just to expand on that briefly, quite often the real debates are not actually about science but they’re about politics and in fact the GM foods debate is as much to do with large corporations controlling the crops and having economic control over issues as much as the gene transfer issue and it all gets mixed together and that’s why it creates so much fire and I think we …Tim Hunt: It’s sort of eased a demonise some giant corporation …Sir Paul Nurse: We need to separate those debates so that there’s a clear scientific issue and a political one because you may find people are on one side of that debate with one issue and on the other with the other. But back to this bridge between science and society, I think there it is also important for the scientists to be listening to the public and to be aware of what their issues are and to be aware of the sorts of questions they want answered and the sorts of approaches that should be taken. Sometimes we may get divorced from what the ordinary person or the politician’s thinking, and that I think is truly potentially dangerous because we can become a priesthood and separate it off as some sort of witch doctor class and I think that is a real danger for us.Tim Hunt: It’s so important that the public should really trust us as far as we’re trustworthy, otherwise everything will break down. |
| Q13 | But somehow you are advisors to the companies and some of you work inside the companies, and you are funded by money from the company. How do you look upon your credibility when it comes to funding in this respect. |
|  | Sir Paul Nurse: This is another huge area of course.About ten minutes left.Sir Paul Nurse: This is a huge area about funding and accountability and these issues. I think that there are a number of misconceptions and I think that often many of the general public think that many scientists are funded simply by private capital and they have this sense that we’re in the pockets of a big industry. That is very often not the case. We have received most of our support from Government funded work, mostly at the front end of work which is available to everybody and indeed one of the nice aspects of science is making that information, that knowledge available for all the societies in the world to make use of, so I think we do have a role here in explaining how work is funded and our accountability within that.Leland Hartwell: But there also is a conflict of interest thing that we need to be very cautious of and within our Institutions we have rules for dealing with conflict of interest, for example if you have an interest in a company, you cannot be involved in clinical trials in a direct way that are testing products that you have a financial interest in and when we make pronouncements to the public about some area of knowledge if we have a financial interest in it we should disclose that. |
| Q13 | I mean have an interest in thing is not only financial interest. Today I think almost every research is interest driven, you have strategic interests, you have environmental interests, you have commercial interests, you have carrier interests, so what about the credibility of a scientist when they are all driven by interests. |
|  | Leland Hartwell: Everybody’s driven by interests. If you don’t limit it to a financial conflict of interest, then of course we’re all interested in all sorts of /- – -/. |
| Q11 | Why do we always distrust the science that are commercial driven interests and not suspicious about the idealistic interests? |
|  | Leland Hartwell: I don’t distrust scientists who have a commercial interest, I just want to know what their biases are, I want to know, that’s all.Tim Hunt: There’s no reason to distrust companies. After all drug companies, the best thing you can do is produce a highly successful drug and the more people it cures the better, so I must say I think their interests and the public interests are one in the same. Where it comes bad is if they try and foist some imperfect product and exaggerate it’s properties, that’s a different matter.Sir Paul Nurse: But you touch upon something which is not quite what you were getting at, but I’d like to draw attention to, which is actually a problem to do with managing good science, because in fact good science is carried out by creative individuals working within the scientific society because it’s very socially interactive but still with lots of freedom to follow their own ideas. Then sitting on top of that is some sort of scientific management that provides money and support which has certain strategic objectives and because we’re not paid as scientists simply to play in our laboratories, we like to think that we are, but in fact society supports us and we’re very expensive to support, because they expect something back. They expect something to increase the health or wealth of the nation and balancing this is actually a very difficult task and I don’t think anybody gets it quite right and it’s very very difficult to explain that to our political masters who would really be much happier sometimes with a very heavy strong strategic top /- – -/.Tim Hunt: They would love to be able to say just solve this problem. In Britain for example BSE is a problem, we really don’t know whether sheep have it, we really don’t know whether humans eating this stuff are going to get it and they would love to be able to direct scientists to solve these problems and the trouble is that people like us are really not very good at behaving under those circumstances.Leland Hartwell: There are a full range of possibilities though. It’s ok to have to fund areas of strategic direction that where you want problems solved and at that point they almost become engineering problems but if you don’t have a foundation of undirected investigation, it’s going to draw you up. |
| Q12 | But given the path, the experience of the path of science you know that when you’re looking for one thing you always pop up with something else, so those who are going to finance you with a specific goal will probably find themselves financing some totally different knowledge not that they really knew they were looking for. |
|  | Sir Paul Nurse: That’s certainly the case, but there is, you know, science is a complex activity and there are roles of different sorts of people at different stages in that process. At the front end you need the explorers, a little later the explorers are no good at turning into practical benefit some of those, or not necessarily good at it.Tim Hunt: And explorers maybe very good exploring mountains but rotten at the seabed.Leland Hartwell: In one place you see this happening is in start-up companies. Very often start-up company starts up with a very specific idea and they get venture capital to go out and six months later they’re doing something entirely different because the first idea didn’t work and they’ve still got to be profitable and that’s an arena in which you see a lot of shifting around. |
| Q55 | But that turns us into what might be the gist of science, the serendipity I mean you are always seeking for something else what you really found. What is the role of serendipity in science? |
|  | Sir Paul Nurse: I’ll kick off with this but I think we’ve all had our own experiences. I think that serendipity does play an important role but in a very particular context. We’re biologists, we’re trying to understand nature and we have to pay real attention to what nature gives us. If we try and impose too much our own thoughts on such complex system, we will either miss things or simply try and force it into a box that is not good for it. I think you have to be very aware of all the possibilities, you have to be very observant and then you can pick up on the serendipitous event, which has certainly happened to me on many occasions in my career and the way I like to think of it, is that nature is giving us the clue that we try and follow.Leland Hartwell: I think there are actually two forms of approaches to science, both of which lend themselves to serendipity. One is Tim’s example which maybe he can amplify, where all of a sudden nature presents you with some observations say, My gosh that’s interesting, I wasn’t looking for that, let’s see what’s there. The other is more /- – -/ approach where we knew what we looking for, but we didn’t know quite how to find it and all of a sudden something popped up that said, Look over here and you might find what you’re looking for.Tim Hunt: In my case it really was complete serendipity and I was really studying one problem but interestingly in a system where actually cell division was very much a part of the system, that’s what it was specialised for, but that aspect of it was just fun for me. It was fun to look at these things down a microscope, I never seriously thought I would make any advance, it was much too difficult a problem. Then suddenly I saw this protein go away and because I’d been sort of half thinking about the nature of the problem, worrying about things, it immediately announced to me what was going on. It was something that nobody for a century had even sort of remotely considered possible but once you see it, bang, it’s obvious. Then you go chasing after it because it leads you in that direction. But nobody would ever have even gone looking for the damn thing in the first place because, precisely, because theoretical biology hadn’t said we should be looking for this so, when nature sort of presents itself to you on a plate then you’re …The secret is to really be open minded …Tim Hunt: You’ve got to be terribly open minded and have …… to the unexpected.Tim Hunt: Yes, absolutely, and all my career I’ve had things like that, you know, suddenly, it’s like walking down the street and seeing something shiny and kneel down and have a look and see whether it’s gold or not.Let’s finish off then with some really easy questions.Sir Paul Nurse: I suspect not. |
| Q55 | It seems as if bioscience is getting into realms that before has been totally occupied by philosophers and theologians. We’re starting to ask those questions about when does a human become human and when do we finish being human. Take for example this stem cell debate and the debate of embryology. How do you look on your own science when you were really going into this field that raises so many existential questions? |
|  | Sir Paul Nurse: First of all you’re right, and this is why biomedical research is now becoming increasingly contentious because we now are addressing really critical problems about the nature of a human being, about the nature of identity when a human being begins and finishes, and this moves us really into the realm of religious thoughts and brings in fact scientists increasingly into a challenging position with well established religious thoughts. Not unlike I would suggest, the Copernican revolution in the 16th century with physics and the heliocentric, the sun centred world, and I have a feeling that biology and biomedicine is really going to take us into that realm which is one reason why I think this two way process of listening to the society and listening to what really bothers people is so important so that we can make a better go at this transition in the brave new world than maybe happened with astronomy and physics in the 16th century.With the big difference that there is no death sentence for scientists these days.Tim Hunt: I find these kind of ethical issues very difficult to deal with and I’m not really used to thinking about them, and I’m not even particularly well informed on the details for example of the stem cell debate which I’ve been asked about a lot. I myself don’t think there’s much wrong with it, I have to say, after all you know things like blood transfusions have been going on for a very long time, that doesn’t seem to bother anybody. I’m slightly confused, I don’t really understand, maybe again it’s a case of what Paul said I should be listening more to the public and finding out what’s really bothering them at the bottom because, scientifically, it seems to be only a good thing. If your leg drops off and you can make a new one from stem cells – who could possibly say that was a bad thing, I just don’t … am I missing something?Leland Hartwell: It’s a moving target, I feel like the ethics and religious and things come up around areas of mystery where we try to develop some concepts about what’s going on and as knowledge accumulates and enlightens these areas, the sort of ethical questions have to move with them and that’s sort of hard. It’s always a difficult transition and as I look forward, one of the things that I see that looks scary to me, I don’t think I’ll live to see it, is the sort of combination of much more integration of machines with people. Now we wear glasses for example to correct eyesight, I don’t think it will be long before we have all sorts of little computer chips in us and you know …Tim Hunt: Yes, you can get false ears that really say work like ears if you are deaf …Leland Hartwell: … and that sort of bothers me you know, it’s going to happen, it’s inevitable.Tim Hunt: Yes, and completely synthetic hearts. |
| Q34 | Finally, many people are really getting scared about what is going to happen. One of the questions thar raises is when you really have managed to find the mechanisms of life, we feel, many of us, that life is also going to be instrumentalised as you decrease the respect for life. What is going on in your own mind when you see the details on how intricate the system is in biology. Are you getting more or less a miracle when you’re looking at it? |
|  | Sir Paul Nurse: I think the more you understand about this beautiful thing we call life the more wonderful it is. Again, it’s easier to look to history because it’s less contentious. Darwin’s theory of evolution by natural selection was such a beautiful idea that you could still have a sense of god who created such a beautiful process and still see it as a wonderful solution to that particular problem. I think if we look at today’s new understanding you can have nothing but a great sense of wonder that comes with that, I think it deepens, in a sense a spiritual understanding beyond simply ignorance and total mystery.Leland Hartwell: I agree in a little bit difference sense. I don’t think we really ever understand anything. I think we only describe it. That we look and look at greater detail and we develop words and concepts to describe it and we’re all just describing the beauty of nature and it doesn’t become any less beautiful just because we describe it.Tim Hunt: Yes exactly, as you walk through a forest, knowing what the trees are growing it doesn’t make it any less the more beautiful forest exactly as Lee says. Inside the cell you find almost every day more wonderful things and say, Oh, that’s how it works, it’s beautiful it’s really beautiful. |
| ID | 0558 |
| Biographical | Prologue: Life in Vienna in the 1930s There was little in my early life to indicate that an interest in biology would become the passion of my academic career. In fact, there was little to suggest I would have an academic career. Rather, my early life was importantly shaped by my experiences in Vienna and I spent many years later coming to grips with the circumstances and place of my birth.I was born in Vienna on November 7, 1929, eleven years after the multiethnic Austro-Hungarian Empire fell apart following its defeat in World War I. Although Austria had been radically reduced in size (from 54 million to only 7 million inhabitants) and in political significance, its capital, the Vienna of my youth, was still intellectually vibrant, one of the great cultural centers of the world. A city of one and a half million people, it was home to Sigmund Freud, Karl Kraus, Robert Musil, Arthur Schnitzler, and for a while Arnold Schoenberg. The music of Gustav Mahler and of the earlier 19th Century Vienna school resonated throughout the city, as did the bold expressionist images of Gustav Klimt, Oskar Kokoschka, and Egon Schiele. Even as it thrived culturally, however, Vienna in the 1930s was the capital city of an oppressive, authoritarian political system. I was too young to appreciate its cultural richness, but I sensed later, from the perspective of a more carefree adolescence in the United States, the oppressive conditions in Vienna that affected my early youth.Even prior to the Anschluss in 1938, anti-Semitism was a chronic feature of Viennese life. Jews, who made up nearly 20% of the city’s population, were discriminated against in the Civil Service and in many aspects of social life. Nonetheless, they were fascinated by the city in which they had lived for over a thousand years. My parents genuinely loved Vienna, and in later years I learned from them why the city exerted a powerful hold on them and other Jews. My parents loved the dialect of Vienna, its cultural sophistication, and artistic values. “The greatest grim irony of all was the fierce attachment of so many Jews to a city that through the years demonstrated its deep-rooted hate for them,” wrote George Berkley, the American historian of Vienna and its Jews. This fierce attachment was considered by the historian Harvey Zohn to be the most tragically unrequited love in world history.In spite of the hostile climate, Austrian Jews continued to make remarkable contributions to theater, music, literature, science, and medicine in the period between the two World Wars. The Salzburg Festival was directed by Max Reinhardt; the Vienna Opera was conducted by Bruno Walter. Stefan Zweig and Franz Werfel were two of the most popular writers in the German language, and [Elias Canetti](https://www.nobelprize.org/nobel_prizes/literature/laureates/1981/index.html), who later won the Nobel Prize in Literature for books describing his youth in Vienna, began writing these in the 1930s. Two of the three Austrians to be awarded the Nobel Prize in Physiology and Medicine in the 1930s were of Jewish origin: [Karl Landsteiner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1930/index.html) was honored in 1930 for his discovery of blood groups and [Otto Loewi](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1936/index.html) in 1936 for discovering acetylcholine, a chemical transmitter that slowed the heart. Of the 52 Olympic medals earned by Austrian athletes from the beginning of modern Olympics to 1936, 18 were won by Jewish Austrians. Fully half of the practicing physicians and medical faculty at the University of Vienna were Jewish. This, in fact, was the last period during which Viennese medicine still attracted students and patients from all over the world. They came to study with, or to be treated by, pioneers in diagnostics and therapeutic medicine, such as the pediatrician Béla Schick, the ear specialist Heinrich von Neumann, and the psychoanalyst Sigmund Freud. As this listing makes clear, the period of my early youth has been characterized, appropriately, as “the final flowering of the Austrian Jewish intellectual activity.”My parents were not born in Vienna, but they had spent much of their lives there, having each come to the city at the beginning of World War I when they were still very young. My mother, Charlotte Zimels, was born in 1897 in Kolomea, a town of about 43,000 inhabitants in Galicia, a region of the Austro-Hungarian Empire. (Kolomea now is part of the Ukraine and has been renamed Kolomyya.) Almost half the population of Kolomea was Jewish, and the Jewish community had a very active culture. My mother came from a well-educated middle-class family, and although she had spent only one year at the university in Vienna, she spoke and wrote English as well as German and Polish.My father Herman was born into a poor family in 1898 in Olesko, a small town of about 3,500 people near Lvov (Lemberg), now also part of the Ukraine. During World War I he was drafted into the Austria-Hungarian Army directly from high school. After the war he worked to support himself and never went back to school.My parents met in Vienna and married in 1923, shortly after my father had established himself as the owner of a small toy store. My brother Lewis was born on November 14, 1924. I was born five years later. We lived in a small apartment at Severingasse 8 in the 9th district, a middle-class neighborhood near the medical school, and not too far from Freud’s apartment, although we had no association with either. Both of my parents worked in the store, and we had a full-time housekeeper to help out at home.I went to a school near our house. As with most elementary schools in Vienna, it was very traditional and very good, and I followed the well-trodden trail that my exceptionally gifted brother Lewis had blazed five years earlier in the same school with the very same teachers. Throughout my years in Vienna I felt that his was an intellectual virtuosity that I would never match. By the time I began reading and writing, he already was starting to master Greek and to play the piano.My fondest early memories are of family get-togethers and vacations. On Sunday afternoons my Aunt Minna (my mother’s sister) and Uncle Srul would come for tea. This was an occasion for my father and uncle to play cards, games at which my father excelled and which brought out great animation and humor in him. We celebrated Passover in a festive way at the home of my grandparents Hersch and Dora Zimels, and we invariably went on vacation in August to Monichkirchen, a small farming village in the southeast portion of Lower Austria, not far from Vienna.It was just as we were about to depart for Monichkirchen in July of 1934 that the Austrian Chancellor, Engelbert Dollfuss, who had outlawed the Nazi Party, was assassinated by a band of Austrian Nazis disguised as policemen – the first political storm to register on my slowly maturing political awareness. Following the Dollfuss assassination and during the early years of the chancellorship of his successor, Kurt von Schuschnigg, the Austrian Nazi Party went further underground, but it continued nonetheless to gain new adherents, especially among teachers and other civil servants. Paradoxically, the Austrian drive toward authoritarianism was abetted by Dollfuss’s own political attitudes and actions. Modeling himself on both Mussolini and Hitler, Dollfuss renamed his Christian Socialist Party the *Fatherland Front*, and took to wearing a modified swastika. To assure his own control of the government he abolished Austria’s Constitution and outlawed not only the Nazi Party but *all* opposition parties. Thus, although Dollfus opposed the efforts of the Austrian National Socialist movement to form a Pan-German state with Germany, his abolition of the Constitution and of other political parties helped open the door for Hitler to march in.And, as I well remember, march in he did. Since his youth, Hitler had dreamed of the union of Austria and Germany. It is therefore not surprising that a key point in the Nazi program, from its beginning in the 1920s, was a merger of all German-speaking people into a Greater Germany. In the fall of 1937 Hitler began to act on this program by raising the level of rhetoric and threatening to move against Austria. Schuschnigg, eager to assert Austria’s independence, met with Hitler on February 12, 1938 in Berchtesgaden. Hitler showed up with two of his generals in tow and threatened to invade Austria unless Schuschnigg, lifted the legal restrictions on the Austrian Nazi Party and appointed three Austrian Nazis to key ministerial positions in the Austrian Cabinet. Schuschnigg refused, but as Hitler continued to intimidate him, Schuschnigg compromised and agreed to a legalization of the Nazi party and to granting it two cabinet positions. The agreement between Schuschnigg and Hitler so emboldened the Austrian Nazis that they began to challenge the Austrian government in a series of incidents that the police had difficulty controlling. Faced with Hitler’s aggression from without and the Austrian Nazi rebellion from within, Schuschnigg took the offensive on March 9th and boldly called for a plebiscite on Austria’s autonomy to be held four days later, on March 13th.This courageous move caught Hitler by complete surprise, an awkward surprise since it seemed almost certain that the vote would favor an independent Austria. Hitler responded by mobilizing troops and threatening to invade Austria unless Schuschnigg postponed the plebiscite, resigned as chancellor, and formed a new government with an Austrian Nazi, Arthur Seyss-Inquart as chancellor. Schuschnigg turned for help to England and Italy, two countries that had formerly supported Austrian independence. But on this occasion both countries failed him and did not respond. Abandoned by his potential allies and concerned about needless bloodshed, Schuschnigg resigned on the evening of March 11th. “Austria is yielding to force,” he announced in an emotional farewell radio address to the nation. “God protect Austria.” Even though Schuschnigg had resigned and President Miklos of Austria gave in to all the German conditions Hitler nonetheless invaded Austria.Hitler’s triumphal march into Vienna and his overwhelming reception by the Viennese public made an indelible impression on me. My brother had just finished building his first short-wave radio receiver, and on the evening of March 13th we both were listening with earphones as the broadcaster described the earlier crossing of the Austrian border by German troops on the morning of March 12th. Hitler followed later in the afternoon of that day, crossing the border first at Braunnau am Inn, his native village, and then moving into Linz, the capitol of Upper Austria, where people welcomed him in the marketplace as their native son, screaming “Heil Hitler.” Of the 120,000 people of Linz, almost 100,000 came out to greet Hitler. In the background the Horst Wessel song, one of the hypnotic Nazi marching songs that even I found captivating, blared forth. On the afternoon of March 14th Hitler’s entourage reached Vienna, where a wildly enthusiastic crowd welcomed him as the hero who had unified the German-speaking people.The extraordinary reception in Linz and Vienna caused Hitler to change his plan. He now realized the Austrians would not demand the status of a relatively independent protectorate of Germany he had planned for them. The enthusiastic welcome convinced him that Austria would readily accept, indeed would welcome, total annexation. For it seemed as if everyone, from the modest shopkeepers to the most elevated members of the academic community, now embraced Hitler. In a shocking move, even Theodor Cardinal Innitzer, the influential Archbischop of Vienna, welcomed Hitler and ordered all the Catholic churches in the city to fly the Nazi flag and to ring the church bells in honor of Hitler’s arrival in Vienna. As the Cardinal personally greeted Hitler, he assured him of his own loyalty and that of all Austrian Catholics – which was most of the population of Austria. The Cardinal promised Hitler that Austria’s Catholics would become “the truest sons of the great Reich into whose arms they had been brought back on this momentous day,” provided that the liberties of the Church were respected and its role in the education of the young guaranteed.That night, and for days on end, all hell broke loose. Viennese mobs erupted in nationalistic fervor, expressed by beating up Jews and destroying their property. Foreign commentators, long accustomed to Nazi tactics in Germany, were astonished by the wanton brutality of the Austrian Nazis, and even German Nazis were amazed and emboldened by the viciousness of the attacks in Vienna.In his autobiography the German playwright Carl Zuckmayer, who had moved to Austria in 1936 to escape Hitler, described Vienna during the days following the annexation of Austria as a city transformed “into a nightmare painting of Hieronymus Bosch.” It was as if:… “Hades had opened its gates and vomited forth the basest, most despicable, most horrible demons. In the course of my life I had seen something of untrammeled human insights of horror or panic. I had taken part in a dozen battles in the First World War, had experienced barrages, gassings, going over the top. I had witnessed the turmoil of the post-war era, the crushing uprisings, street battles, meeting hall brawls. I was present among the bystanders during the Hitler Putsch in 1923 in Munich. I saw the early period of Nazi rule in Berlin. But none of this was comparable to those days in Vienna. What was unleashed upon Vienna had nothing to do with seizure of power in Germany … What was unleashed upon Vienna was a torrent of envy, jealousy, bitterness, blind, malignant craving for revenge. All better instincts were silenced … only the torpid masses had been unchained … It was the witch’s Sabbath of the mob. All that makes for human dignity was buried.”Having watched the build-up of anti-Jewish laws in Germany following Hitler’s rise to power in 1933, my parents did not need much convincing to realize that the violence at the time of the annexation was not likely to fade away. We knew that we had to leave – and to leave as soon as possible. My mother’s brother, Berman Zimels, had emigrated a decade earlier to New York and established himself as an accountant. He provided us expeditiously with affidavits that assured he would support us upon our arrival in the United States. Even with these affidavits it took about a year for my parents’ Polish quota number to be called. When our number finally was called, we had to emigrate in stages because of United States immigration laws. My mother’s parents left first in February 1939, my brother and I next in April 1939, and finally my parents in September 1939, only days before World War II broke out.During the one year that we lived under Nazi rule, we experienced directly Vienna’s humiliating form of anti-Semitism. The day after Hitler marched into Vienna, every one of my non-Jewish classmates – the entire class with the exception of one girl – stopped talking and interacting with me. In the park where I played I was taunted and roughed up. This viciousness toward Jews, of which my treatment was a mild example, culminated in the horrors of Kristallnacht, November 8, 1938. On the morning of November 7, 1938, a 17 year-old Jewish youth, who was distraught over his parent’s tragic fate at the hands of the Nazis, shot a third secretary in the German Embassy in Paris, mistaking him for the German Ambassador. In retaliation for this single act, almost every synagogue in Germany and Austria was set on fire. Of all the cities under Nazi control, the destructiveness in Vienna on Kristallnacht was particularly wanton. Jews were taunted and brutally beaten, expelled from their businesses, and temporarily evicted from their homes so that both could be looted by their neighbors. My father was rounded up by the police together with hundreds of other Jewish men. He was released a few days later only because he had fought in the Austria-Hungarian army as a soldier in World War I. I remember Kristallnacht even today, more than 60 years later, almost as if it were yesterday. It fell two days after my ninth birthday, on which I was showered with toys from my father’s shop. When we returned to our apartment a week or so after having been evicted, everything of value was gone, including my toys.My last year in Vienna was, in a way, a defining year, and it fostered the profound sense of gratitude I came to feel for the life I have led in the United States. It is probably futile, even for someone trained in psychoanalytic thinking as I am, to attempt to trace the complex interests and actions of my later life to a few selected experiences of my youth. Nevertheless I cannot help but think that the experiences of my last year in Vienna helped to determine my later interests in the mind, in how people behave, the unpredictability of motivation, and the persistence of memory. Over the years I have returned to these subjects repeatedly as my professional interests evolved from a youthful interest in European intellectual history at Harvard, where I studied the motivation of German intellectuals during the Nazi era, to an interest in psychoanalysis with its more systematic approach to mental processes, and finally to my interests in the biology of conscious and unconscious memory.My early experiences in Vienna almost certainly contributed to my curiosity about the contradictions and complexities of human behavior. How are we to understand the sudden release of such great viciousness in so many people? How could a highly educated and cultured society, a society that at one historical moment nourished the music of Haydn, Mozart, and Beethoven, in the next historical moment sink into barbarism?Clearly the answer to this question is complex, and many scholars of this period have attempted partial answers. One conclusion, troubling to an academic like myself, is that a society’s culture is not a reliable indicator of its respect for human life. This rather simplistic conclusion, of course, raises the question: How can values within a society become so radically dissociated? As far as I can tell, the Viennese achieved this dissociation by shifting their frame of reference. By defining Jews in racial rather than religious terms, they were able to exclude Jews from the “more highly evolved European Aryan race,” the race they believed to be responsible for the rise of Western civilization.My last year in Vienna was likely also an important factor in my more specific later interest in the mechanisms of memory. I am struck, as others have been, at how deeply these traumatic events of my childhood became burned into memory – and I would emphasize that my experiences were trivial compared to those of so many who were seriously harmed or killed. For me, the frightening experiences of my last year in Vienna are certainly the most powerful of my “flashbulb memories,” the emotionally charged and vivid memory of significant events that came to fascinate me.Resettlement in the United States Needless to say, arriving in the United States in April of 1939 was like a breath of fresh air. I never actually said “free at last,” but I felt it then and have ever since. We settled in Brooklyn and lived at first with my mother’s parents. My grandfather Hersch Zimels was a religious and scholarly man who was somewhat unworldly. My brother said that my grandfather was the only man he knew who could speak seven languages but could not make himself understood in any one of them. My grandfather and I liked each other a great deal, and he readily convinced me that he should tutor me in Hebrew during the summer of 1939 so that I might be eligible for a scholarship at the Yeshiva of Flatbush, an excellent Hebrew parochial school that offered both secular and religious studies at a very high level. With his tutelage I entered the Yeshiva in the fall of 1939. By the time I graduated in 1944 I spoke Hebrew almost as well as English, had read through the five books of Moses, the books of Kings, the Prophets and the Judges in Hebrew, and also learned a smattering of the Talmud.After my parents arrived, my father worked in a toothbrush factory. Even though he was not fond of working in this factory, he threw himself into the work with his usual energy and was soon reprimanded by the union steward for producing toothbrushes too quickly and making other workers appear slow. My father was undeterred. He simply loved America – he often referred to it as the “goldene Medina,” the golden state. Even while still in Vienna he had read avidly the novels of Karl May, an author whose books celebrated the conquest of the American West and the bravery of the American Indians.With time my father managed to save enough money to rent and outfit a modest clothing store at 411 Church Avenue in Brooklyn. We lived in an apartment above the store. My father and mother worked together and sold simple women’s dresses and aprons, and men’s shirts, ties, underwear, and pajamas. In this way my parents earned enough not only to support us all but also to send me to college and medical school. My father worked in that store until the week before he died at age 78 in 1976. My mother sold the store soon thereafter and died in 1991 at age 94.Erasmus Hall High School and Harvard College In 1944, when I graduated from the Yeshiva of Flatbush elementary school, it did not as yet have a high school. I went instead to Erasmus Hall High School, a local public high school in Brooklyn that was then academically very strong. Here I became interested in history, in writing, and in girls. I worked on the school newspaper and became sports editor. I also played soccer and was co-captain of the track team. At the urging of one of my history teachers, John Campagna, a Harvard alumnus, I applied to Harvard College and was one of two students out of my class of about 1,400 to be admitted, both of us on scholarships! Fair Harvard indeed!Even though I was thrilled by my good fortune, I was apprehensive about leaving Erasmus, convinced that I would never again feel the sheer joy I had experienced there. It was at Erasmus that I first sensed myself emerging from behind the shadow of my brother Lewis. I now had distinctive interests of my own – jazz music, sports, American constitutional history – things that did not interest Lewis. At Harvard I majored in 19th and 20th century European history and literature and wrote my honors dissertation on *The Attitude Toward National Socialism of Three German Writers: Carl Zuckmayer, Hans Carossa, and Ernst Junger*. Each of these writers was then still alive and represented a different position on the political spectrum of fascism – uncompromising liberal opposition and emigration (Zuckmayer), resigned acceptance and internal (spiritual) emigration (Carossa), and intellectual support (Junger). I came to the rather depressing conclusion that many German artists, intellectuals, and academics succumbed all too eagerly and opportunistically to the nationalistic fervor and racist propaganda of National Socialism. Historical studies have found that Hitler did not have widespread popular support in his first year in office. Had intellectuals mobilized effectively and brought along segments of the general population, Hitler’s government might well have been toppled.I originally thought of doing graduate work in European intellectual history, along the lines of my undergraduate dissertation. However, in the course of my studies at Harvard I befriended a fellow student, Anna Kris, who had also emigrated from Vienna with her parents, Ernst and Marianne Kris, both prominent psychoanalysts from Freud’s circle. Anna and her parents were very influential in getting me interested in psychoanalysis. It is difficult to recapture now the extraordinary fascination that psychoanalysis held for young people in 1950. During the first half of the 20th century psychoanalysis provided a remarkable set of insights into the mind – insights about unconscious mental processes, psychic determinism, and perhaps most interesting, the irrationality of human motivation. As a result, in 1950, psychoanalysis outlined by far the most coherent, interesting, and nuanced view of the human mind than did any other school of psychology. In addition, Anna’s parents, who represented academic psychoanalysis in its most intellectual and interesting form, were extraordinary people – intelligent, cultured, and filled with enthusiasm. Ernst Kris, a former curator of applied art at the Kunsthistorisches Museum in Vienna, had been a world class art historian before becoming a psychoanalyst. After taking up psychoanalysis, he focused on the psychology of art, an area in which he helped train among others the great historian Ernst Gombrich. Marianne Kris, a wonderful therapist, was the daughter of Oskar Rie, a well-known Viennese pediatrician and Freud’s best friend. Marianne in turn was a close friend of Freud’s distinguished daughter, Anna Freud.Both Ernst and Marianne Kris were extremely generous and encouraging to me, as they were to Anna’s other friends. As a result of my frequent interactions with them and their colleagues, I was converted to their view that psychoanalysis offered a fascinating new approach, perhaps the only approach, to understanding the mind, including the irrational nature of motivation and unconscious and conscious memory. With time this began to seem much more exciting and interesting to me than European literature and intellectual history.Medical School at N.Y.U. To become a practicing psychoanalyst, however, it was best to go to medical school, become a physician, and train as a psychiatrist – a course of study I had not previously considered. So in 1951, almost impulsively, I went to summer school at Harvard and took the required course in introductory chemistry. That summer in Cambridge I shared a house with Robert Goldberger, Henry Nunberg, James Schwartz, and Robert Spitzer, and we all became lifelong friends. A few months later, based on this one chemistry course and my overall college record, I was accepted at N.Y.U. Medical School, with the proviso that I complete the remaining course requirements before I entered medical school in the fall of 1952.I entered N.Y.U. Medical School dedicated to studying psychiatry and becoming a psychoanalyst. Although I stayed with this career plan through my internship and psychiatric residency, by my senior year in medical school I had become so interested in the biological basis of medical practice (as had everyone else in my class) that I decided I had to learn something about the biology of the mind. In the 1950s most psychoanalysts thought of the mind in nonbiological terms. However, several psychoanalysts – particularly two that I got to know personally and who had a background in neurology, Lawrence Kubie and Mortimer Ostow – had begun to discuss the potential importance of the biology of the brain for the future of psychoanalysis. After considerable discussion with them and with another biologically oriented psychoanalyst, Sydney Margolin, I decided to take an elective period at Columbia University with Harry Grundfest. At that time N.Y.U. had no one on the faculty who was doing basic neural science, and in 1955, Grundfest was the most intellectually interesting neurobiologist in the New York area.Harry Grundfest’s laboratory at Columbia University Grundfest had obtained his Ph.D. in zoology and physiology at Columbia in 1930 and went on to a post-doctoral fellowship at Columbia, studying with Selig Hecht, an outstanding psychophysicist interested in phototransduction – the transformation of light into neural signals. (Hecht also was the teacher of [George Wald](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1967/index.html), who won the Nobel Prize in 1967 for discovering the chemical structure of the visual pigments.) Grundfest then joined the Rockefeller Institute in 1935, where he remained for a decade collaborating with [Herbert Gasser](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1944/index.html). In 1944, while Grundfest was in his lab, Gasser shared the Nobel Prize in Physiology or Medicine with [Joseph Erlanger](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1944/index.html) for introducing the oscilloscope to neurophysiological studies. This methodology allowed accurate temporal resolution of the waveform and conduction velocities of the propagated action potential. In collaboration with Grundfest, Gasser elaborated on his discovery that the conduction velocity of the action potential is a function of the diameter of the axon. Grundfest also carried out reconstructions of the compound action potential from cross-sectional measurements of axonal diameters in mixed nerves, work that formed much of [Gasser’s Nobel Prize Lecture](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1944/gasser-lecture.html).In my decision to work with Grundfest, I was strongly encouraged by a new friend, Denise Bystryn, an extremely attractive and interesting French woman I had just met and would later marry. Denise is also Jewish. Her mother helped her father escape from a French concentration camp, and her parents survived the war by hiding from the Nazis in the southwest of France. During a good part of that time Denise was separated from her parents, hidden in a Catholic convent near Cahors. Denise’s experiences, although more difficult, paralleled mine in a number of ways that seemed significant to her but did not seem at all important to me when we first met. However, over the years, our shared experiences in Europe proved to be defining in both our lives.In 1949, Denise, her brother Jean-Claude, and her parents emigrated to the United States. Denise attended the Lycée Français de New York for one year and was admitted at age 17 to Bryn Mawr College as a junior. On graduating from Bryn Mawr at age 19, she enrolled at Columbia University as a graduate student in sociology. When we met she had just started research for her Ph.D. thesis in medical sociology with Robert Merton. Denise’s father, a gifted mechanical engineer who unfortunately died one year before I met Denise, had advised her to marry a poor intellectual because he would likely be sufficiently ambitious to do interesting scholarship. Denise believed she was following that advice (she certainly married someone who was poor) and always encouraged me to make decisions that favored my doing science.In Grundfest’s lab I spent the first several months working on a number of projects with Dominick Purpura, an independent young scientist just starting out on his own career of cortical physiology. To my surprise I found my first experience in a lab really interesting, and very different from the classroom. Of course the research questions we were asking fascinated me and the discussions were penetrating and enjoyable. Dominick was very bright and very entertaining. (I have referred to him as the Woody Allen of neurobiology.) But the actual performance of the experiments was also pleasurable and, when successful, very satisfying. Nevertheless, I began to worry about the methods we were using to address rather sophisticated questions about the electrical properties of dendrites. We were using evoked responses that were initiated by stimulating small areas of cortex, thereby activating thousands of neurons, and I thought these methods were too indirect to give easily interpretable results. Grundfest and Purpura, of course, were also concerned and talked repeatedly about doing direct intracellular recordings from cortical neurons, but neither thought this was likely to succeed.An introduction to Stephen Kuffler It was in this frame of mind that I was introduced to Stephen Kuffler, a Viennese trained physician turned physiologist, who (together with [Bernard Katz](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1970/index.html) and [John Eccles](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html)) was to become one of my great neurobiological heroes. One evening Grundfest threw into my lap the September 20, 1955 issue of the *Journal of General Physiology*, with three of Kuffler’s papers on excitation and inhibition in the dendrites and soma of isolated sensory nerve cells of the lobster and crayfish. Grundfest said something about Kuffler’s being very good, and that these papers provided direct evidence for the graded properties of dendrites evidence that was consistent with what he and Purpura were seeing in cortica; neurons. I took the issue home and read the papers as best I could. Although I understood relatively little, one thing stood out immediately. Kuffler was studying the dendrites in a preparation in which he actually saw the dendrites and could record from them directly. For studying dendrites Kuffler used an invertebrate sensory neuron that sent its dendrites into skeletal muscle much like the muscle spindles of vertebrates. In the introduction to the three papers Kuffler wrote:“The greatest advantage of the present preparation lies in its accessibility, since all cellular components can be isolated and visually observed. Further, the state of excitability of the structures could be controlled and graded by utilizing the physiological mechanisms given by the stretch receptor nature of the preparation…It seems of special interest that the sensory cell of crustacea possessed numerous anatomical features, which bear a striking resemblance to many central nervous system cells of vertebrates.”I learned from Kuffler’s papers a new criterion for how good science is done – the importance of having a preparation suitable to testing the questions to be answered. Kuffler taught me to respect the power of invertebrate neurobiology.On graduating from medical school in June 1956, I married Denise and, after a brief honeymoon in Tanglewood, I started an internship at Montefiore Hospital as she continued her thesis research at Columbia. I returned to Grundfest’s lab, spending six weeks with Stanley Crain, who had pioneered the electrophysiological study of nerve cells in tissue culture. Stanley taught me how to make microelectrodes and how to obtain and interpret intracellular recordings from the crayfish giant axon. These experiments confirmed the insights I had gained from reading Kuffler’s paper. From Stanley I also received my first insights into the universality of cellular processes.Based on my two brief periods in his laboratory, Grundfest offered to nominate me for a position at the NIH, an alternative to serving in the physician’s draft, which provided medical personnel for the military during the years following the Korean War. On the basis of Grundfest’s recommendation, I was accepted by Wade Marshall, Chief of the Laboratory of Neurophysiology at NIMH/NINCDS.The laboratory of neurophysiology at the National Institutes of Health By the time I arrived in Bethesda, Wade Marshall had passed the peak of what had been a remarkable career. In the 1930s he was arguably the most promising and accomplished young scientist working on the brain in the United States. As a graduate student at the University of Chicago in Ralph Gerard’s lab in 1936, he discovered that one could record electrical deflections in the somatosensory processing area of the cerebral cortex by moving the hairs of a cat’s limb. He appreciated that one might use this electrical signal (the evoked response) to map the representation of the body surface on the brain.To study this further, he joined Phillip Bard, Chairman of the Department of Physiology at the Johns Hopkins Medical School, as a post-doctoral fellow. In 1937, Bard had already established himself as a major presence in American neurophysiology. Together with his student Clinton Woolsey, Bard had surgically removed the somatic sensory cortex of the monkey and studied its effect on the “placing reaction,” a form of tactile behavior. Marshall joined up with Woolsey and Bard and together they carried out a classic series of studies in which they mapped sensory inputs from the body surface in the somatic sensory cortex and showed that a topographical representation of the entire body is wired into the brain. This provided the first systematic view of the neural representation in the brain of a sensory system. Today, this map is still shown in every textbook of neural science. Marshall next collaborated with John Talbott and mapped the retinal inputs in the striate cortex. Finally, with Harlow W. Ades, he mapped the cochlear inputs in the auditory cortex.With these classic studies Marshall revolutionized the study of the sensory representations in the brain and showed that the brain had systematic topographical maps of the sensory surface for each of the three major sensations – touch, vision, and hearing. These marvelous scientific achievements came at a price, however, leaving Marshall so psychologically fatigued that he collapsed and, for a number of years, left science altogether. When he returned, in about 1945, he moved on to a completely new problem: the study of spreading cortical depression, a propagating, reversible silencing of cortical electrical activity. Marshall enjoyed doing occasional experiments, but he had lost his scientific drive and now focused much of his energy and interests on administrative matters, which he did well. Although eccentric, moody, and somewhat unpredictable, he was a wonderful lab chief. In particular, he was supportive and generous to young scientists and gave us a great deal of freedom.Just before I arrived at NIH in 1957, the neurosurgeon William Scoville and the cognitive psychologist Brenda Milner had described the now-famous patient H.M. In order to treat intractable bilateral temporal lobe epilepsy, Scoville had removed on both sides of H.M.’s brain the medial temporal lobes, including a structure deep to them called the hippocampus. As a result of this procedure, H.M.’s seizures were largely eliminated. But, while retaining all cognitive functions, H.M. lost the ability to put new information into long-term memory. These findings pinpointed the medial temporal lobe and the hippocampus as sites specialized for memory storage.Until the Scoville and Milner paper, the person most identified with attempts to localize memory was Karl Lashley, Professor of Psychology at Harvard and perhaps the dominant figure in American neuropsychology in the first half of the 20th century. Lashley explored the surface of the cerebral cortex in the rat, and systematically removed different cortical areas. In so doing, he failed to identify any particular brain region that was special to or necessary for the storage of memory. Based on these experiments, Lashley formulated the law of mass action, according to which memory is not localized to any specific region of the cortex but was a distributed property of the cortex as a whole. The extent of any memory defect, Lashley argued, was correlated with the size of the cortical area removed, not with its specific location.Since I had already begun to think about problems in psychiatry and psychoanalysis in biological terms, the cell and molecular mechanisms of learning and memory struck me as a wonderful problem to study. I had first become interested in the study of learning at Harvard, where B.F. Skinner, the great behaviorist, was a dominant force in the 1950s. It was clear to me even then that learning and memory were central to behavior, and thus to psychopathology and to psychotherapy. Nothing was known about the cellular mechanisms of learning and memory, and now the cellular techniques for studying them were just becoming available – some beginnings of which I had learned from Stanley Crain in Grundfest’s lab.My initial ideas about how to tackle the biology of memory upon arrival at the NIH were confused and vague. Because intracellular recordings seemed to me such a powerful analytic tool for studying nerve cells, and because the hippocampus seemed particularly important for memory, I wanted to explore the hippocampus in cellular terms. This was made even more attractive for me because, as the great Spanish anatomists [Ramón y Cajal](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1906/index.html) and Lorente de Nó had pointed out, the cellular architecture of the hippocampus is remarkably conserved among mammals, and the main cell type, the pyramidal cell, is found in a discrete layer that is easy to target with microelectrodes. In addition, the pyramidal cells send their axons into a large fiber tract (the fornix), which allows the pyramidal cells to be identified electrophysiologically by stimulating the axons in the fornix and backfiring the pyramidal cells. I thought it would be interesting to compare the pyramidal neurons to the only other mammalian neurons that had been well studied at that time – the motor neurons of the spinal cord. I had the idea that the properties of the pyramidal cells themselves might reveal something about memory storage. I was emboldened to try this technically demanding study because Karl Frank was in the laboratory next to ours, pioneering the examination of spinal motor neurons with intracellular recordings in parallel with John Eccles. Although Frank himself thought that studying the hippocampus was chancy, he was not discouraging.Almost as soon as I began, my research took an extremely fortunate turn in the person of Alden Spencer, who arrived in Marshall’s lab having just graduated from the University of Oregon Medical School. Like me, Alden was becoming interested in the biology of learning and memory. It therefore took little effort for me to convince him that we should join forces on the hippocampus. Although Alden had no experience with intracellular recordings, he had done electrophysiological research on the brain at the University of Oregon Medical School, where he worked with John Brookhardt. Among Alden’s many remarkable talents, he had good surgical skills and a fine knowledge of the anatomical organization of the mammalian brain.Being both naïve and brash, we were not reluctant to tackle what appeared to Frank and others to be technically difficult problems, namely obtaining intracellular recordings from cortical neurons in a pulsating brain. Alden and I developed a simple way of reducing pulsations in the hippocampus that allowed us to obtain, on occasion, high-quality recordings for a long enough period – up to one hour – to carry out an initial analysis of the electrical properties of the hippocampal pyramidal cells. By applying to the hippocampus the powerful methodologies we learned from Frank, we easily picked some low-lying intellectual fruit. First, we found that action potentials in hippocampal neurons were initiated not only at the axon hillock, as in motor neurons, but also at a second site, which we inferred to be the apical dendrites. These putative dendritic action potentials, which we called fast prepotentials, appeared to trigger the firing at the axon hillock. Second, we found that the hippocampal neurons, unlike motor neurons, were not silent in the absence of synaptic activity, but tended to fire spontaneously, and that this firing often took the form of bursts of spikes that were maintained by summation of depolarizing afterpotentials. Third, we found that the hippocampal neurons engaged a powerful recurrent inhibitory system that gave rise to a prolonged inhibition – several orders of magnitude longer than the inhibition seen in the spinal cord.The mere technical success of obtaining intracellular recordings from hippocampal neurons, and the few interesting questions we were able to address, caught the enthusiastic attention of, and drew encouragement and help from, our senior colleagues at the NIH – Marshall, Frank, Michael Fuortes, Frank’s gifted colleague and the great Japanese-American biophysicist Ichiji Tasaki. When John Eccles visited the NIH, he also was generous in his comments. But even in our brashest moments, we both realized that ours was a typical NIH story. In the Intramural Program at the NIH, young inexperienced people were given the opportunity to try things on their own, knowing that wherever they turned there were experienced people to help out.Moreover, as Alden and I reviewed our work we realized that the cellular properties of hippocampal neurons were not sufficiently different from those of spinal neurons to explain the ability of the hippocampus to store memory. Thus, it dawned on us what in retrospect is quite obvious: that the neuronal mechanisms of learning and memory probably did not reside in the properties of the neurons themselves. Rather, because the signaling properties of neurons are quite alike, we began to think that what must matter is how neurons are functionally connected. The basis of learning must reside in the modification of interconnections by appropriate sensory signals. This conclusion, so clear in retrospect, emerged only gradually as we learned, mostly through reading and discussions with one another, to think more effectively about the biology of learning and memory.This realization led us to reappraise our strategy. Since the hippocampus has a large number of neurons and an immense number of interconnections, it was not the place to begin. Even though we were now quite familiar with the hippocampus, it would be extremely difficult to work out how sensory information specific to learning reached the hippocampus or how learned information processed by the hippocampus might influence motor output.Alden and I therefore became convinced that to make headway with the study of learning at the cellular level required a very different approach. Alden, a committed mammalian neurophysiologist, turned to the study of the spinal cord, particularly the modifiability of spinal reflexes, and went on to make important contributions in collaboration with Richard Thompson.However, even the spinal cord proved too difficult for a detailed cellular analysis, and both Alden and Thompson ended up leaving it.The search for a tractable system for studying learning Influenced by Kuffler, Grundfest, and Crain, I yearned for a more radically reductionist approach to the biology of learning and memory. I wanted a system that would serve the cellular study of learning as well as the squid giant axon had served for studies of the action potential, or the nerve-muscle synapse of the frog had served for the study of synaptic transmission. I wanted to examine learning in an experimental animal in which a simple behavior was modifiable by learning. Ideally that behavior should be controlled by only a small number of large and accessible nerve cells, so that the animal’s overt behavior could be related to events occurring in the cells that control that behavior.Such a reductionist approach has been traditional in biology. In neurobiology it is exemplified by the work on the squid giant axon by [Hodgkin](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html) and [Huxley](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html), the nerve-muscle synapse of the frog by Bernard Katz, and the eye of *Limulus* by [Keefer Hartline](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1967/index.html). When it came to the study of behavior, however, most investigators were reluctant to apply a strict reductionist strategy. In the 1950s and 1960s it was often said that behavior was the area in biology in which simple animal models, particularly invertebrate ones, were least likely to produce fruitful results because the brain that really learns, the mammalian brain, especially the human brain, is so complex that inferences from studies of invertebrates would not stand up. It was thought that humans, because of higher-order capabilities not found in simpler animals, must have types of neuronal organization that are qualitatively different from those found in invertebrates. Although these arguments held some truth, they overlooked certain critical issues. Work by students of comparative behavior, such as [Konrad Lorenz](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1973/index.html), [Niko Tinbergen](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1973/index.html), and [Karl von Frisch](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1973/index.html), had already shown that certain behavior patterns, including elementary forms of learning, were common to humans and simple animals. From the outset I therefore believed that the mechanisms of memory storage were likely to be conserved in phylogeny, and that a cellular analysis of learning in a simple animal would reveal universal mechanisms that are also employed in more complex organisms.Not surprisingly, I was strongly discouraged in the early days from pursuing this strategy by some senior researchers in neurobiology, particularly John Eccles. His concern reflected, in part, the existing hierarchy of acceptable research questions in neurobiology. Few self-respecting neurophysiologists, I was told, would leave the study of learning in mammals to work on an invertebrate. Was I compromising my career? Of an even greater concern to me were the doubts expressed by some very knowledgeable psychologists I knew, who were sincerely skeptical that anything interesting about learning and memory could be found in a simple invertebrate animal. I had made up my mind, however. Since we knew nothing about the cell biology of learning and memory, I believed that any insight into the modification of behavior by experience, no matter how simple the animal or the task, would prove to be highly informative.After an extensive search that included crayfish, lobster, flies, and the nematode worm *Ascaris*, I settled on *Aplysia*, the giant marine snail. *Aplysia* offered three major technical advantages: (1) its nervous system has a small number of cells, (2) the cells are unusually large, and, as I realized with time, (3) many of the cells are invariant and identifiable as unique individuals. Before leaving the NIH in 1960, I arranged with Ladislav Tauc, one of the two people in the world then working on *Aplysia*, to join him in September 1962, as a postdoctoral fellow, as soon as I had completed my residency training. Here again, Denise’s advice was decisive. The only two people working on *Aplysia* were French – Tauc’s lab was in Paris, and Angelique Arvanitaki-Chalazonitis worked in Marseilles. So far so good! But, Denise, ever the Parisian chauvinist, thought that living in Marseilles would be like living in Albany (a small town in upstate New York). So Tauc and Paris it was, and that proved an excellent choice.Residency training in psychiatry at the Harvard Medical School However, before I would leave for Paris I had already committed to a two-year residency training in psychiatry. I therefore left the NIH in the spring of 1960 to start my psychiatric residency at the Massachusetts Mental Health Center of the Harvard Medical School. When I arrived at Harvard, I found an unanticipated bonus. Steven Kuffler, whose thinking had so influenced my own, had been recruited one year earlier from Johns Hopkins to build up neurophysiology at Harvard. Kuffler brought with him several young post-doctoral fellows – [David Hubel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/index.html), [Torsten Wiesel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/index.html), Ed Furshpan, and David Potter – each of whom was extraordinarily gifted. In this way Kuffler succeeded, in one fell swoop, in setting up at Harvard the premier group of neural scientists in the country. I now had my first opportunity to interact with Kuffler and with the remarkable people he had assembled around him. Even though I was in fulltime residency training, Kuffler and his group were extremely accessible, and their generosity allowed me to remain intellectually engaged in neurobiology. Moreover, Jack Ewalt, the Professor of Psychiatry at the Massachusetts Mental Health Center, provided me with funds and space so that I even managed to do some research in my spare time. I obtained the first intracellular recording from hypothalamic neuro-endocrine cells and found that these hormone-releasing cells had all the electrical properties of normal nerve cells.During my psychiatric residency I began to think about simple forms of learning in preparation for work on *Aplysia*. I read Kimble’s wonderful revision of Hilgard and Marquis’s classical text *Conditioning and Learning*, and I reread Skinner’s great book *The Behavior of Organisms*. This reading made me realize that the paradigms of simple learning articulated by [Pavlov](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1904/index.html) and Thorndyke, describing changes in behavior in response to controlled stimulation, included precise protocols for stimulating experimental animals. It occurred to me that the paradigms they described – habituation, sensitization, classical conditioning, and operant conditioning – could readily be adapted to experiments with an isolated *Aplysia* ganglion using artificial electrical rather than natural sensory stimuli. While recording the behavior of a single cell in a ganglion, one nerve axon pathway to the ganglion could be stimulated weakly electrically as a conditioned stimulus, while another pathway was stimulated as an unconditioned stimulus, following the exact protocol used for classical conditioning with natural stimuli in intact animals. One could then see whether synapses changed systematically in response to these patterns of stimulation, and, if so, whether the synaptic changes in any way paralleled changes in the overt behavior of intact animals, which classical psychologists had described. It thus dawned on me that in this way one could begin to take an initial step toward the study of learning in the intact animal by analyzing what I soon began to call *analogs of learning* – higher-order stimulus sequences based on patterns of stimulation used in learning experiments in intact behaving organisms, but applied directly to a neuronal system.Paris, Aplysia, and neural analogs of learning: chemical synapses prove to be remarkably plastic Based on this idea, I wrote a successful application for an NINCDS postdoctoral fellowship for work to be done in Tauc’s laboratory. And in September 1962, about a year after our son Paul was born, the three of us took off for Paris. Tauc proved an excellent person to work with; both our interests and our areas of competence complemented each other. He was, of course, completely at home with *Aplysia*, but he also had a strong background in physics and biophysics, which I lacked. Born in Czechoslovakia, Tauc had originally studied the electrical properties of plant cells. As a result, he had no experience with behavior and had up to this point thought little about the problems of neuronal integration that dominated thinking about the mammalian brain – problems that Alden and I had discussed incessantly. Tauc was quite enthusiastic about my approach, which proved even more effective than anticipated. In my cellular studies of analogs of habituation, sensitization, and classical conditioning in *Aplysia*, I found synaptic changes that paralleled the behavioral changes seen in experiments on intact animals. This encouraged us to write in our 1965 paper in the *British Journal of Physiology*:“The fact that the EPSPs (excitatory postsynaptic potentials) can be facilitated for over half-an-hour with an input pattern scheme designed to simulate a behavioral conditioning paradigm, also suggests that the concomitant changes in the efficacy of synaptic transmission may underlie certain simple forms of information storage in the intact animal.”A brief return to the Harvard Medical School Upon completing a very productive 16-month stay in Tauc’s laboratory, I returned to Harvard in November 1963. More than a year and a half later, in July of 1965, our daughter Minouche was born, completing our family – one boy, one girl – exactly what we had hoped for.During this period I struggled with three choices that were to have a profound effect on my subsequent career. First, I realized that to do effective science I could not combine basic research and a clinical practice in psychoanalysis, as I had earlier hoped. I therefore decided not to apply to the Boston Psychoanalytic Institute, a decision which meant that I would not attempt to become a psychoanalyst but devote myself full-time to science. It was my strong sense that one of the problems within academic psychiatry, a problem that has become only worse with time, is that young people take on much more than they can handle effectively. I concluded that I could not and would not do that.The second choice arose a few months later when Dr. Ewalt and Dr. Howard Hiatt, then chairmen of the Department of Medicine at the Beth Israel Hospital at Harvard, suggested that I take on the newly vacated chairmanship of the Department of Psychiatry at the Beth Israel Hospital. For a moment I was forced to rethink my decision to focus full time on science. The person who had just left that position, Grete Bibring, was a leading psychoanalyst who had been a colleague of Marianne and Ernst Kris in Vienna. Earlier in my life achieving this position would have represented my highest aspiration. But by 1965, my thinking had moved in a very different direction, and I decided against it with Denise’s strong encouragement. (Denise summarized it simply: ‘What?” she said, “throw your scientific career away?”) Instead, I made my third decision. I decided to leave Harvard and accept an invitation to start a small neurophysiology group focused specifically on the neurobiology of behavior in the Departments of Physiology and Psychiatry at the New York University Medical School.Harvard was quite wonderful, and it was not easy to leave that intellectually heady neurobiology environment. My interaction with Kuffler had increased after my return from Paris and, until his death in 1980, Kuffler proved a marvelous friend and counselor. Moreover, my interactions during this period with members of Kuffler’s group – Hubel, Wiesel, Furshpan, Potter, and Ed Kravitz, a biochemist who joined them later – were extensive and I learned much from them. Many years later, at a small meeting at the Marine Biological Laboratory in Woods Hole in honor of Steve Kuffler, I was surrounded by Steve’s Harvard entourage, some of whom were struggling with the decision of whether to leave Harvard for attractive positions elsewhere. I could not resist beginning my lecture with the remark, “I am here as living proof that there is life after Harvard.”New York University and a focus on the behavior of Aplysia The position at N.Y.U. had several great attractions that, in the long run, proved critical. First, it brought us back to New York and closer to my parents and to Denise’s mother, all of whom were having medical problems that benefited from our being nearby. Second, N.Y.U. gave me the opportunity to recruit an additional senior neurophysiologist, and Alden Spencer agreed to move to N.Y.U. from the University of Oregon Medical School where he had returned after his stay at the NIH, and to occupy the laboratory next to mine. Although Alden and I never collaborated experimentally again, we talked daily not only about our science – the neurobiology of behavior – but also about almost everything else, until his untimely early death at age 46 from amyotrophic lateral sclerosis in 1977, when we had already moved to Columbia University. During the period he was alive, no one influenced my thinking on matters of science as much as Alden. I still think about him frequently.Alden and I arrived at N.Y.U. together in the winter of 1965. Within a year we were joined by a biochemist, James H. Schwartz, whom I had first met in the summer of 1951 at Harvard summer school and who was now a member of the Department of Microbiology at N.Y.U. and was becoming interested in behavior. The three of us formed the nucleus of the Division of Neurobiology and Behavior at N.Y.U.With several important decisions behind me, I made a strong effort to focus on whole-animal behavior. In France I had found that chemical synapses are remarkably plastic; they could readily undergo long-lasting changes in strength. But I had no evidence that these analogs of learning were in fact behaviorally meaningful. I had no reason to believe that these are the sorts of changes that actually occur when an animal learns something. Although during my last few weeks in France I had begun to replicate my results by substituting natural stimuli for electrical stimulation of nerves, I still had not shown that synaptic plasticity actually occurred during behavioral learning. As a first step I thought it essential to show that *Aplysia* was capable of learning. With this in mind, I set about recruiting a postdoctoral fellow with a specific interest in behavioral learning. I was fortunate to recruit, first to Harvard and then to N.Y.U., Irving Kupfermann, an extremely critical and thoughtful student of behavior. We were later joined by another learning psychologist, Harold Pinsker, and together we set about delineating a very simple behavior that we could study: the gill-withdrawal reflex. We quickly found that this simple reflex could readily be modified by two forms of learning: habituation and sensitization.As we explored the two forms of learning, we focused on short-term memory. In 1971, we were joined by another experienced behavioral psychologist, Tom Carew, who brought a new level of energy and insight to our behavioral studies. He arrived as Pinsker was leaving, and soon after we shifted from working with restrained to unrestrained animals, thus opening up the study of long-term memory. Tom found that spaced repetition converted the memory for short-term habituation and sensitization to longer-lasting memories. In 1981, after several unsuccessful attempts, Carew, Terry Walters, Tom Abrams, and Robert Hawkins finally were able to define the conditions for reliably producing classical conditioning in *Aplysia*. This was a particularly exciting period; Carew, Walters, Hawkins, and I met regularly to discuss how to explore whether a simple reflex, in a simple invertebrate, could show the higher-order cognitive features of classical conditioning recently demonstrated in mammals by Leo Kamin and somewhat later by Robert Rescorla and Alan Wagner. Soon, Hawkins indeed was able to demonstrate that the gill-withdrawal reflex can undergo second-order conditioning, blocking, overshadowing and other cognitive aspects of associative learning, features that were surprising to uncover in such a simple behavior.We thus were able to describe a rather rich repertory of learning in *Aplysia*. But long before this inventory of the animal’s behavior was complete, we returned to our initial concerns. What happens in the brain of an animal when it actually learns a task? How does it remember? We proceeded, first with Kupfermann and Vincent Castellucci and then with Jack Byrne and Hawkins, to work out most of the neural circuit of the gill-withdrawal reflex. We identified specific sensory neurons and motor cells that produced movements of the gill. Next, we found that the sensory neurons made direct connections to the motor neurons as well as indirect connections through interneurons, both excitatory and inhibitory. The aversive tail stimuli that produced sensitization of the gill-withdrawal reflex activated modulatory interneurons that acted on terminals of the sensory neurons. We now could turn to think about how learning might occur in this reflex.Cellular mechanisms of learning At the end of the 19th century Ramón y Cajal introduced the principle of connection specificity, according to which, during development, a neuron will form connections only with certain neurons and not with others. Kupfermann, Castellucci, and I saw in the circuitry of the gill-withdrawal reflex of *Aplysia* this remarkable regularity of connections that Cajal referred to and we saw, in exquisite detail, that specific identified cells made invariant connections to one another. But this invariant organization of neurons posed deep questions. How could we reconcile hardwired circuits in the nervous system and the specificity of connections with the animal’s capability for learning? Once acquired, where or how is learned information retained in the nervous system?One solution was proposed by Ramón y Cajal in his Croonian Lecture to the Royal Society of London in 1894 when he suggested that “… mental exercise facilitates a greater development of the protoplasmic apparatus and of the nervous collaterals in the part of the brain in use. In this way, pre-existing connections between groups of cells could be reinforced by multiplication of the terminal branches of protoplasmic appendices and nervous collaterals.”This remarkably prescient idea was by no means generally accepted. On the contrary, different theories of learning at various times held the attention of neural scientists. Two decades after Ramón y Cajal’s proposal, the physiologist Alexander Forbes suggested that memory is sustained not by changes in synaptic strength of the sort suggested by Ramón y Cajal, but by dynamic changes resulting from reverberating activity within a closed loop of self-exciting neurons. This idea was elaborated by Ramón y Cajal’s student, Rafael Lorente de Nó, who found in his own and in Ramón y Cajal’s analyses of neural circuitry neurons that were interconnected in closed pathways and could thereby sustain reverberatory activity, thus providing a dynamic mechanism for information storage. In his influential book *The Organization of Behavior* (1949), D.O. Hebb proposed that a “coincident activity” initiated the growth of new synaptic connections as part of long-term memory storage. But for short-term memory, Hebb invoked a reverberatory circuit:“To account for permanence, some structural change seems necessary, but structural growth presumably would require an appreciable time. If some way can be found of supposing that a reverberatory trace might cooperate with the structural change, and carry the memory until the growth change is made, we should be able to recognize the theoretical value of the trace, which is an activity only without having to ascribe all memory to it. The conception of a transient, unstable reverberatory trace is therefore useful. It is possible to suppose also some more permanent structural change reinforces it.”Similarly, in *The Mammalian Cerebral Cortex*, an influential book of 1958, B. Deslisle Burns challenged the relevance of synaptic plasticity to memory.“The mechanisms of synaptic facilitation which have been offered as candidates for an explanation of memory … have proven disappointing. Before any of them can be accepted as the cellular changes accompanying conditioned reflex formation, one would have to extend considerably the scale of time on which they have been observed to operate. The persistent failure of synaptic facilitation to explain memory makes one wonder whether neurophysiologists have not been looking for the wrong kind of mechanisms.”Indeed, some scholars even minimized the importance of specific neuronal connections in the brain, advocating instead mechanisms of learning that were partially or even totally independent of “pre-established” conduction pathways. This view was held by Wolfgang Kohler and the famous Gestalt psychologists, and subsequently by the neurophysiologists Ross Adey and Frank Morrell. Thus, in 1965, Adey wrote:“No neuron in natural or artificial isolation from other neurons has been shown capable of storing information in the usual notion of memory. … In particular, the possibility exists that extraneuronal compartments may participate importantly in the modulation of the wave process that characterize the intracellular records, and that these wave processes may rank at least equivalently with neuronal firing in the transaction of information and even more importantly in its deposition and recall.”Finally, there were memory macromolecular notions advocated by Holger Hyden, based upon his finding of changes in the nucleotide composition of RNA. He proposed that learning gave rise to a specific pattern of instructional neural activity that altered the stability of RNA molecules, so that one base can exchange for another. In this way, new RNA molecules are formed with new base sequences that are specific to the instructing pattern of neural activity induced by learning. Hyden’s hypothesis thus implied that the patterns of stimulation activated by learning could introduce changes in RNA.We were now therefore in a position to test experimentally which, if any, of these ideas had merit. Using the gill-withdrawal reflex, we quickly established that memory in the *Aplysia* nervous system is not represented in self-exciting loops of neurons but in changes in synaptic strength. We found that all three simple forms of learning – habituation, sensitization, and classical conditioning – lead to changes in the synaptic strength of specific sensory pathways, and that these changes parallel the time course of the memory process. These findings, which had been fully anticipated by our earlier studies of analogs of learning, gave rise to one of the major themes in our thinking about the molecular mechanisms of memory storage. Even though the anatomical connections between neurons develop according to a definite plan, the strength and effectiveness of those connections is not fully determined developmentally and can be altered by experience.We therefore concluded the third of our 1970 series of consecutive papers in Science on the cellular mechanisms of learning with the following comments:“… the data indicate that habituation and dishabituation (sensitization) both involve a change in the functional effectiveness of previously existing excitatory connections. Thus, at least in the simple cases, it seems unnecessary to explain the behavioral modifications by invoking electrical and chemical fields or a unique statistical distribution in a neural aggregate. The capability for behavioral modification seems to be built directly into the neural architecture of the behavioral reflex.Finally, these studies strengthen the assumption … that a prerequisite for studying behavioral modification is the analysis of the wiring diagram underlying the behavior. We have, indeed, found that once the wiring diagram of the behavior is known, the analysis of its modification becomes greatly simplified. Thus, although this analysis pertains to only relatively simple and short-term behavioral modifications, a similar approach may perhaps also be applied to more complex as well as longer lasting learning processes.”A beginning molecular analysis of memory storage Having defined a critical site of plasticity, the situation became ripe for a molecular analysis. Here again I could not have been more fortunate. As I mentioned earlier, soon after I arrived at N.Y.U. I ran into James Schwartz. Jimmy had attended N.Y.U. Medical School two years behind me, but we had not really talked since I left N.Y.U. in 1956. After medical school Jimmy obtained a Ph.D. with Fritz Lipmann at the Rockefeller University, studying enzyme mechanisms and protein translation in cell-free bacteria extracts. As he and I began to talk again, he mentioned that he was thinking of moving from *E. coli* to the brain. *Aplysia* seemed ideal for biochemical study of individual nerve cells, so in 1966, Schwartz and I joined forces to carry out biochemical studies on individual identified nerve cells of *Aplysia*.Jimmy soon showed that each nerve cell in *Aplysia* had a specific transmitter biochemistry. Cells that we had presumed on pharmacological grounds to be cholinergic did in fact synthesize and release acetylcholine. With time, Jimmy became interested in the molecular mechanisms of synaptic plasticity, and together we began to examine the role of protein synthesis in memory storage. We knew from the work of Louis Flexner and Bernard Agranoff in the mid 1960s that long-term memory in vertebrates required protein synthesis whereas short-term memory did not. In our first study together in 1971, we found that blocking protein synthesis for 24 hours did not prevent the short-term synaptic changes associated with habituation and sensitization. That finding made us think that short-term changes representing memory storage might involve activation of a second-messenger pathway, for example, the cyclic AMP (cAMP) cascade, whose actions might persist for periods longer than the millisecond duration of conventional synaptic actions.In the discussion of our 1971 paper on the role of protein synthesis and synaptic plasticity, we wrote:“Alterations in molecular configuration would not be expected to persist for long periods of time, although molecular changes lasting for several minutes have been observed. … Most likely, the biochemical mechanisms underlying these short-term plastic changes are composed of a series of sequential reactions which result in a new distribution of transmitter substance. Mechanisms involving cyclic 3′,5’AMP might serve as one example of a series of reactions which result in transient enhancement in the activity of a critical enzyme system. A pathway of this kind might trigger the mobilization of transmitter from one component (a long term store) to another (an immediately releasable store).… If our conclusion is correct, … rapidly synthesized RNA cannot immediately play a role in neuronal functions; it might however, be important for long-term neuronal processes.”Sutherland and Rall had already shown in brain slices that several neurotransmitters known to exist in the brain could increase the concentrations of cAMP by activating the enzyme adenylyl cyclase that converted ATP to cAMP. We appreciated that we had a particularly good experimental preparation for examining, on the cellular level, the role of second-messenger pathways in synaptic transmission, synaptic plasticity, and memory storage. In 1972, Schwartz, Howard Cedar, and I found that stimulation of the pathway involved in sensitization increased the level of cAMP in the entire abdominal ganglion. Schwartz and Cedar next found that the transmitter serotonin could also increase cAMP, providing the initial evidence that serotonin might activate an adenylyl cyclase in *Aplysia*.Columbia University and the molecular analysis of short-term memory It was at this time that I was invited to move from N.Y.U. to the Columbia University College of Physicians and Surgeons to become the founding director of the Center for Neurobiology and Behavior. I was able to persuade James Schwartz, Alden Spencer, and Irving Kupfermann (who was by then an Associate Professor, having established an independent research program concerned with feeding and motivational state in *Aplysia*) to join me. This move was attractive to me for several reasons. Historically, Columbia has had a strong tradition in neurology and psychiatry, and a friend and former clinical teacher, Lewis Rowland, was about to assume the chairmanship of the Department of Neurology. In addition, I had my first experience in neurobiology at Columbia with Harry Grundfest who was now retiring and I was being recruited to replace him. Finally, Denise was on the Columbia faculty and our house in Riverdale was near Columbia, thereby greatly simplifying our lives.In 1974, just after arriving at Columbia, Castellucci and I went back to the elementary circuit of the gill-withdrawal reflex to determine the exact site of the synaptic change produced by short-term sensitization. We wanted to know which component of the synapse changes. Is it, as we suspected, based on indirect evidence, the presynaptic element of the synapse where chemical transmitter is released, or is it the postsynaptic site which contains the receptors which bind and respond to the transmitter? Using a quantal analysis, we found that the synaptic facilitation characteristic of sensitization is presynaptic and that inhibitors of serotonin block this presynaptic facilitation. Later, Hawkins and I found that tail stimuli that initiate sensitization activate a set of modulatory interneurons, the most important of which are serotonergic. The serotonergic and other modulatory interneurons all acted on the sensory neurons and on their presynaptic terminals to enhance transmitter release from their presynaptic terminals. We could now ask for the first time: Was cAMP directly involved in facilitation? In 1976, Marcello Brunelli could take advantage of the size of the *Aplysia* neurons and inject cAMP directly into the presynaptic sensory cell and thereby find a clear enhancement of synaptic transmission. This cAMP-induced enhancement paralleled the enhancement produced by serotonin or tail stimulation.I now began to interact with Paul Greengard, who was demonstrating that cAMP produced its actions in the brain through the cAMP-dependent protein kinase, or PKA. In 1980, Schwartz, Castellucci, and I collaborated with Greengard. We injected a purified catalytic subunit of bovine PKA into presynaptic sensory neurons and found that it simulated the actions of cAMP or serotonin. Moreover, we could block the actions of serotonin by injecting into the sensory neuron the specific peptide inhibitor of PKA, protein kinase inhibitor PKI. With Steven Siegelbaum we next began to define some of the targets of PKA and focused on one target, a novel K+ channel. Steve showed that this channel is closed by serotonin and by PKA and that this closure is achieved in a manner consistent with the channel being phosphorylated directly by PKA.The Howard Hughes Medical Institute and the molecular analysis of long-term memory Just before I arrived at Columbia, Arnold Kriegstein, an M.D.-Ph.D. student, succeeded in culturing embryonic *Aplysia* in the N.Y.U. laboratory, a quest which had intrigued biologists and eluded their efforts for almost a century. Most of us who were there will not readily forget Kriegstein’s extraordinary in-house seminar in December, 1973 when he first described his discovery that the red seaweed *Laurencia pacifica* is required to trigger metamorphosis from a free-swimming veliger larva to a small crawling snail, a discovery that allowed him to show the first pictures of the beautiful tiny post-metamorphic juvenile *Aplysia*. I remember saying to myself. “Babies are always so beautiful!” Kriegstein’s work opened up the study of development and cell culture in *Aplysia*.Because we now had young animals at all stages of development, we at last had the essential requirements for the generation of dissociated cell culture. This was taken on by Sam Schacher and Eric Proshansky. With the help of Steven Rayport (another M.D.-Ph.D. student at Columbia University), Schacher soon succeeded in culturing the individual sensory neurons, motor neurons, and serotonergic neurons of the gill-withdrawal reflex. The development of the culture system coincided with two other events that allowed me to begin studying the molecular mechanisms of long-term memory storage. The first was my encounter with [Richard Axel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2004/index.html) and my collaboration in 1979, with him and with Richard Scheller, who became a joint post-doctoral fellow. The second was my being recruited to become a senior investigator at the Howard Hughes Medical Institute.Axel and Scheller’s success in 1982 in cloning the gene encoding the egglaying hormone in *Aplysia* seeded Axel’s long-term interest in neurobiology and gave me not only a wonderful friend but also an exposure to the methods of recombinant DNA and modern molecular biology. The very next year, in 1983, Donald Fredrickson, the newly appointed President of the Howard Hughes Medical Research Institute, asked Schwartz, Axel, and me to form the nucleus of a Howard Hughes Medical Research Institute at Columbia devoted to molecular neural science. The Howard Hughes Medical Research Institute gave us the opportunity to recruit from Harvard both Tom Jessell and Gary Struhl, as well as to keep Steven Siegelbaum at Columbia.My first goal on becoming a Highes Investigator was to examine the molecular mechanisms underlying the synaptic changes that parallel long-term memory storage. In 1885, Herman Ebbinghaus transformed speculation about memory into a laboratory science by having subjects memorize lists of nonsense syllables. In this way Ebbinghaus generated two basic principles about memory storage. First, he found that the transition from short-term memory to long-term memory is graded; practice makes perfect. Second, he anticipated the existence of a fundamental distinction between short- and long-term memory.What, then, was the molecular basis for this fundamental distinction between short- and long-term memory? As we have seen, in the mid-1960s Flexner and Agranoff examined this distinction biochemically and found that inhibitors of protein synthesis disrupt long-term memory without adversely affecting learning, or short-term memory. We found that long-term sensitization in *Aplysia* is similarly dependent on protein synthesis, whereas short-term sensitization is not. These findings illustrated the generality of the distinction between short-term and long-term memory processes for both invertebrates and vertebrates. In each case spaced repetition of the learning stimulus acts to transform a transient memory into a more stable (long-term) form by means of a process that depends on new protein synthesis. But how this occurred was a mystery.We had earlier found in *Aplysia* that long-term sensitization involved a persistent increase in the strength of the same synaptic connection altered by the shortterm process – the connections between the sensory and motor neurons of the gill-withdrawal reflex. To study this process more effectively we turned to dissociated cell culture and found that we could reconstitute both short- and long-term synaptic facilitation in a culture consisting of only a single sensory neuron and a single motor neuron. We did this together with Sam Schacher, Philip Goelet, and Pier Giorgio Montarolo by applying either one or five brief spaced pulses of serotonin to the sensory neuron and motor neuron in the culture dish. Much like behavioral long-term memory, the long-term synaptic changes required new protein synthesis while the short-term changes did not. Thus, we had trapped the protein synthesis-dependent component of memory storage in the elementary synaptic connection between two identified cells. We now could address directly the question: Why is protein synthesis required for long-term and not short-term facilitation? What are the molecular steps that switch on long-term facilitation and, once switched on, how is it maintained?We next found that steps for new proteins are activated by a cascade of genes initiated by the cAMP-dependent protein kinase. With repeated application of serotonin, PKA translocates to the nucleus and in so doing activates the MAP kinase (mitogen activated protein kinase), another kinase often recruited for growth. Thus, one of the functions of repeated stimulation was to cause both kinases to move into the nucleus. Pramod Dash and Binyamin Hochner and later Cristina Alberini, Mirella Ghirardi, and Dusan Bartsch provided the first evidence that in the nucleus, these kinases act on a gene regulator called CREB-1 (the cAMP response element binding proteins) to initiate a cascade of gene actions. With David Glanzman and Craig Bailey, we found that the CREB-mediated gene cascade which triggers the synthesis of new protein is required for the growth of new synaptic connections and it is the formation of these new synapses that sustains the long-term change.The requirement for transcription in long-term facilitation explained why long-term memory requires the synthesis of new proteins. However, this requirement now posed a cell-biological puzzle: if long-term synaptic change relies on the activation of genes in the nucleus, that means there is ready communication between the nucleus and the synapse. If that is so, must all such long-lasting changes in the signaling ability of the neuron be cell-wide? Or can long-term synaptic changes be restricted to individual synapses. Experiments by Kelsey Martin, based on a beautiful new cell culture system she developed, revealed that individual synapses or groups of synapses within a cell can be modified independently.A return to the hippocampus: genetically modified mice and the study of complex spatial memory storage In our studies in *Aplysia* we focused on the simplest forms of memory, called implicit (or procedural) memory. These memories are concerned with the unconscious recall of perceptual and motor skills and do not require a hippocampus. The hippocampus is involved in explicit (or declarative) memory, memory for people, objects, or places, memories that require conscious participation for recall. For years I tried to encourage people who left my lab to turn their attention to the hippocampus, but to no avail. Finally in 1990, when I reached my 60th birthday, I returned to the study of the hippocampus myself. I was emboldened to do so in great part because of the development of methods for inserting and for knocking out individual genes in mice. This work made it clear to me that mice offered a superb genetic system for examining the role of individual genes in synaptic modification on the one hand, and intact behavior – explicit memory storage – on the other. Mice have a well developed medial temporal lobe and hippocampus, and these are important for explicit memory of objects and space. Moreover, in 1972, Tim Bliss and Terje Lomo in Per Andersen’s laboratory in Oslo, had discovered that electrically stimulating any one of the three major pathways in the hippocampus gives rise to a synaptic facilitation, called long-term potentiation or LTP. We were interested in two questions: (1) What are the molecular signaling pathways that are important for LTP? (2) Is LTP important for explicit memory storage? In the move to genetically modified mice, the contributions of Seth Grant and Mark Mayford were particularly influential.Grant was the driving force in our first studies, in which we showed a role for nonreceptor tyrosine kinases in long-term potentiation, and in spatial memory in the hippocampus. Mayford’s critical thinking became important somewhat later, as we began to realize the limitations in the first generation of genetically modified mice. The limitations stimulated Mayford to develop regionally restricted promoters that limited the expression of genes to only certain regions of the brain, and methods for controlling the timing of gene expression. Those two technical advances by Mayford proved important in allowing us, and Susumu Tonegawa (whose laboratory was now also focusing on studying memory in genetically modified mice), to generate mice whose phenotypes were more specific and in whom a genetic defect could be more readily interpreted than in the first generation of genetically modified mice because the defect could be related, somewhat more directly to specific synaptic changes and to behavior. Over the next few years Mayford, Ted Abel, Mark Barad, Isabelle Mansuy, Chris Pittenger, Amy Chen, and Angel Barco created a number of regionally restricted and regulated transgenic animals that allowed us to examine the role of the PKA- CREB-1 and CREB-2 and the protein synthesis-dependent transcriptional switch within the hippocampus, and to find that it was quite similar in principle to what we had encountered in *Aplysia*. Our lab and those of Alcino Silva and Dan Storm found that the cAMP, PKA, and CREB switch were required for long-term forms of synaptic plasticity in the hippocampus, was also required for spatial memory.A molecular approach to the cognitive map of space in the hippocampus: steps toward a molecular biology of attention With this background information about genes, LTP, and spatial memory, we now could ask a deeper question: How does an animal learn about extrapersonal space? Why does spatial memory go awry with defects in PKA signaling? What is the function of the transcriptional switch? To address these questions, we turned to studying how space is represented in the hippocampus.One of the key insights to emerge from the study of higher cognitive functions is that each perceptual or motor act has an internal or neural representation in the brain. These representations can be either simple or complex. The simplest internal representations are those evident in the sensory systems where the afferent fibers are arranged as topographic maps of the receptor surface. These are the representations which Wade Marshall, my former mentor at the NIH, had discovered in the 1930s and early 1940s. Marshall showed that this map is most clearly evident in the neural representation of *personal space*, the representation of touch. The neural representation of the space surrounding the body, the *extrapersonal space*, is far more complex. Here the representation is not topographical but encoded in the pattern of firing of cells that do not have any specific topographic relation to one another with respect to the receptor surface. Thus, adjacent cells need not encode adjacent regions of extrapersonal space.This representation was discovered in 1971, by [John O’Keefe](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2014/okeefe-facts.html) at University College London, who made the brilliant observation that the hippocampus has a cognitive map – a complete representation of extrapersonal space. O’Keefe discovered that all the pyramidal cells in the hippocampus, the very same cells that are used to study long-term potentiation have, as a natural function in the intact animal, the ability to encode space. He found that when an animal moves around in a familiar environment, different pyramidal cells in the hippocampus fire as the animal traverses different regions of the environment. This tendency is so marked that O’Keefe referred to the pyramidal cells as *place cells*. Some place cells may fire only when the animal’s head enters one position in a given space. Other pyramidal cells will fire when the animal’s head enters another position in the same space. Thus, a mouse’s brain breaks up the space in which it walks into many small overlapping fields, and each field is assigned to specific cells in the hippocampus, forming a spatial map of the animal’s surroundings. When the animal enters a new environment, a new place map is formed within minutes.These observations have given rise to the idea that the hippocampus contains a map-like representation of the animal’s current extrapersonal environment, and that the firing of place cells in the hippocampus signals the animal’s moment-to-moment location within the environment. This spatial map is the best-understood example of a complex internal representation in the brain, a true cognitive map. It differs in several ways from the classical sensory maps found by Wade Marshall for touch, vision, or hearing. Unlike sensory maps, the map of space is not topographic, that is, neighboring cells in the hippocampus do not represent neighboring regions in the environment. Furthermore, a place cell will fire in the same place regardless of what the animal is looking at. Moreover, the firing of place cells can persist after pertinent sensory cues are removed and even in the dark. Thus, although the activity of a place cell can be modulated by sensory input, it is not determined by sensory input as is the case for the activity of neurons in a sensory system. It appears that the place cells do not map the current sensory input, but the location where the animal thinks it is in space.Place fields are formed in minutes, and once formed the map to which they contribute can remain stable for weeks. It struck me in 1995 that formation of this internal representation – this cognitive map of space – was a learning process and that synaptic plasticity related to LTP might have a role in stabilizing this cognitive representation.Although place cells have been studied since 1971, nothing was known about the cellular or molecular mechanisms whereby new place fields are formed, and specifically no one had attempted to relate the biology of place cells to the molecular mechanisms of LTP or hippocampal-based memory. To explore this problem, I was fortunate to start a collaboration with Robert Muller at Downstate Medical Center in Brooklyn, who had pioneered the systematic study of place cells. This problem was taken on by Cliff Kentros, a postdoctoral fellow in my lab, by Naveen Agnihotri, a graduate student, and by Alex Rotenberg, a joint student with Muller and myself. Using a combination of pharmacological and genetic approaches, we demonstrated a link between recruitment of PKA and protein synthesis on the one hand, and on the other, the long-term, but *not* short-term stability of the hippocampal representation of space. Thus, PKA and protein synthesis are required for longterm memories of extrapersonal space because that memory is based on a learned internal representation of space whose long-term stability requires PKA and new protein synthesis.This raised a final question: Explicit memory in humans differs from implicit memory in requiring conscious attention for recall. How does conscious attention come to bear on explicit memory? Indeed, how can one study consciousness in the mouse? In the course of our work on place fields, Kentros, Agnihotri, Hawkins, and I found that the long-term stability of the place field map correlated strongly with the degree to which the animal was required to attend to its environment. This demonstrates that, rather than being an implicit, automatic, process, the long-term recall of a stably formed place cell map requires the mouse to attend to its environment, as would be expected for explicit memory in human beings. The finding that attention, the recruitment of PKA, and new protein synthesis are required to form and recall a stable map in the mouse has opened up a molecular biological approach to an attentional process.From psychoanalysis to Aplysia to the role of attention in the cognitive representation of extrapersonal space During the past 10 years my career has begun to come full circle. From an initial interest in the complex cognitive problems of psychoanalysis and memory storage, my research on memory led me first to the mammalian hippocampus, which proved too difficult as a first step and forced me to take a more reductionist approach and study initially the simplest forms of memory in *Aplysia*, and then, only much later, the more complex forms of memory in mice. I found that despite important differences in detail, simple implicit and explicit memories have a similar short- and long-term storage form. In each form, short-term storage requires covalent modification of pre-existing proteins leading to the alteration of pre-existing synaptic connections, whereas long-term memory storage requires gene activation, new protein synthesis, and the growth of new synaptic connections.In the course of this work we began to explore how explicit memory storage for space affects the internal representation of space. We found that on the level of internal representation the storage mechanisms for explicit memory are similar to those in human beings in requiring attention. Attention is a component of conscious response, perhaps the great challenge of all research on mental processes. It thus seems likely that in future decades, the study of memory, perhaps even in mice, is likely to allow molecular insights into even the deepest problems of human behavior.A personal perspective Although doing research on *Aplysia* and the hippocampus and discussing science with colleagues in my lab have given me the greatest intellectual satisfactions, I have loved teaching and have learned a great deal from lecturing to medical and graduate students. It was in the context of the neural science course at Columbia that the idea arose of doing a textbook, *Principles of Neural Science*. In college and medical school I was never a good note-taker. I always preferred sitting back, enjoying the lecture, and just scribbling down a few words here and there. When I came to Columbia to develop the neural science course, I was struck by how much energy students were devoting to writing out every single word of lectures, and I wanted to help them get over that. I therefore encouraged the faculty to provide a syllabus for each lecture, and with time I edited the syllabus, added figures to it and improved it. Then Jimmy Schwartz and I decided that the syllabus was becoming sufficiently useful that we might make a textbook out of it. Our textbook was the first attempt to bridge cell and molecular biology to neural science and neural science to behavior and clinical states. The response to the first edition was so gratifying that we made an effort to make the book better and more complete. With the second edition, not only students but also scientists began to regard our textbook as useful. With the help of Tom Jessell, we further improved the third and fourth editions. The widespread reception of this book, both in the United States and abroad, has been a source of deep satisfaction to me and to the other contributors.Outside of our work and our family, Denise and I enjoy the visual arts and classical music, especially opera. Our interest in both of these activities is greatly enriched by having within easy reach of our home the great museums and galleries of Manhattan as well as the Metropolitan Opera. We also are inveterate – I am tempted to say *addicted* – collectors of art and antiques. We have lived for 36 years in a now 150-year-old house in the Riverdale section of the Bronx, with wonderful views of the Hudson River and the Palisades. We collect French art nouveau furniture, vases, and lamps, an interest that originated with Denise and her mother, and graphic art of the Austrian and German Expressionists, an interest which originated with me. As I write this, I am beginning to suspect that our collecting may well be an attempt to recapture a part of our hopelessly lost youth.In the course of my career I have incurred many debts both personal and scientific. First and foremost I owe an enormous personal debt to my parents and my brother Lewis. My parents were able in mid-life to relocate to a foreign country – my father spoke not a word of English when he first arrived in New York – and to create a new life for themselves and their sons. My parents not only succeeded in establishing themselves in their small store in Brooklyn, but were sufficiently successful to support me through college and medical school. They were so occupied with their store that throughout their life in America they did not share in the cultural life of New York, which Lewis and I were beginning to enjoy. Despite their constant labor they were always extremely optimistic and supportive of us, and never tried to dictate decisions about my work or play. Lewis was also an enormous influence on me in my early years, and my interest in classical music and my joy in learning were importantly influenced by him. While a graduate student at Brown University writing his dissertation in linguistics and Middle High German, he was called to service as an intelligence officer in the Korean War. He and his wife, Elise, went first in 1951 to Germany and then in 1953 to Paris, France, where he had a position as a civilian in Air Force Intelligence. He so enjoyed his life in France, that he lost his interest in an academic life and stayed in France for 13 years, where he and Elise raised five children. He eventually returned to the United States and finished his career in a series of administrative positions, in the Health Department of the City of New York. He died in 1979, at age 54 of a recurrence of a cancer of the kidney, which we all thought had been successfully removed when it first presented 10 years earlier.Second, I have been privileged to enjoy a wonderfully supportive, endlessly interesting, and stable family life with Denise, my partner, best friend, and most honest critic for now 45 years. Throughout our life together she has consistently encouraged my love of research and supported my scientific aspirations. Denise is a professor in the Department of Psychiatry and in the School of Public Health at Columbia University, and has pioneered the study of drug abuse in adolescence. Her work on the epidemiology of drug abuse has become the basis of the current understanding of the developmental sequence whereby adolescents become involved in drugs. I am also greatly in debted to our two children, Paul and Minouche, for the joy they gave Denise and me while growing up and the satisfaction they have given us in seeing what principled and interesting people they have become and how thoughtful they are as parents to their own children. Our son Paul majored in economics at Haverford College and graduated from the Columbia Business School. He now manages a set of investment funds at Dreyfus-Mellon. Paul is married to Emily Kaplan, an interior designer; they live in Scarsdale, N.Y. and have two daughters, Allison (born on January 5, 1992) and Libby (born on October 14, 1995). Our daughter Minouche went to Yale College and Harvard Law School. She practices public interest law in San Francisco specializing in women’s rights and family violence. Minouche is married to Rick Sheinfield, also a public interest lawyer, and they have a son, Izak (born on November 10, 1998) and a daughter, Maya (born on March 12, 2001).In retrospect it seems a very long way for me from Vienna to Stockholm. My timely departure from Vienna made for a remarkably fortunate life in the United States. The freedom that I have experienced in America and in its academic institutions made Stockholm possible for me, as it has for many others.Postscripts: a Curriculum Vitae I began my academic career at the Harvard Medical School, where from 1963 to 1965, I was an instructor in the Department of Psychiatry. In 1965, I moved to New York University as associate professor where, together with Alden Spencer and James Schwartz, we developed the first group in the country devoted to both cellular neurobiology and behavior. At the time I was recruited to N.Y.U., Denise was recruited to the Columbia University College of Physicians and Surgeons, where she gradually rose to the rank of professor.In 1974, Harry Grundfest retired and I was recruited to Columbia to replace him. At Columbia I was the founding director of the Center for Neurobiology and Behavior. In 1983, I became a University Professor at Columbia. In 1984, I resigned as director of the Center to become a senior investigator at the newly formed Howard Hughes Medical Research Institute at Columbia.Since 1974, I have been a member of the National Academy of Sciences USA. Later I became a member of the National Science Academies of Germany and France, the American Academy of Arts and Sciences, the American Philosophical Society, the National Institute of Medicine, and most recently, Germany’s Orden Pour Le Mérite für Wissenschaften und Künste. Being invited to join the Orden was for me a particularly great honor. The collection of scholars and scientists in the Orden is extraordinary; as an extra bonus it includes old friends such as the great German historian Fritz Stern, and a sterling group of biologists including [Max Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/index.html), [Christiane Nüsslein-Volhard](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1995/index.html), [Bert Sakmann](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1991/index.html), [Erwin Neher](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1991/index.html), Walter Gehring, Charles Weissman, and Robert Weinberg.I have been awarded the Lester N. Hofheimer Prize for Research of the American Psychiatric Association (1977), the Karl Spencer Lashley Prize in Neurobiology from the American Philosophical Society (1981), the Dickson Prize in Biology and Medicine from the University of Pittsburgh (1982), the Albert Lasker Award (1983), the Rosenstiel Award of Brandeis University (1984), the Howard Crosby Warren Medal by the Society of Experimental Psychologists (1984), the American Association of Medical Colleges Award for Distinguished Research in the Biomedical Sciences (1985), the Gairdner International Award of Canada for Outstanding Achievement in Medical Science (1987), the National Medal of Science (1988), the J. Murray Luck Award for Scientific Reviewing from the National Academy of Sciences (1988), the American College of Physicians Award in Basic Science (1989), the Robert J. and Claire Pasarow Foundation Award in Neuroscience (1989), the Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research (1991), the Warren Triennial Prize from the Massachusetts General Hospital (1992), the Harvey Prize of the Technion in Haifa (1993), the Stevens Triennial Prize from Columbia University (1995), the Dana Award (1997), the Gerard Prize of the Society of Neuroscience (1997), the Wolf Prize of Israel (1999), and the Dr. A.H. Heineken Prize for Medicine from the Royal Netherlands Academy of Arts and Sciences in Amsterdam (2000).I have received honorary degrees from nine universities, including three European universities: the University of Vienna, Edinburgh, and Turin. Surprisingly, the first honorary degree I received, in 1983, was from the Jewish Theological Seminary in New York. I was thrilled that they would even know of my work. I suspect they learned of that from my colleague Mortimer Ostow, one of the psychoanalysts who first stirred my interest in relating psychoanalysis and the brain. My father had already died but my mother came to the graduation ceremony, and in his introductory remarks Gerson D. Cohen, the chancellor of the seminary, referred to my having received a good Hebrew education at the Yeshiva of Flatbush, an acknowledgement which filled my mother’s Jewish heart with pride. As this recitation makes clear, I also owe a profound intellectual debt to my scientific teachers – Harry Grundfest, Dominick Purpura, Wade Marshall, and Ladislav Tauc – who tolerated my naivete and encouraged my brashness. I also benefited greatly from Steve Kuffler’s sage insight and advice and from Alden Spencer’s generous friendship. I also am indebted to the extraordinary collection of colleagues, fellows, and students that I have had the privilege of interacting and collaborating with and whose individual contributions I describe in more detail in my Nobel Lecture. Finally, I am deeply grateful to Columbia University and the Howard Hughes Medical Research Institute, two great institutions that have created open environments supportive of scholarship and research. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0558 |
| Interview |  |
| Q41 | So, there is a little discrepancy between you on this one anyhow. But if I rephrase the question and say, will it ever be possible to understand the mechanisms of mind? What is your answer then? |
|  | Arvid Carlsson: To understand there is physiological and physiochemical processes that underlie the mind, that we could perhaps reach. But the actual conversion, how these physical phenomena become consciousness, that is what I think is the real tough thing. |
| Q41 | But if you understand the mechanisms or the things that are changing, you can see them, you can measure them, then you can influence the whole system. |
|  | Arvid Carlsson: That is very true.In that way, if my question contains the possibility of interfere with all aspects of mind, your answer is yes.Arvid Carlsson: Yes.Paul Greengard?Paul Greengard: I think that the history of science indicates that one by one various barriers have disappeared in areas that the human race thought were impossible to resolve. And everything seems to be solvable. And I don’t see why an understanding of how we think and what consciousness is wouldn’t be approachable in the same way. I think it’s going to be a very long time till we understand the nature of consciousness, even today with these imaging techniques you can start finding out precisely which type of cells are active when you do this or this type of thinking. It certainly should be possible to do similar imaging and understand when people are awake and asleep and I don’t think it’s a huge step beyond that to understand the nature of consciousness. |
| Q34 | So you’re only putting more weight to the answer that all the different mechanisms that at the end lead to the consciousness experience, those mechanisms can be known and cleared. Is science limitless? |
|  | Paul Greengard: In certain principles such as the [Heisenberg](https://www.nobelprize.org/prizes/physics/1932/heisenberg/facts/) uncertainty principle I think yes it’s limitless. I didn’t always feel that way, it just seems that if you look what happened in the last 30 years it’s unbelievable what the human mind can achieve. |
| Q34 | Eric Kandel, on the mechanisms of mind, of course you would have to answer yes on that question as well. |
|  | Eric R Kandel: I sort of come down more on Paul’s side. First of all, I think one needs to distinguish between mechanisms of mind, which involves all operations related to mental processes, action, thoughts, memory, perception, and consciousness. There’s lots of perception, mental processes going on of which we’re unconscious for example. You’re shaking your head as we talk, you’re probably not completely aware of the fact that you’re engaged in sort of reflexive autonomic movements as you talk. Those are mental processes but they’re not necessarily conscious ones. And we have made very good progress in understanding aspects of perception and motor action and I’m confident we will continue to do that.The mechanism of consciousness is a fascinating one, and one that is getting a lot of attention. Not necessarily a lot of scientific progress, but a lot of attention. [Francis Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/) has developed a paradigm for looking at attention and consciousness, saying that one ought to look at a simple version of it, which is selective attention. You know, when I sit in this room, I attend to you but I’m also in the background perceiving pictures on the wall and things like this. But there’s a special effort involved in selectively attending to you, so the difference between perceiving something and the heightened selection that goes on with attention, is something he’s been studying in experimental animals with the help of other people. And there is now pretty good understanding of how a monkey, for example, attends to a visual image compared to just looking at the image without attention. So simple cases of conscious awareness are beginning to be analysable. To what degree consciousness of oneself, the most interesting parts of consciousness, become understood is unclear as yet. I sort of agree with Paul that a lot of problems that seemed insoluble became soluble with time. When there’s no add of time, we haven’t reached the limit by any means. It is conceivable that this problem is so difficult that the human mind may not have the computational power to analyse it, but we are far from reaching that particular barrier. |
| Q23 | But you stick to some of the mechanisms to start with, the one that Arvid Carlsson has discovered is dopamine, and I think there is a fascinating correlation between too little dopamine – then you lose control over your body – and too much dopamine – you lose control over your mind. Is that so Arvid Carlsson? |
|  | Arvid Carlsson: As well as the body. |
| Q23 | But is there some sort of relation between the mind and the body in this respect that is basically the same mechanism that in a way controls the material world and the mental world? |
|  | Arvid Carlsson: That’s a very interesting question. Anatomically the wiring that analyse movements and the wiring that analyse mental processes are very similar. The balance between different neurotransmitters involved in either of these two is very similar. And have probably evolved along with each other which, in a way, makes a lot of sense because if one goes ahead of the other you’ll have no use for it. The mind and movement have to evolve in parallel. |
| Q23 | And in this system you have discovered the chemical signal substances between the connection between the nerves, and Paul Greengard your discovery is really what is happening inside the cell. How does your discovery relate to how we react and how we are, how we experience the world? Are there any connections that you have thought of? |
|  | Paul Greengard: The work that we did elucidates how these chemicals, the neurotransmitters which are the mechanism by which the nerve cells communicate with each other, how they produce their responses in the target cells on which they act. |
| Q23 | And they are related to what sort of mental phenomena? |
|  | Paul Greengard: All mental phenomena, memory, consciousness and everything else, is all attributable to the behaviour of nerve cells and what the three of us are doing is trying to understand how one nerve cell communicates with another. It’s through the release of a chemical, a neurotransmitter which activates the second nerve cell and then what happens in the second nerve cell once the neurotransmitter activates it and then how that in turn sends a neurotransmitter to the third nerve cell. What we’re doing at this present level, all three of us, is to understand these biological systems going on, these biochemical molecular systems. Other types of neuroscientists, brain scientists, will take the kind of things that we’re doing and try to relate them to the higher order of behaviour in the nervous system. |
| Q23 | But if Arvid Carlsson has done something in between the synapses where the signals are changing the connections between them, you’re only working with molecules inside the cell and how molecules are changing their shape and their effectiveness, what they do, the proteins we are talking about. |
|  | Paul Greengard: What we’ve done is to take these neurotransmitters that Arvid Carlsson had been studying and study exactly how they produce chemical and electrical changes in the nerve cells, working out what those biochemical steps are. |
| Q23 | And they are related to memory in what way? |
|  | Paul Greengard: That remains to be understood to a large extent. Except Eric Kandel’s work addresses that and maybe he’d like to speak to that. |
| Q23 | So, memory and changes inside the nerve cells, Eric Kandel. What is the concept or idea? |
|  | Eric R Kandel: Let me pick up what Paul Greengard was saying. One way to conceive of the contribution the three of us have made is to think of two sets of processes in the brain – mediating and modulating. That there are vast synoptic connections that are responsible for mediating many of the actions, for example motor actions, sensory perception. But the wonderful thing about the brain is that it can regulate the strength of connections. And my colleagues and I have shown that this occurs during learning, that the strength of connections are not fixed, but that inputs such as serotonergic input or dopaminergic input can modulate the strength of synoptic connections. And it does so by activating processes similar to the kind that Paul Greengard has described. In *Aplysia* one can show … |
| Q23 | *Aplysia*, that is the sea snake that you have been working with? |
|  | Yes, one can show that in fact that a very simple withdrawal reflex, like the withdrawal of a hand from a hot object, can be dramatically amplified by an aversive stimulus. And that amplification involves activation of one of these modular choice systems, the serotonergic system that activates a signalling system within the cell. And activation of that signalling system causes strengthening of the synoptic connection, which is responsible for the enhanced withdrawal.That means that there is a physical change of the size, so memories are actually made of these changes.Eric R Kandel: Anatomical changes. That’s right.This is somewhat exciting that the fast reactions, that is electricity and the somewhat slower …Eric R Kandel: The fast, and not simply electricity, the faster also chemical transmitters but they act on different receptors.But long term things are also represented by long term changes.Eric R Kandel: That’s right. |
| Q14 | You have all been part of a dramatic shift in paradigm when it comes to looking at the brain because all electrophysiology before and when you entered this stage you changed the picture totally into biochemistry. Arvid Carlsson, why did you choose to go contrary and against everyone else? |
|  | Arvid Carlsson: I think it depended to some extent on ignorance. I was not so well read in the field of brain physiology, so I could look at the facts in a simple, straight forward way, whereas those people who were burdened by a lot of knowledge, they had to think in other terms. They were, so to speak, fixed in the dogma. I was outside, just because of my ignorance, I think. |
| Q11 | Eric Kandel and Paul Greengard, what makes someone want to go towards the conventional wisdom of the time? |
|  | Paul Greengard: In the case of the study of the brain at the time that Arvid, Eric and I did our work, there were two approaches to understanding brain function. There were physiologists who worked in physiology departments and studied the electrical properties of nerve cells. And there were biochemists working in biochemistry laboratories who took a brain or a liver or a muscle and threw it into a homogeniser and studied the chemicals in the brain. And the two groups did not interact. The people sitting biochemistry were only interested in the biochemistry of the brain. The people doing physiology were only interested in the electrical property of the brain. In one sense we were not going against dogma. There was very little prior art out there. In my own case, my work was guided by the hypothesis that a particular mechanism that had been shown to work in the endocrine system, in which hormone released from one cell activates a target cell, that that system might be analogous to how two nerve cells communicate with each other. And that is through a chemical mechanism, that hypothesis turned out to be correct. |
| Q11 | Eric Kandel, you started off as being a psychoanalyst interested in psychoanalysis and everyone thought that was the gateway to the brain at that time. How come that you didn’t believe it? |
|  | Eric R Kandel: I did at the beginning and I still find the psychoanalytic view a rich and nuance view of the mind. I just became disappointed as I continued my medical education with how much empirical evidence there was to support it and how devoid it was in thinking about the brain. I became a little bit interested in the brain and as I got more deeply involved I became fascinated with it. And it struck me that memory is the central question in psychoanalysis. And in the 1950s when I began, the dominant view of the brain was that of Karl Lashley at Harvard, who showed that memory was not localisable. That you could remove many regions of the brain and not interfere with memory. What Lashley did not realise is that animals are very smart and if you remove a part of the brain, for example, let’s just say they’re doing a spatial task, if you remove the visual part of the brain, they will use tactile stimuli to find the way, or smell. They have lots of different strategies they can use. I thought one needed to take an extremely simple animal, an extremely simple reflex, where there would be no question about localizability. |
| Q22 | Excuse me for interrupting, but I got so curious, but this is true that you have all entered a new way of looking at things that were contrary to the conventional views of the time. And still the question I am really curious about is how is your mental set up to want to go against this? |
|  | Eric R Kandel: I think each of the three of us gave a somewhat similar answer, in the sense that we did not think of ourselves as revolutionaries at the barricades. We were working along and we thought that one way of moving in the field was the sound one, it’s almost an intuition that this is the right way to go. It turned out be in opposition to what other people were thinking, but one wants to think in original ways, you try to tackle a problem you think is interesting and approach it in the way that you think is most profound.Paul Greengard: To amplify what Eric said, it’s not that we were going against conventional wisdom, we were following our own instinct. This must be the way it works. And then more conservative folks would say we were disagreeing with them, but we weren’t, we were just looking at things in a different way.So in a way it was a very unconscious way of …Eric R Kandel: That’s right. I think that’s absolutely right.Paul Greengard: No, I don’t understand what you mean, an unconscious way?You didn’t really think about going against what was the convention, you just did what you thought was working.Paul Greengard: It was nothing that they had done was wrong, we were exploring an area that other people hadn’t explored, I would say.Do you agree Arvid Carlsson?Arvid Carlsson: No. I was taken by surprise, I must say, when we reported on our data and all the big figures in the field said, no this can’t be true.Paul Greengard: But that’s true for all three of us.Arvid Carlsson: I mean, I was right and they were wrong. I mean that is how I experienced it. I wouldn’t like to give them any sort of excuse that we were right, all of us, after all. I don’t agree.Paul Greengard: Maybe add a certain limited truth, we said, look we think that there are other things going on than what you’ve been studying and there’s all this and this. And then we’d say, yes, there’s all this and this. And then we’d show it and they’d say, no, you’re wrong. We were never saying they were wrong, I don’t think. They were saying we were wrong.Arvid Carlsson: They were wrong, in my opinion.Eric R Kandel: I must say that Roy Spencer and I wrote an article in 1968, when we first began to realise that learning could be localised to specific synopses. And we pointed out that Lashley’s view, which was the dominant view, had misled the field. |
| Q34 | But if we look then in the future, this is not the last time where things are going to be turned upside down. Have you seen anything in the current science that indicates that there will be maybe a totally new model coming up of how the brain is working? Maybe adding some fundamental new knowledge to the function of the brain? |
|  | Paul Greengard: It’s exactly what I’m saying. There will be totally new ways of looking that will not necessarily be contradictory to what we did. What we’re doing is eliminating truths just like the people before us had even more eliminating truths, and the next people add on to that. And they’re not going to prove that the work that we did was incorrect, they’re going to show a new dimension.Eric R Kandel: It’s almost probabilistic in a sense. The views that we have ended up supporting existed before, just to a minor degree, so people had seen in the endocrine system the kinds of things that Paul discovered in the nervous system. Kajal had spoken about the fact that synopsis could be the site of memory storage. But at the time that we were working those views were rare, very few people held that. Most people held the opposing point of view. For example, many people felt that [Bernhard Katz](https://www.nobelprize.org/prizes/medicine/1970/katz/facts/) and [Eccles](https://www.nobelprize.org/prizes/medicine/1963/eccles/facts/) had described synoptic transmission in the nervous system, it was fast synoptic transmission. So they thought all synoptic transmission in the brain was fast. When Paul and I began to study slow synoptic transmission, they thought there’s something unusual about this and people were initially sceptical that this could be of importance. |
| Q35 | But when the two models that has exchanged for each other, the electrophysiological model, the biochemistry model, what do you think about the future, Arvid Carlsson, are there totally new things coming up? |
|  | Arvid Carlsson: I guess there will be paradigm shifts in the future. But I think it’s inherent in the definition of dogma that we cannot identify it. As soon as we identify it as a dogma, it’s no more a dogma. |
| Q35 | But before there’s a thunderstorm coming up you can always see a little glimpse of the lightening coming, do you see any glimpse here? |
|  | Eric R Kandel: We certainly see that. For example, we thought that the nervous system by the time a child is four or five years old, does not generate any more nerve cells. We thought that the number of nerve cells in the brain are limited – if you lose nerve cells as a result of disease, stroke, Alzheimer’s disease, there’s no way of replenishing those nerve cells from the cells in the brain. There’s now increasing evidence that there is a primitive population of cells that stays around in the brain and they can be the source of additional cells later on. That could be the basis of a new development that would enrich our understanding. So I think that’s a very important development. |
| Q35 | And what would be the conceptual change of that idea? |
|  | Paul Greengard: Right now it’s thought that the brain has very little ability to repair itself. And with these new ideas that’s not the case. I would like to go back and correct something that I said, refer to something Arvid said on this. The people who are our predecessors, what they did was not wrong, their interpretation was wrong. For example, in his case, they said no, this molecule dopamine cannot be a neurotransmitter, so in that sense they were wrong. The experimental work they had done was correct, their interpretation was not correct. This is, in my case, they said these slow biochemical reactions cannot be involved in mediating communication between nerve cells, they were wrong about that. |
| Q24 | But then finally, Arvid Carlsson, do you agree with Eric Kandel that there may be a totally new way of looking on the dynamics of the brain, which is really at the heart of his statements? |
|  | Arvid Carlsson: One direction that I think will become very important is the understanding of the interaction between the different neurotransmitters in complex neuro-circuitries. And there are new possibilities to approach these complex problems. And that deals with something that we can call pattern analysis. You can collect enormous number of data and feed into computers and the computers will feed back to you pictures of the data, that actually are patterns of very, very complex processes in the brain, by means of which you can come closer to these very, very complex mechanisms that deal with the mind, feelings and cognition and so forth.And maybe even get a picture of the conscious experience then on the screen.Arvid Carlsson: Yes, and also to distinguish between different personalities. By means of imaging you will tell this is a happy fellow and this other fellow here has a short fuse, that kind of thing.Eric R Kandel: I also think that the human genome is going to enlighten our understanding of mental processes. One of the deep questions that is a confronted analysis of the mind, has been to what degree is the mind built on the base of genetic information? What is nature versus nurture? What do you inherit versus what do you acquire? And most personality traits are quite complex, so they’re not attributable to one or two genes, so they’ve been very hard to decipher. But now that we will have the whole human genome, we’ll be able to look at patterns of genes and we’ll see to what degree any of our behavioural patterns derive from familial traits versus acquired or learned traits. I think that’s going to be a very rich area for investigation.Paul Greengard: I would like to go back to your original question and ask you and my two colleagues whether there is any reason to think that we won’t be able to understand the nature of consciousness or any other aspect of the brain. What reason is there for pessimism, given the history of the last decade?Eric R Kandel: I think it’s hard to know what the limitations of knowledge are. I think it is hard to know at this particular point whether the optimism that we all share, that science can solve all problems in the universe, is in fact true. We’ve solved many problems so far, but there is the possibility that there are limitations to human understanding which we and the computers that we develop will not be able to solve.Paul Greengard: At the moment we have not reached that point.Eric R Kandel: We have not reached that point. |
| ID | 0559 |
| Biographical | My paternal great, great grandfather emigrated from Koenigsberg, currently Kaliningrad, to St. Louis during the 1850s, a time of large-scale movement of Germans, including German Jews, to the Mid-Western United States. My paternal grandfather moved to Binghamton, New York, where my father was born. My father had success in vaudeville as a singer/dancer/comedian. He eventually became a businessman working first in retail and then in wholesale in the cosmetics field.I was born on December 11, 1925 in New York City under tragic circumstances – my mother, née Pearl Meister, died giving birth to me. My father remarried when I was 13 months old. In contrast to my mother, who had been Jewish, my stepmother, who raised me, was Episcopalian. From that time on I was brought up in the Christian tradition, celebrating Easter, Christmas, etc. I was prevented access to my biological mother’s family with whom I became familiar only very recently. I have been delighted to learn that many members of that family are highly creative individuals working in various fields of science, government, etc.I attended public schools in Brooklyn and Queens. During World War II, I spent three years in the Navy as an electronics technician. After appropriate training, I was assigned to a team at the Massachusetts Institute of Technology that was involved in developing an early-warning system to intercept Japanese kamikaze planes before they could reach the ships of the U.S. fleet.After the war, I attended Hamilton College, a small liberal arts college located in Clinton, New York, where I majored in mathematics and physics, and from which I graduated in 1948. I had been interested in going to graduate school in theoretical physics, but decided not to do so because at that time the only fellowship support for such graduate studies came from the Atomic Energy Commission. This was only three years after dropping the atomic bombs on Japan, and I didn’t want to contribute to research the fruits of which might contribute to creating more powerful weapons of mass destruction. In thinking about various options, I settled on the then nascent field of biophysics. At that time there were two groups of academic biophysicists. One, at the University of California, was engaged in biological and medical applications of radioisotopes. The other, at the University of Pennsylvania, headed by Detlev W. Bronk, used electrophysiological techniques to study nerve function. I chose the latter. Shortly after I arrived in Philadelphia, Bronk announced that he was accepting the Presidency of The Johns Hopkins University and invited a group of us to move there with him and form a new department of biophysics. The most senior member of the group was [H. Keffer Hartline](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1967/index.html), who became Chairman of the Department of Biophysics at Johns Hopkins and who was later to win a Nobel Prize in Physiology or Medicine for his work on vision. I did my first laboratory research under the supervision of Hartline.Shortly after our move to Hopkins, [Allen Hodgkin](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html) gave a lecture on the still unpublished work that he and [Andrew Huxley](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html) had carried out on the ionic basis of the nerve impulse – work that was later recognized by the Nobel Prize in Physiology or Medicine. That work, carried out exclusively with biophysical techniques, filled me with admiration. At the same time, the elegance of that study made me feel that it might be a long time until biophysical techniques would by themselves make further major contributions to our understanding of nerve cell function. Thus it was Hodgkin’s lecture that led me to consider combining biophysical and biochemical techniques to understand the molecular and cellular basis of how nerve cells work. Since, at that time, neuroscience as a field had not yet been created, my Ph.D. thesis was carried out under the joint supervision of Frank Brink, a distinguished biophysicist in our Department of Biophysics, and Sidney Colowick, a prominent biochemist who was a Professor in the Department of Biology – I remain to this day very grateful for their nurture and support.Upon graduation from The Johns Hopkins University in 1953, I went to Europe for postdoctoral studies. My first year was with Henry McIlwain, at the Maudsley Hospital, of the University of London. My second year was with E.C. Slater, first at Cambridge University and then at the University of Amsterdam. At the end of my six-month period in Amsterdam, I returned to London to work in the laboratory of Wilhelm Feldberg, who was Head of the Department of Pharmacology at the National Institute for Medical Research at Mill Hill, London. At that time, the only departments that had both electrophysiological and biochemical facilities were pharmacology departments. Feldberg was a great scientist and a wonderful human being and provided an atmosphere in which I could continue to explore the relationships between biochemistry and electrophysiology in the nervous system. I seriously considered staying in England, which I found particularly compatible with my personality, which at that time was relatively reserved. However, the low level of financial support for scientific research in England, my ignorance of the nuances of the complex British educational system (two sons had been born in England), and the lack of central heating all conspired towards my returning to the United States. Upon my return, I spent one year working in the laboratory of Sidney Udenfriend at the NIH following which I became director of the Department of Biochemistry at the Geigy Research Laboratories. My prime motivation for going to Geigy was the prospect of applying basic scientific principles to the development of new drugs for the treatment of neurological and psychiatric disorders. Unfortunately, at that time, Geigy, like most, if not all, other pharmaceutical companies, was very conservative with regard to the nature of the research programs which they found acceptable. It was extremely difficult to obtain authorization to embark on innovative research approaches. In 1967, I left Geigy. After spending one year as a Visiting Professor, the first semester in Alfred Gilman’s Department of Pharmacology at Albert Einstein College of Medicine and the second semester with Sidney Colowick and Earl Sutherland at the Vanderbilt University School of Medicine, I took a position as Professor in the Department of Pharmacology at Yale University. My years at Yale saw the early development of my work on signal transduction in the nervous system. Although I was very happy throughout my 15 years at Yale, the offer to move to The Rockefeller University was irresistible and so I moved to New York in 1983 where I have been located since. It has been at Rockefeller that most of the work described in my Nobel Lecture was performed. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview | 0559 |
| Interview |  |
| Q41 | So, there is a little discrepancy between you on this one anyhow. But if I rephrase the question and say, will it ever be possible to understand the mechanisms of mind? What is your answer then? |
|  | Arvid Carlsson: To understand there is physiological and physiochemical processes that underlie the mind, that we could perhaps reach. But the actual conversion, how these physical phenomena become consciousness, that is what I think is the real tough thing. |
| Q41 | But if you understand the mechanisms or the things that are changing, you can see them, you can measure them, then you can influence the whole system. |
|  | Arvid Carlsson: That is very true.In that way, if my question contains the possibility of interfere with all aspects of mind, your answer is yes.Arvid Carlsson: Yes.Paul Greengard?Paul Greengard: I think that the history of science indicates that one by one various barriers have disappeared in areas that the human race thought were impossible to resolve. And everything seems to be solvable. And I don’t see why an understanding of how we think and what consciousness is wouldn’t be approachable in the same way. I think it’s going to be a very long time till we understand the nature of consciousness, even today with these imaging techniques you can start finding out precisely which type of cells are active when you do this or this type of thinking. It certainly should be possible to do similar imaging and understand when people are awake and asleep and I don’t think it’s a huge step beyond that to understand the nature of consciousness. |
| Q34 | So you’re only putting more weight to the answer that all the different mechanisms that at the end lead to the consciousness experience, those mechanisms can be known and cleared. Is science limitless? |
|  | Paul Greengard: In certain principles such as the [Heisenberg](https://www.nobelprize.org/prizes/physics/1932/heisenberg/facts/) uncertainty principle I think yes it’s limitless. I didn’t always feel that way, it just seems that if you look what happened in the last 30 years it’s unbelievable what the human mind can achieve. |
| Q34 | Eric Kandel, on the mechanisms of mind, of course you would have to answer yes on that question as well. |
|  | Eric R Kandel: I sort of come down more on Paul’s side. First of all, I think one needs to distinguish between mechanisms of mind, which involves all operations related to mental processes, action, thoughts, memory, perception, and consciousness. There’s lots of perception, mental processes going on of which we’re unconscious for example. You’re shaking your head as we talk, you’re probably not completely aware of the fact that you’re engaged in sort of reflexive autonomic movements as you talk. Those are mental processes but they’re not necessarily conscious ones. And we have made very good progress in understanding aspects of perception and motor action and I’m confident we will continue to do that.The mechanism of consciousness is a fascinating one, and one that is getting a lot of attention. Not necessarily a lot of scientific progress, but a lot of attention. [Francis Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/) has developed a paradigm for looking at attention and consciousness, saying that one ought to look at a simple version of it, which is selective attention. You know, when I sit in this room, I attend to you but I’m also in the background perceiving pictures on the wall and things like this. But there’s a special effort involved in selectively attending to you, so the difference between perceiving something and the heightened selection that goes on with attention, is something he’s been studying in experimental animals with the help of other people. And there is now pretty good understanding of how a monkey, for example, attends to a visual image compared to just looking at the image without attention. So simple cases of conscious awareness are beginning to be analysable. To what degree consciousness of oneself, the most interesting parts of consciousness, become understood is unclear as yet. I sort of agree with Paul that a lot of problems that seemed insoluble became soluble with time. When there’s no add of time, we haven’t reached the limit by any means. It is conceivable that this problem is so difficult that the human mind may not have the computational power to analyse it, but we are far from reaching that particular barrier. |
| Q23 | But you stick to some of the mechanisms to start with, the one that Arvid Carlsson has discovered is dopamine, and I think there is a fascinating correlation between too little dopamine – then you lose control over your body – and too much dopamine – you lose control over your mind. Is that so Arvid Carlsson? |
|  | Arvid Carlsson: As well as the body. |
| Q23 | But is there some sort of relation between the mind and the body in this respect that is basically the same mechanism that in a way controls the material world and the mental world? |
|  | Arvid Carlsson: That’s a very interesting question. Anatomically the wiring that analyse movements and the wiring that analyse mental processes are very similar. The balance between different neurotransmitters involved in either of these two is very similar. And have probably evolved along with each other which, in a way, makes a lot of sense because if one goes ahead of the other you’ll have no use for it. The mind and movement have to evolve in parallel. |
| Q23 | And in this system you have discovered the chemical signal substances between the connection between the nerves, and Paul Greengard your discovery is really what is happening inside the cell. How does your discovery relate to how we react and how we are, how we experience the world? Are there any connections that you have thought of? |
|  | Paul Greengard: The work that we did elucidates how these chemicals, the neurotransmitters which are the mechanism by which the nerve cells communicate with each other, how they produce their responses in the target cells on which they act. |
| Q23 | And they are related to what sort of mental phenomena? |
|  | Paul Greengard: All mental phenomena, memory, consciousness and everything else, is all attributable to the behaviour of nerve cells and what the three of us are doing is trying to understand how one nerve cell communicates with another. It’s through the release of a chemical, a neurotransmitter which activates the second nerve cell and then what happens in the second nerve cell once the neurotransmitter activates it and then how that in turn sends a neurotransmitter to the third nerve cell. What we’re doing at this present level, all three of us, is to understand these biological systems going on, these biochemical molecular systems. Other types of neuroscientists, brain scientists, will take the kind of things that we’re doing and try to relate them to the higher order of behaviour in the nervous system. |
| Q23 | But if Arvid Carlsson has done something in between the synapses where the signals are changing the connections between them, you’re only working with molecules inside the cell and how molecules are changing their shape and their effectiveness, what they do, the proteins we are talking about. |
|  | Paul Greengard: What we’ve done is to take these neurotransmitters that Arvid Carlsson had been studying and study exactly how they produce chemical and electrical changes in the nerve cells, working out what those biochemical steps are. |
| Q23 | And they are related to memory in what way? |
|  | Paul Greengard: That remains to be understood to a large extent. Except Eric Kandel’s work addresses that and maybe he’d like to speak to that. |
| Q23 | So, memory and changes inside the nerve cells, Eric Kandel. What is the concept or idea? |
|  | Eric R Kandel: Let me pick up what Paul Greengard was saying. One way to conceive of the contribution the three of us have made is to think of two sets of processes in the brain – mediating and modulating. That there are vast synoptic connections that are responsible for mediating many of the actions, for example motor actions, sensory perception. But the wonderful thing about the brain is that it can regulate the strength of connections. And my colleagues and I have shown that this occurs during learning, that the strength of connections are not fixed, but that inputs such as serotonergic input or dopaminergic input can modulate the strength of synoptic connections. And it does so by activating processes similar to the kind that Paul Greengard has described. In *Aplysia* one can show … |
| Q23 | *Aplysia*, that is the sea snake that you have been working with? |
|  | Yes, one can show that in fact that a very simple withdrawal reflex, like the withdrawal of a hand from a hot object, can be dramatically amplified by an aversive stimulus. And that amplification involves activation of one of these modular choice systems, the serotonergic system that activates a signalling system within the cell. And activation of that signalling system causes strengthening of the synoptic connection, which is responsible for the enhanced withdrawal.That means that there is a physical change of the size, so memories are actually made of these changes.Eric R Kandel: Anatomical changes. That’s right.This is somewhat exciting that the fast reactions, that is electricity and the somewhat slower …Eric R Kandel: The fast, and not simply electricity, the faster also chemical transmitters but they act on different receptors.But long term things are also represented by long term changes.Eric R Kandel: That’s right. |
| Q14 | You have all been part of a dramatic shift in paradigm when it comes to looking at the brain because all electrophysiology before and when you entered this stage you changed the picture totally into biochemistry. Arvid Carlsson, why did you choose to go contrary and against everyone else? |
|  | Arvid Carlsson: I think it depended to some extent on ignorance. I was not so well read in the field of brain physiology, so I could look at the facts in a simple, straight forward way, whereas those people who were burdened by a lot of knowledge, they had to think in other terms. They were, so to speak, fixed in the dogma. I was outside, just because of my ignorance, I think. |
| Q11 | Eric Kandel and Paul Greengard, what makes someone want to go towards the conventional wisdom of the time? |
|  | Paul Greengard: In the case of the study of the brain at the time that Arvid, Eric and I did our work, there were two approaches to understanding brain function. There were physiologists who worked in physiology departments and studied the electrical properties of nerve cells. And there were biochemists working in biochemistry laboratories who took a brain or a liver or a muscle and threw it into a homogeniser and studied the chemicals in the brain. And the two groups did not interact. The people sitting biochemistry were only interested in the biochemistry of the brain. The people doing physiology were only interested in the electrical property of the brain. In one sense we were not going against dogma. There was very little prior art out there. In my own case, my work was guided by the hypothesis that a particular mechanism that had been shown to work in the endocrine system, in which hormone released from one cell activates a target cell, that that system might be analogous to how two nerve cells communicate with each other. And that is through a chemical mechanism, that hypothesis turned out to be correct. |
| Q11 | Eric Kandel, you started off as being a psychoanalyst interested in psychoanalysis and everyone thought that was the gateway to the brain at that time. How come that you didn’t believe it? |
|  | Eric R Kandel: I did at the beginning and I still find the psychoanalytic view a rich and nuance view of the mind. I just became disappointed as I continued my medical education with how much empirical evidence there was to support it and how devoid it was in thinking about the brain. I became a little bit interested in the brain and as I got more deeply involved I became fascinated with it. And it struck me that memory is the central question in psychoanalysis. And in the 1950s when I began, the dominant view of the brain was that of Karl Lashley at Harvard, who showed that memory was not localisable. That you could remove many regions of the brain and not interfere with memory. What Lashley did not realise is that animals are very smart and if you remove a part of the brain, for example, let’s just say they’re doing a spatial task, if you remove the visual part of the brain, they will use tactile stimuli to find the way, or smell. They have lots of different strategies they can use. I thought one needed to take an extremely simple animal, an extremely simple reflex, where there would be no question about localizability. |
| Q22 | Excuse me for interrupting, but I got so curious, but this is true that you have all entered a new way of looking at things that were contrary to the conventional views of the time. And still the question I am really curious about is how is your mental set up to want to go against this? |
|  | Eric R Kandel: I think each of the three of us gave a somewhat similar answer, in the sense that we did not think of ourselves as revolutionaries at the barricades. We were working along and we thought that one way of moving in the field was the sound one, it’s almost an intuition that this is the right way to go. It turned out be in opposition to what other people were thinking, but one wants to think in original ways, you try to tackle a problem you think is interesting and approach it in the way that you think is most profound.Paul Greengard: To amplify what Eric said, it’s not that we were going against conventional wisdom, we were following our own instinct. This must be the way it works. And then more conservative folks would say we were disagreeing with them, but we weren’t, we were just looking at things in a different way.So in a way it was a very unconscious way of …Eric R Kandel: That’s right. I think that’s absolutely right.Paul Greengard: No, I don’t understand what you mean, an unconscious way?You didn’t really think about going against what was the convention, you just did what you thought was working.Paul Greengard: It was nothing that they had done was wrong, we were exploring an area that other people hadn’t explored, I would say.Do you agree Arvid Carlsson?Arvid Carlsson: No. I was taken by surprise, I must say, when we reported on our data and all the big figures in the field said, no this can’t be true.Paul Greengard: But that’s true for all three of us.Arvid Carlsson: I mean, I was right and they were wrong. I mean that is how I experienced it. I wouldn’t like to give them any sort of excuse that we were right, all of us, after all. I don’t agree.Paul Greengard: Maybe add a certain limited truth, we said, look we think that there are other things going on than what you’ve been studying and there’s all this and this. And then we’d say, yes, there’s all this and this. And then we’d show it and they’d say, no, you’re wrong. We were never saying they were wrong, I don’t think. They were saying we were wrong.Arvid Carlsson: They were wrong, in my opinion.Eric R Kandel: I must say that Roy Spencer and I wrote an article in 1968, when we first began to realise that learning could be localised to specific synopses. And we pointed out that Lashley’s view, which was the dominant view, had misled the field. |
| Q34 | But if we look then in the future, this is not the last time where things are going to be turned upside down. Have you seen anything in the current science that indicates that there will be maybe a totally new model coming up of how the brain is working? Maybe adding some fundamental new knowledge to the function of the brain? |
|  | Paul Greengard: It’s exactly what I’m saying. There will be totally new ways of looking that will not necessarily be contradictory to what we did. What we’re doing is eliminating truths just like the people before us had even more eliminating truths, and the next people add on to that. And they’re not going to prove that the work that we did was incorrect, they’re going to show a new dimension.Eric R Kandel: It’s almost probabilistic in a sense. The views that we have ended up supporting existed before, just to a minor degree, so people had seen in the endocrine system the kinds of things that Paul discovered in the nervous system. Kajal had spoken about the fact that synopsis could be the site of memory storage. But at the time that we were working those views were rare, very few people held that. Most people held the opposing point of view. For example, many people felt that [Bernhard Katz](https://www.nobelprize.org/prizes/medicine/1970/katz/facts/) and [Eccles](https://www.nobelprize.org/prizes/medicine/1963/eccles/facts/) had described synoptic transmission in the nervous system, it was fast synoptic transmission. So they thought all synoptic transmission in the brain was fast. When Paul and I began to study slow synoptic transmission, they thought there’s something unusual about this and people were initially sceptical that this could be of importance. |
| Q35 | But when the two models that has exchanged for each other, the electrophysiological model, the biochemistry model, what do you think about the future, Arvid Carlsson, are there totally new things coming up? |
|  | Arvid Carlsson: I guess there will be paradigm shifts in the future. But I think it’s inherent in the definition of dogma that we cannot identify it. As soon as we identify it as a dogma, it’s no more a dogma. |
| Q35 | But before there’s a thunderstorm coming up you can always see a little glimpse of the lightening coming, do you see any glimpse here? |
|  | Eric R Kandel: We certainly see that. For example, we thought that the nervous system by the time a child is four or five years old, does not generate any more nerve cells. We thought that the number of nerve cells in the brain are limited – if you lose nerve cells as a result of disease, stroke, Alzheimer’s disease, there’s no way of replenishing those nerve cells from the cells in the brain. There’s now increasing evidence that there is a primitive population of cells that stays around in the brain and they can be the source of additional cells later on. That could be the basis of a new development that would enrich our understanding. So I think that’s a very important development. |
| Q35 | And what would be the conceptual change of that idea? |
|  | Paul Greengard: Right now it’s thought that the brain has very little ability to repair itself. And with these new ideas that’s not the case. I would like to go back and correct something that I said, refer to something Arvid said on this. The people who are our predecessors, what they did was not wrong, their interpretation was wrong. For example, in his case, they said no, this molecule dopamine cannot be a neurotransmitter, so in that sense they were wrong. The experimental work they had done was correct, their interpretation was not correct. This is, in my case, they said these slow biochemical reactions cannot be involved in mediating communication between nerve cells, they were wrong about that. |
| Q24 | But then finally, Arvid Carlsson, do you agree with Eric Kandel that there may be a totally new way of looking on the dynamics of the brain, which is really at the heart of his statements? |
|  | Arvid Carlsson: One direction that I think will become very important is the understanding of the interaction between the different neurotransmitters in complex neuro-circuitries. And there are new possibilities to approach these complex problems. And that deals with something that we can call pattern analysis. You can collect enormous number of data and feed into computers and the computers will feed back to you pictures of the data, that actually are patterns of very, very complex processes in the brain, by means of which you can come closer to these very, very complex mechanisms that deal with the mind, feelings and cognition and so forth.And maybe even get a picture of the conscious experience then on the screen.Arvid Carlsson: Yes, and also to distinguish between different personalities. By means of imaging you will tell this is a happy fellow and this other fellow here has a short fuse, that kind of thing.Eric R Kandel: I also think that the human genome is going to enlighten our understanding of mental processes. One of the deep questions that is a confronted analysis of the mind, has been to what degree is the mind built on the base of genetic information? What is nature versus nurture? What do you inherit versus what do you acquire? And most personality traits are quite complex, so they’re not attributable to one or two genes, so they’ve been very hard to decipher. But now that we will have the whole human genome, we’ll be able to look at patterns of genes and we’ll see to what degree any of our behavioural patterns derive from familial traits versus acquired or learned traits. I think that’s going to be a very rich area for investigation.Paul Greengard: I would like to go back to your original question and ask you and my two colleagues whether there is any reason to think that we won’t be able to understand the nature of consciousness or any other aspect of the brain. What reason is there for pessimism, given the history of the last decade?Eric R Kandel: I think it’s hard to know what the limitations of knowledge are. I think it is hard to know at this particular point whether the optimism that we all share, that science can solve all problems in the universe, is in fact true. We’ve solved many problems so far, but there is the possibility that there are limitations to human understanding which we and the computers that we develop will not be able to solve.Paul Greengard: At the moment we have not reached that point.Eric R Kandel: We have not reached that point. |
| ID | 0560 |
| Biographical | Prologue: Life in Vienna in the 1930s There was little in my early life to indicate that an interest in biology would become the passion of my academic career. In fact, there was little to suggest I would have an academic career. Rather, my early life was importantly shaped by my experiences in Vienna and I spent many years later coming to grips with the circumstances and place of my birth.I was born in Vienna on November 7, 1929, eleven years after the multiethnic Austro-Hungarian Empire fell apart following its defeat in World War I. Although Austria had been radically reduced in size (from 54 million to only 7 million inhabitants) and in political significance, its capital, the Vienna of my youth, was still intellectually vibrant, one of the great cultural centers of the world. A city of one and a half million people, it was home to Sigmund Freud, Karl Kraus, Robert Musil, Arthur Schnitzler, and for a while Arnold Schoenberg. The music of Gustav Mahler and of the earlier 19th Century Vienna school resonated throughout the city, as did the bold expressionist images of Gustav Klimt, Oskar Kokoschka, and Egon Schiele. Even as it thrived culturally, however, Vienna in the 1930s was the capital city of an oppressive, authoritarian political system. I was too young to appreciate its cultural richness, but I sensed later, from the perspective of a more carefree adolescence in the United States, the oppressive conditions in Vienna that affected my early youth.Even prior to the Anschluss in 1938, anti-Semitism was a chronic feature of Viennese life. Jews, who made up nearly 20% of the city’s population, were discriminated against in the Civil Service and in many aspects of social life. Nonetheless, they were fascinated by the city in which they had lived for over a thousand years. My parents genuinely loved Vienna, and in later years I learned from them why the city exerted a powerful hold on them and other Jews. My parents loved the dialect of Vienna, its cultural sophistication, and artistic values. “The greatest grim irony of all was the fierce attachment of so many Jews to a city that through the years demonstrated its deep-rooted hate for them,” wrote George Berkley, the American historian of Vienna and its Jews. This fierce attachment was considered by the historian Harvey Zohn to be the most tragically unrequited love in world history.In spite of the hostile climate, Austrian Jews continued to make remarkable contributions to theater, music, literature, science, and medicine in the period between the two World Wars. The Salzburg Festival was directed by Max Reinhardt; the Vienna Opera was conducted by Bruno Walter. Stefan Zweig and Franz Werfel were two of the most popular writers in the German language, and [Elias Canetti](https://www.nobelprize.org/nobel_prizes/literature/laureates/1981/index.html), who later won the Nobel Prize in Literature for books describing his youth in Vienna, began writing these in the 1930s. Two of the three Austrians to be awarded the Nobel Prize in Physiology and Medicine in the 1930s were of Jewish origin: [Karl Landsteiner](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1930/index.html) was honored in 1930 for his discovery of blood groups and [Otto Loewi](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1936/index.html) in 1936 for discovering acetylcholine, a chemical transmitter that slowed the heart. Of the 52 Olympic medals earned by Austrian athletes from the beginning of modern Olympics to 1936, 18 were won by Jewish Austrians. Fully half of the practicing physicians and medical faculty at the University of Vienna were Jewish. This, in fact, was the last period during which Viennese medicine still attracted students and patients from all over the world. They came to study with, or to be treated by, pioneers in diagnostics and therapeutic medicine, such as the pediatrician Béla Schick, the ear specialist Heinrich von Neumann, and the psychoanalyst Sigmund Freud. As this listing makes clear, the period of my early youth has been characterized, appropriately, as “the final flowering of the Austrian Jewish intellectual activity.”My parents were not born in Vienna, but they had spent much of their lives there, having each come to the city at the beginning of World War I when they were still very young. My mother, Charlotte Zimels, was born in 1897 in Kolomea, a town of about 43,000 inhabitants in Galicia, a region of the Austro-Hungarian Empire. (Kolomea now is part of the Ukraine and has been renamed Kolomyya.) Almost half the population of Kolomea was Jewish, and the Jewish community had a very active culture. My mother came from a well-educated middle-class family, and although she had spent only one year at the university in Vienna, she spoke and wrote English as well as German and Polish.My father Herman was born into a poor family in 1898 in Olesko, a small town of about 3,500 people near Lvov (Lemberg), now also part of the Ukraine. During World War I he was drafted into the Austria-Hungarian Army directly from high school. After the war he worked to support himself and never went back to school.My parents met in Vienna and married in 1923, shortly after my father had established himself as the owner of a small toy store. My brother Lewis was born on November 14, 1924. I was born five years later. We lived in a small apartment at Severingasse 8 in the 9th district, a middle-class neighborhood near the medical school, and not too far from Freud’s apartment, although we had no association with either. Both of my parents worked in the store, and we had a full-time housekeeper to help out at home.I went to a school near our house. As with most elementary schools in Vienna, it was very traditional and very good, and I followed the well-trodden trail that my exceptionally gifted brother Lewis had blazed five years earlier in the same school with the very same teachers. Throughout my years in Vienna I felt that his was an intellectual virtuosity that I would never match. By the time I began reading and writing, he already was starting to master Greek and to play the piano.My fondest early memories are of family get-togethers and vacations. On Sunday afternoons my Aunt Minna (my mother’s sister) and Uncle Srul would come for tea. This was an occasion for my father and uncle to play cards, games at which my father excelled and which brought out great animation and humor in him. We celebrated Passover in a festive way at the home of my grandparents Hersch and Dora Zimels, and we invariably went on vacation in August to Monichkirchen, a small farming village in the southeast portion of Lower Austria, not far from Vienna.It was just as we were about to depart for Monichkirchen in July of 1934 that the Austrian Chancellor, Engelbert Dollfuss, who had outlawed the Nazi Party, was assassinated by a band of Austrian Nazis disguised as policemen – the first political storm to register on my slowly maturing political awareness. Following the Dollfuss assassination and during the early years of the chancellorship of his successor, Kurt von Schuschnigg, the Austrian Nazi Party went further underground, but it continued nonetheless to gain new adherents, especially among teachers and other civil servants. Paradoxically, the Austrian drive toward authoritarianism was abetted by Dollfuss’s own political attitudes and actions. Modeling himself on both Mussolini and Hitler, Dollfuss renamed his Christian Socialist Party the *Fatherland Front*, and took to wearing a modified swastika. To assure his own control of the government he abolished Austria’s Constitution and outlawed not only the Nazi Party but *all* opposition parties. Thus, although Dollfus opposed the efforts of the Austrian National Socialist movement to form a Pan-German state with Germany, his abolition of the Constitution and of other political parties helped open the door for Hitler to march in.And, as I well remember, march in he did. Since his youth, Hitler had dreamed of the union of Austria and Germany. It is therefore not surprising that a key point in the Nazi program, from its beginning in the 1920s, was a merger of all German-speaking people into a Greater Germany. In the fall of 1937 Hitler began to act on this program by raising the level of rhetoric and threatening to move against Austria. Schuschnigg, eager to assert Austria’s independence, met with Hitler on February 12, 1938 in Berchtesgaden. Hitler showed up with two of his generals in tow and threatened to invade Austria unless Schuschnigg, lifted the legal restrictions on the Austrian Nazi Party and appointed three Austrian Nazis to key ministerial positions in the Austrian Cabinet. Schuschnigg refused, but as Hitler continued to intimidate him, Schuschnigg compromised and agreed to a legalization of the Nazi party and to granting it two cabinet positions. The agreement between Schuschnigg and Hitler so emboldened the Austrian Nazis that they began to challenge the Austrian government in a series of incidents that the police had difficulty controlling. Faced with Hitler’s aggression from without and the Austrian Nazi rebellion from within, Schuschnigg took the offensive on March 9th and boldly called for a plebiscite on Austria’s autonomy to be held four days later, on March 13th.This courageous move caught Hitler by complete surprise, an awkward surprise since it seemed almost certain that the vote would favor an independent Austria. Hitler responded by mobilizing troops and threatening to invade Austria unless Schuschnigg postponed the plebiscite, resigned as chancellor, and formed a new government with an Austrian Nazi, Arthur Seyss-Inquart as chancellor. Schuschnigg turned for help to England and Italy, two countries that had formerly supported Austrian independence. But on this occasion both countries failed him and did not respond. Abandoned by his potential allies and concerned about needless bloodshed, Schuschnigg resigned on the evening of March 11th. “Austria is yielding to force,” he announced in an emotional farewell radio address to the nation. “God protect Austria.” Even though Schuschnigg had resigned and President Miklos of Austria gave in to all the German conditions Hitler nonetheless invaded Austria.Hitler’s triumphal march into Vienna and his overwhelming reception by the Viennese public made an indelible impression on me. My brother had just finished building his first short-wave radio receiver, and on the evening of March 13th we both were listening with earphones as the broadcaster described the earlier crossing of the Austrian border by German troops on the morning of March 12th. Hitler followed later in the afternoon of that day, crossing the border first at Braunnau am Inn, his native village, and then moving into Linz, the capitol of Upper Austria, where people welcomed him in the marketplace as their native son, screaming “Heil Hitler.” Of the 120,000 people of Linz, almost 100,000 came out to greet Hitler. In the background the Horst Wessel song, one of the hypnotic Nazi marching songs that even I found captivating, blared forth. On the afternoon of March 14th Hitler’s entourage reached Vienna, where a wildly enthusiastic crowd welcomed him as the hero who had unified the German-speaking people.The extraordinary reception in Linz and Vienna caused Hitler to change his plan. He now realized the Austrians would not demand the status of a relatively independent protectorate of Germany he had planned for them. The enthusiastic welcome convinced him that Austria would readily accept, indeed would welcome, total annexation. For it seemed as if everyone, from the modest shopkeepers to the most elevated members of the academic community, now embraced Hitler. In a shocking move, even Theodor Cardinal Innitzer, the influential Archbischop of Vienna, welcomed Hitler and ordered all the Catholic churches in the city to fly the Nazi flag and to ring the church bells in honor of Hitler’s arrival in Vienna. As the Cardinal personally greeted Hitler, he assured him of his own loyalty and that of all Austrian Catholics – which was most of the population of Austria. The Cardinal promised Hitler that Austria’s Catholics would become “the truest sons of the great Reich into whose arms they had been brought back on this momentous day,” provided that the liberties of the Church were respected and its role in the education of the young guaranteed.That night, and for days on end, all hell broke loose. Viennese mobs erupted in nationalistic fervor, expressed by beating up Jews and destroying their property. Foreign commentators, long accustomed to Nazi tactics in Germany, were astonished by the wanton brutality of the Austrian Nazis, and even German Nazis were amazed and emboldened by the viciousness of the attacks in Vienna.In his autobiography the German playwright Carl Zuckmayer, who had moved to Austria in 1936 to escape Hitler, described Vienna during the days following the annexation of Austria as a city transformed “into a nightmare painting of Hieronymus Bosch.” It was as if:… “Hades had opened its gates and vomited forth the basest, most despicable, most horrible demons. In the course of my life I had seen something of untrammeled human insights of horror or panic. I had taken part in a dozen battles in the First World War, had experienced barrages, gassings, going over the top. I had witnessed the turmoil of the post-war era, the crushing uprisings, street battles, meeting hall brawls. I was present among the bystanders during the Hitler Putsch in 1923 in Munich. I saw the early period of Nazi rule in Berlin. But none of this was comparable to those days in Vienna. What was unleashed upon Vienna had nothing to do with seizure of power in Germany … What was unleashed upon Vienna was a torrent of envy, jealousy, bitterness, blind, malignant craving for revenge. All better instincts were silenced … only the torpid masses had been unchained … It was the witch’s Sabbath of the mob. All that makes for human dignity was buried.”Having watched the build-up of anti-Jewish laws in Germany following Hitler’s rise to power in 1933, my parents did not need much convincing to realize that the violence at the time of the annexation was not likely to fade away. We knew that we had to leave – and to leave as soon as possible. My mother’s brother, Berman Zimels, had emigrated a decade earlier to New York and established himself as an accountant. He provided us expeditiously with affidavits that assured he would support us upon our arrival in the United States. Even with these affidavits it took about a year for my parents’ Polish quota number to be called. When our number finally was called, we had to emigrate in stages because of United States immigration laws. My mother’s parents left first in February 1939, my brother and I next in April 1939, and finally my parents in September 1939, only days before World War II broke out.During the one year that we lived under Nazi rule, we experienced directly Vienna’s humiliating form of anti-Semitism. The day after Hitler marched into Vienna, every one of my non-Jewish classmates – the entire class with the exception of one girl – stopped talking and interacting with me. In the park where I played I was taunted and roughed up. This viciousness toward Jews, of which my treatment was a mild example, culminated in the horrors of Kristallnacht, November 8, 1938. On the morning of November 7, 1938, a 17 year-old Jewish youth, who was distraught over his parent’s tragic fate at the hands of the Nazis, shot a third secretary in the German Embassy in Paris, mistaking him for the German Ambassador. In retaliation for this single act, almost every synagogue in Germany and Austria was set on fire. Of all the cities under Nazi control, the destructiveness in Vienna on Kristallnacht was particularly wanton. Jews were taunted and brutally beaten, expelled from their businesses, and temporarily evicted from their homes so that both could be looted by their neighbors. My father was rounded up by the police together with hundreds of other Jewish men. He was released a few days later only because he had fought in the Austria-Hungarian army as a soldier in World War I. I remember Kristallnacht even today, more than 60 years later, almost as if it were yesterday. It fell two days after my ninth birthday, on which I was showered with toys from my father’s shop. When we returned to our apartment a week or so after having been evicted, everything of value was gone, including my toys.My last year in Vienna was, in a way, a defining year, and it fostered the profound sense of gratitude I came to feel for the life I have led in the United States. It is probably futile, even for someone trained in psychoanalytic thinking as I am, to attempt to trace the complex interests and actions of my later life to a few selected experiences of my youth. Nevertheless I cannot help but think that the experiences of my last year in Vienna helped to determine my later interests in the mind, in how people behave, the unpredictability of motivation, and the persistence of memory. Over the years I have returned to these subjects repeatedly as my professional interests evolved from a youthful interest in European intellectual history at Harvard, where I studied the motivation of German intellectuals during the Nazi era, to an interest in psychoanalysis with its more systematic approach to mental processes, and finally to my interests in the biology of conscious and unconscious memory.My early experiences in Vienna almost certainly contributed to my curiosity about the contradictions and complexities of human behavior. How are we to understand the sudden release of such great viciousness in so many people? How could a highly educated and cultured society, a society that at one historical moment nourished the music of Haydn, Mozart, and Beethoven, in the next historical moment sink into barbarism?Clearly the answer to this question is complex, and many scholars of this period have attempted partial answers. One conclusion, troubling to an academic like myself, is that a society’s culture is not a reliable indicator of its respect for human life. This rather simplistic conclusion, of course, raises the question: How can values within a society become so radically dissociated? As far as I can tell, the Viennese achieved this dissociation by shifting their frame of reference. By defining Jews in racial rather than religious terms, they were able to exclude Jews from the “more highly evolved European Aryan race,” the race they believed to be responsible for the rise of Western civilization.My last year in Vienna was likely also an important factor in my more specific later interest in the mechanisms of memory. I am struck, as others have been, at how deeply these traumatic events of my childhood became burned into memory – and I would emphasize that my experiences were trivial compared to those of so many who were seriously harmed or killed. For me, the frightening experiences of my last year in Vienna are certainly the most powerful of my “flashbulb memories,” the emotionally charged and vivid memory of significant events that came to fascinate me.Resettlement in the United States Needless to say, arriving in the United States in April of 1939 was like a breath of fresh air. I never actually said “free at last,” but I felt it then and have ever since. We settled in Brooklyn and lived at first with my mother’s parents. My grandfather Hersch Zimels was a religious and scholarly man who was somewhat unworldly. My brother said that my grandfather was the only man he knew who could speak seven languages but could not make himself understood in any one of them. My grandfather and I liked each other a great deal, and he readily convinced me that he should tutor me in Hebrew during the summer of 1939 so that I might be eligible for a scholarship at the Yeshiva of Flatbush, an excellent Hebrew parochial school that offered both secular and religious studies at a very high level. With his tutelage I entered the Yeshiva in the fall of 1939. By the time I graduated in 1944 I spoke Hebrew almost as well as English, had read through the five books of Moses, the books of Kings, the Prophets and the Judges in Hebrew, and also learned a smattering of the Talmud.After my parents arrived, my father worked in a toothbrush factory. Even though he was not fond of working in this factory, he threw himself into the work with his usual energy and was soon reprimanded by the union steward for producing toothbrushes too quickly and making other workers appear slow. My father was undeterred. He simply loved America – he often referred to it as the “goldene Medina,” the golden state. Even while still in Vienna he had read avidly the novels of Karl May, an author whose books celebrated the conquest of the American West and the bravery of the American Indians.With time my father managed to save enough money to rent and outfit a modest clothing store at 411 Church Avenue in Brooklyn. We lived in an apartment above the store. My father and mother worked together and sold simple women’s dresses and aprons, and men’s shirts, ties, underwear, and pajamas. In this way my parents earned enough not only to support us all but also to send me to college and medical school. My father worked in that store until the week before he died at age 78 in 1976. My mother sold the store soon thereafter and died in 1991 at age 94.Erasmus Hall High School and Harvard College In 1944, when I graduated from the Yeshiva of Flatbush elementary school, it did not as yet have a high school. I went instead to Erasmus Hall High School, a local public high school in Brooklyn that was then academically very strong. Here I became interested in history, in writing, and in girls. I worked on the school newspaper and became sports editor. I also played soccer and was co-captain of the track team. At the urging of one of my history teachers, John Campagna, a Harvard alumnus, I applied to Harvard College and was one of two students out of my class of about 1,400 to be admitted, both of us on scholarships! Fair Harvard indeed!Even though I was thrilled by my good fortune, I was apprehensive about leaving Erasmus, convinced that I would never again feel the sheer joy I had experienced there. It was at Erasmus that I first sensed myself emerging from behind the shadow of my brother Lewis. I now had distinctive interests of my own – jazz music, sports, American constitutional history – things that did not interest Lewis. At Harvard I majored in 19th and 20th century European history and literature and wrote my honors dissertation on *The Attitude Toward National Socialism of Three German Writers: Carl Zuckmayer, Hans Carossa, and Ernst Junger*. Each of these writers was then still alive and represented a different position on the political spectrum of fascism – uncompromising liberal opposition and emigration (Zuckmayer), resigned acceptance and internal (spiritual) emigration (Carossa), and intellectual support (Junger). I came to the rather depressing conclusion that many German artists, intellectuals, and academics succumbed all too eagerly and opportunistically to the nationalistic fervor and racist propaganda of National Socialism. Historical studies have found that Hitler did not have widespread popular support in his first year in office. Had intellectuals mobilized effectively and brought along segments of the general population, Hitler’s government might well have been toppled.I originally thought of doing graduate work in European intellectual history, along the lines of my undergraduate dissertation. However, in the course of my studies at Harvard I befriended a fellow student, Anna Kris, who had also emigrated from Vienna with her parents, Ernst and Marianne Kris, both prominent psychoanalysts from Freud’s circle. Anna and her parents were very influential in getting me interested in psychoanalysis. It is difficult to recapture now the extraordinary fascination that psychoanalysis held for young people in 1950. During the first half of the 20th century psychoanalysis provided a remarkable set of insights into the mind – insights about unconscious mental processes, psychic determinism, and perhaps most interesting, the irrationality of human motivation. As a result, in 1950, psychoanalysis outlined by far the most coherent, interesting, and nuanced view of the human mind than did any other school of psychology. In addition, Anna’s parents, who represented academic psychoanalysis in its most intellectual and interesting form, were extraordinary people – intelligent, cultured, and filled with enthusiasm. Ernst Kris, a former curator of applied art at the Kunsthistorisches Museum in Vienna, had been a world class art historian before becoming a psychoanalyst. After taking up psychoanalysis, he focused on the psychology of art, an area in which he helped train among others the great historian Ernst Gombrich. Marianne Kris, a wonderful therapist, was the daughter of Oskar Rie, a well-known Viennese pediatrician and Freud’s best friend. Marianne in turn was a close friend of Freud’s distinguished daughter, Anna Freud.Both Ernst and Marianne Kris were extremely generous and encouraging to me, as they were to Anna’s other friends. As a result of my frequent interactions with them and their colleagues, I was converted to their view that psychoanalysis offered a fascinating new approach, perhaps the only approach, to understanding the mind, including the irrational nature of motivation and unconscious and conscious memory. With time this began to seem much more exciting and interesting to me than European literature and intellectual history.Medical School at N.Y.U. To become a practicing psychoanalyst, however, it was best to go to medical school, become a physician, and train as a psychiatrist – a course of study I had not previously considered. So in 1951, almost impulsively, I went to summer school at Harvard and took the required course in introductory chemistry. That summer in Cambridge I shared a house with Robert Goldberger, Henry Nunberg, James Schwartz, and Robert Spitzer, and we all became lifelong friends. A few months later, based on this one chemistry course and my overall college record, I was accepted at N.Y.U. Medical School, with the proviso that I complete the remaining course requirements before I entered medical school in the fall of 1952.I entered N.Y.U. Medical School dedicated to studying psychiatry and becoming a psychoanalyst. Although I stayed with this career plan through my internship and psychiatric residency, by my senior year in medical school I had become so interested in the biological basis of medical practice (as had everyone else in my class) that I decided I had to learn something about the biology of the mind. In the 1950s most psychoanalysts thought of the mind in nonbiological terms. However, several psychoanalysts – particularly two that I got to know personally and who had a background in neurology, Lawrence Kubie and Mortimer Ostow – had begun to discuss the potential importance of the biology of the brain for the future of psychoanalysis. After considerable discussion with them and with another biologically oriented psychoanalyst, Sydney Margolin, I decided to take an elective period at Columbia University with Harry Grundfest. At that time N.Y.U. had no one on the faculty who was doing basic neural science, and in 1955, Grundfest was the most intellectually interesting neurobiologist in the New York area.Harry Grundfest’s laboratory at Columbia University Grundfest had obtained his Ph.D. in zoology and physiology at Columbia in 1930 and went on to a post-doctoral fellowship at Columbia, studying with Selig Hecht, an outstanding psychophysicist interested in phototransduction – the transformation of light into neural signals. (Hecht also was the teacher of [George Wald](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1967/index.html), who won the Nobel Prize in 1967 for discovering the chemical structure of the visual pigments.) Grundfest then joined the Rockefeller Institute in 1935, where he remained for a decade collaborating with [Herbert Gasser](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1944/index.html). In 1944, while Grundfest was in his lab, Gasser shared the Nobel Prize in Physiology or Medicine with [Joseph Erlanger](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1944/index.html) for introducing the oscilloscope to neurophysiological studies. This methodology allowed accurate temporal resolution of the waveform and conduction velocities of the propagated action potential. In collaboration with Grundfest, Gasser elaborated on his discovery that the conduction velocity of the action potential is a function of the diameter of the axon. Grundfest also carried out reconstructions of the compound action potential from cross-sectional measurements of axonal diameters in mixed nerves, work that formed much of [Gasser’s Nobel Prize Lecture](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1944/gasser-lecture.html).In my decision to work with Grundfest, I was strongly encouraged by a new friend, Denise Bystryn, an extremely attractive and interesting French woman I had just met and would later marry. Denise is also Jewish. Her mother helped her father escape from a French concentration camp, and her parents survived the war by hiding from the Nazis in the southwest of France. During a good part of that time Denise was separated from her parents, hidden in a Catholic convent near Cahors. Denise’s experiences, although more difficult, paralleled mine in a number of ways that seemed significant to her but did not seem at all important to me when we first met. However, over the years, our shared experiences in Europe proved to be defining in both our lives.In 1949, Denise, her brother Jean-Claude, and her parents emigrated to the United States. Denise attended the Lycée Français de New York for one year and was admitted at age 17 to Bryn Mawr College as a junior. On graduating from Bryn Mawr at age 19, she enrolled at Columbia University as a graduate student in sociology. When we met she had just started research for her Ph.D. thesis in medical sociology with Robert Merton. Denise’s father, a gifted mechanical engineer who unfortunately died one year before I met Denise, had advised her to marry a poor intellectual because he would likely be sufficiently ambitious to do interesting scholarship. Denise believed she was following that advice (she certainly married someone who was poor) and always encouraged me to make decisions that favored my doing science.In Grundfest’s lab I spent the first several months working on a number of projects with Dominick Purpura, an independent young scientist just starting out on his own career of cortical physiology. To my surprise I found my first experience in a lab really interesting, and very different from the classroom. Of course the research questions we were asking fascinated me and the discussions were penetrating and enjoyable. Dominick was very bright and very entertaining. (I have referred to him as the Woody Allen of neurobiology.) But the actual performance of the experiments was also pleasurable and, when successful, very satisfying. Nevertheless, I began to worry about the methods we were using to address rather sophisticated questions about the electrical properties of dendrites. We were using evoked responses that were initiated by stimulating small areas of cortex, thereby activating thousands of neurons, and I thought these methods were too indirect to give easily interpretable results. Grundfest and Purpura, of course, were also concerned and talked repeatedly about doing direct intracellular recordings from cortical neurons, but neither thought this was likely to succeed.An introduction to Stephen Kuffler It was in this frame of mind that I was introduced to Stephen Kuffler, a Viennese trained physician turned physiologist, who (together with [Bernard Katz](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1970/index.html) and [John Eccles](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html)) was to become one of my great neurobiological heroes. One evening Grundfest threw into my lap the September 20, 1955 issue of the *Journal of General Physiology*, with three of Kuffler’s papers on excitation and inhibition in the dendrites and soma of isolated sensory nerve cells of the lobster and crayfish. Grundfest said something about Kuffler’s being very good, and that these papers provided direct evidence for the graded properties of dendrites evidence that was consistent with what he and Purpura were seeing in cortica; neurons. I took the issue home and read the papers as best I could. Although I understood relatively little, one thing stood out immediately. Kuffler was studying the dendrites in a preparation in which he actually saw the dendrites and could record from them directly. For studying dendrites Kuffler used an invertebrate sensory neuron that sent its dendrites into skeletal muscle much like the muscle spindles of vertebrates. In the introduction to the three papers Kuffler wrote:“The greatest advantage of the present preparation lies in its accessibility, since all cellular components can be isolated and visually observed. Further, the state of excitability of the structures could be controlled and graded by utilizing the physiological mechanisms given by the stretch receptor nature of the preparation…It seems of special interest that the sensory cell of crustacea possessed numerous anatomical features, which bear a striking resemblance to many central nervous system cells of vertebrates.”I learned from Kuffler’s papers a new criterion for how good science is done – the importance of having a preparation suitable to testing the questions to be answered. Kuffler taught me to respect the power of invertebrate neurobiology.On graduating from medical school in June 1956, I married Denise and, after a brief honeymoon in Tanglewood, I started an internship at Montefiore Hospital as she continued her thesis research at Columbia. I returned to Grundfest’s lab, spending six weeks with Stanley Crain, who had pioneered the electrophysiological study of nerve cells in tissue culture. Stanley taught me how to make microelectrodes and how to obtain and interpret intracellular recordings from the crayfish giant axon. These experiments confirmed the insights I had gained from reading Kuffler’s paper. From Stanley I also received my first insights into the universality of cellular processes.Based on my two brief periods in his laboratory, Grundfest offered to nominate me for a position at the NIH, an alternative to serving in the physician’s draft, which provided medical personnel for the military during the years following the Korean War. On the basis of Grundfest’s recommendation, I was accepted by Wade Marshall, Chief of the Laboratory of Neurophysiology at NIMH/NINCDS.The laboratory of neurophysiology at the National Institutes of Health By the time I arrived in Bethesda, Wade Marshall had passed the peak of what had been a remarkable career. In the 1930s he was arguably the most promising and accomplished young scientist working on the brain in the United States. As a graduate student at the University of Chicago in Ralph Gerard’s lab in 1936, he discovered that one could record electrical deflections in the somatosensory processing area of the cerebral cortex by moving the hairs of a cat’s limb. He appreciated that one might use this electrical signal (the evoked response) to map the representation of the body surface on the brain.To study this further, he joined Phillip Bard, Chairman of the Department of Physiology at the Johns Hopkins Medical School, as a post-doctoral fellow. In 1937, Bard had already established himself as a major presence in American neurophysiology. Together with his student Clinton Woolsey, Bard had surgically removed the somatic sensory cortex of the monkey and studied its effect on the “placing reaction,” a form of tactile behavior. Marshall joined up with Woolsey and Bard and together they carried out a classic series of studies in which they mapped sensory inputs from the body surface in the somatic sensory cortex and showed that a topographical representation of the entire body is wired into the brain. This provided the first systematic view of the neural representation in the brain of a sensory system. Today, this map is still shown in every textbook of neural science. Marshall next collaborated with John Talbott and mapped the retinal inputs in the striate cortex. Finally, with Harlow W. Ades, he mapped the cochlear inputs in the auditory cortex.With these classic studies Marshall revolutionized the study of the sensory representations in the brain and showed that the brain had systematic topographical maps of the sensory surface for each of the three major sensations – touch, vision, and hearing. These marvelous scientific achievements came at a price, however, leaving Marshall so psychologically fatigued that he collapsed and, for a number of years, left science altogether. When he returned, in about 1945, he moved on to a completely new problem: the study of spreading cortical depression, a propagating, reversible silencing of cortical electrical activity. Marshall enjoyed doing occasional experiments, but he had lost his scientific drive and now focused much of his energy and interests on administrative matters, which he did well. Although eccentric, moody, and somewhat unpredictable, he was a wonderful lab chief. In particular, he was supportive and generous to young scientists and gave us a great deal of freedom.Just before I arrived at NIH in 1957, the neurosurgeon William Scoville and the cognitive psychologist Brenda Milner had described the now-famous patient H.M. In order to treat intractable bilateral temporal lobe epilepsy, Scoville had removed on both sides of H.M.’s brain the medial temporal lobes, including a structure deep to them called the hippocampus. As a result of this procedure, H.M.’s seizures were largely eliminated. But, while retaining all cognitive functions, H.M. lost the ability to put new information into long-term memory. These findings pinpointed the medial temporal lobe and the hippocampus as sites specialized for memory storage.Until the Scoville and Milner paper, the person most identified with attempts to localize memory was Karl Lashley, Professor of Psychology at Harvard and perhaps the dominant figure in American neuropsychology in the first half of the 20th century. Lashley explored the surface of the cerebral cortex in the rat, and systematically removed different cortical areas. In so doing, he failed to identify any particular brain region that was special to or necessary for the storage of memory. Based on these experiments, Lashley formulated the law of mass action, according to which memory is not localized to any specific region of the cortex but was a distributed property of the cortex as a whole. The extent of any memory defect, Lashley argued, was correlated with the size of the cortical area removed, not with its specific location.Since I had already begun to think about problems in psychiatry and psychoanalysis in biological terms, the cell and molecular mechanisms of learning and memory struck me as a wonderful problem to study. I had first become interested in the study of learning at Harvard, where B.F. Skinner, the great behaviorist, was a dominant force in the 1950s. It was clear to me even then that learning and memory were central to behavior, and thus to psychopathology and to psychotherapy. Nothing was known about the cellular mechanisms of learning and memory, and now the cellular techniques for studying them were just becoming available – some beginnings of which I had learned from Stanley Crain in Grundfest’s lab.My initial ideas about how to tackle the biology of memory upon arrival at the NIH were confused and vague. Because intracellular recordings seemed to me such a powerful analytic tool for studying nerve cells, and because the hippocampus seemed particularly important for memory, I wanted to explore the hippocampus in cellular terms. This was made even more attractive for me because, as the great Spanish anatomists [Ramón y Cajal](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1906/index.html) and Lorente de Nó had pointed out, the cellular architecture of the hippocampus is remarkably conserved among mammals, and the main cell type, the pyramidal cell, is found in a discrete layer that is easy to target with microelectrodes. In addition, the pyramidal cells send their axons into a large fiber tract (the fornix), which allows the pyramidal cells to be identified electrophysiologically by stimulating the axons in the fornix and backfiring the pyramidal cells. I thought it would be interesting to compare the pyramidal neurons to the only other mammalian neurons that had been well studied at that time – the motor neurons of the spinal cord. I had the idea that the properties of the pyramidal cells themselves might reveal something about memory storage. I was emboldened to try this technically demanding study because Karl Frank was in the laboratory next to ours, pioneering the examination of spinal motor neurons with intracellular recordings in parallel with John Eccles. Although Frank himself thought that studying the hippocampus was chancy, he was not discouraging.Almost as soon as I began, my research took an extremely fortunate turn in the person of Alden Spencer, who arrived in Marshall’s lab having just graduated from the University of Oregon Medical School. Like me, Alden was becoming interested in the biology of learning and memory. It therefore took little effort for me to convince him that we should join forces on the hippocampus. Although Alden had no experience with intracellular recordings, he had done electrophysiological research on the brain at the University of Oregon Medical School, where he worked with John Brookhardt. Among Alden’s many remarkable talents, he had good surgical skills and a fine knowledge of the anatomical organization of the mammalian brain.Being both naïve and brash, we were not reluctant to tackle what appeared to Frank and others to be technically difficult problems, namely obtaining intracellular recordings from cortical neurons in a pulsating brain. Alden and I developed a simple way of reducing pulsations in the hippocampus that allowed us to obtain, on occasion, high-quality recordings for a long enough period – up to one hour – to carry out an initial analysis of the electrical properties of the hippocampal pyramidal cells. By applying to the hippocampus the powerful methodologies we learned from Frank, we easily picked some low-lying intellectual fruit. First, we found that action potentials in hippocampal neurons were initiated not only at the axon hillock, as in motor neurons, but also at a second site, which we inferred to be the apical dendrites. These putative dendritic action potentials, which we called fast prepotentials, appeared to trigger the firing at the axon hillock. Second, we found that the hippocampal neurons, unlike motor neurons, were not silent in the absence of synaptic activity, but tended to fire spontaneously, and that this firing often took the form of bursts of spikes that were maintained by summation of depolarizing afterpotentials. Third, we found that the hippocampal neurons engaged a powerful recurrent inhibitory system that gave rise to a prolonged inhibition – several orders of magnitude longer than the inhibition seen in the spinal cord.The mere technical success of obtaining intracellular recordings from hippocampal neurons, and the few interesting questions we were able to address, caught the enthusiastic attention of, and drew encouragement and help from, our senior colleagues at the NIH – Marshall, Frank, Michael Fuortes, Frank’s gifted colleague and the great Japanese-American biophysicist Ichiji Tasaki. When John Eccles visited the NIH, he also was generous in his comments. But even in our brashest moments, we both realized that ours was a typical NIH story. In the Intramural Program at the NIH, young inexperienced people were given the opportunity to try things on their own, knowing that wherever they turned there were experienced people to help out.Moreover, as Alden and I reviewed our work we realized that the cellular properties of hippocampal neurons were not sufficiently different from those of spinal neurons to explain the ability of the hippocampus to store memory. Thus, it dawned on us what in retrospect is quite obvious: that the neuronal mechanisms of learning and memory probably did not reside in the properties of the neurons themselves. Rather, because the signaling properties of neurons are quite alike, we began to think that what must matter is how neurons are functionally connected. The basis of learning must reside in the modification of interconnections by appropriate sensory signals. This conclusion, so clear in retrospect, emerged only gradually as we learned, mostly through reading and discussions with one another, to think more effectively about the biology of learning and memory.This realization led us to reappraise our strategy. Since the hippocampus has a large number of neurons and an immense number of interconnections, it was not the place to begin. Even though we were now quite familiar with the hippocampus, it would be extremely difficult to work out how sensory information specific to learning reached the hippocampus or how learned information processed by the hippocampus might influence motor output.Alden and I therefore became convinced that to make headway with the study of learning at the cellular level required a very different approach. Alden, a committed mammalian neurophysiologist, turned to the study of the spinal cord, particularly the modifiability of spinal reflexes, and went on to make important contributions in collaboration with Richard Thompson.However, even the spinal cord proved too difficult for a detailed cellular analysis, and both Alden and Thompson ended up leaving it.The search for a tractable system for studying learning Influenced by Kuffler, Grundfest, and Crain, I yearned for a more radically reductionist approach to the biology of learning and memory. I wanted a system that would serve the cellular study of learning as well as the squid giant axon had served for studies of the action potential, or the nerve-muscle synapse of the frog had served for the study of synaptic transmission. I wanted to examine learning in an experimental animal in which a simple behavior was modifiable by learning. Ideally that behavior should be controlled by only a small number of large and accessible nerve cells, so that the animal’s overt behavior could be related to events occurring in the cells that control that behavior.Such a reductionist approach has been traditional in biology. In neurobiology it is exemplified by the work on the squid giant axon by [Hodgkin](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html) and [Huxley](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1963/index.html), the nerve-muscle synapse of the frog by Bernard Katz, and the eye of *Limulus* by [Keefer Hartline](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1967/index.html). When it came to the study of behavior, however, most investigators were reluctant to apply a strict reductionist strategy. In the 1950s and 1960s it was often said that behavior was the area in biology in which simple animal models, particularly invertebrate ones, were least likely to produce fruitful results because the brain that really learns, the mammalian brain, especially the human brain, is so complex that inferences from studies of invertebrates would not stand up. It was thought that humans, because of higher-order capabilities not found in simpler animals, must have types of neuronal organization that are qualitatively different from those found in invertebrates. Although these arguments held some truth, they overlooked certain critical issues. Work by students of comparative behavior, such as [Konrad Lorenz](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1973/index.html), [Niko Tinbergen](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1973/index.html), and [Karl von Frisch](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1973/index.html), had already shown that certain behavior patterns, including elementary forms of learning, were common to humans and simple animals. From the outset I therefore believed that the mechanisms of memory storage were likely to be conserved in phylogeny, and that a cellular analysis of learning in a simple animal would reveal universal mechanisms that are also employed in more complex organisms.Not surprisingly, I was strongly discouraged in the early days from pursuing this strategy by some senior researchers in neurobiology, particularly John Eccles. His concern reflected, in part, the existing hierarchy of acceptable research questions in neurobiology. Few self-respecting neurophysiologists, I was told, would leave the study of learning in mammals to work on an invertebrate. Was I compromising my career? Of an even greater concern to me were the doubts expressed by some very knowledgeable psychologists I knew, who were sincerely skeptical that anything interesting about learning and memory could be found in a simple invertebrate animal. I had made up my mind, however. Since we knew nothing about the cell biology of learning and memory, I believed that any insight into the modification of behavior by experience, no matter how simple the animal or the task, would prove to be highly informative.After an extensive search that included crayfish, lobster, flies, and the nematode worm *Ascaris*, I settled on *Aplysia*, the giant marine snail. *Aplysia* offered three major technical advantages: (1) its nervous system has a small number of cells, (2) the cells are unusually large, and, as I realized with time, (3) many of the cells are invariant and identifiable as unique individuals. Before leaving the NIH in 1960, I arranged with Ladislav Tauc, one of the two people in the world then working on *Aplysia*, to join him in September 1962, as a postdoctoral fellow, as soon as I had completed my residency training. Here again, Denise’s advice was decisive. The only two people working on *Aplysia* were French – Tauc’s lab was in Paris, and Angelique Arvanitaki-Chalazonitis worked in Marseilles. So far so good! But, Denise, ever the Parisian chauvinist, thought that living in Marseilles would be like living in Albany (a small town in upstate New York). So Tauc and Paris it was, and that proved an excellent choice.Residency training in psychiatry at the Harvard Medical School However, before I would leave for Paris I had already committed to a two-year residency training in psychiatry. I therefore left the NIH in the spring of 1960 to start my psychiatric residency at the Massachusetts Mental Health Center of the Harvard Medical School. When I arrived at Harvard, I found an unanticipated bonus. Steven Kuffler, whose thinking had so influenced my own, had been recruited one year earlier from Johns Hopkins to build up neurophysiology at Harvard. Kuffler brought with him several young post-doctoral fellows – [David Hubel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/index.html), [Torsten Wiesel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1981/index.html), Ed Furshpan, and David Potter – each of whom was extraordinarily gifted. In this way Kuffler succeeded, in one fell swoop, in setting up at Harvard the premier group of neural scientists in the country. I now had my first opportunity to interact with Kuffler and with the remarkable people he had assembled around him. Even though I was in fulltime residency training, Kuffler and his group were extremely accessible, and their generosity allowed me to remain intellectually engaged in neurobiology. Moreover, Jack Ewalt, the Professor of Psychiatry at the Massachusetts Mental Health Center, provided me with funds and space so that I even managed to do some research in my spare time. I obtained the first intracellular recording from hypothalamic neuro-endocrine cells and found that these hormone-releasing cells had all the electrical properties of normal nerve cells.During my psychiatric residency I began to think about simple forms of learning in preparation for work on *Aplysia*. I read Kimble’s wonderful revision of Hilgard and Marquis’s classical text *Conditioning and Learning*, and I reread Skinner’s great book *The Behavior of Organisms*. This reading made me realize that the paradigms of simple learning articulated by [Pavlov](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1904/index.html) and Thorndyke, describing changes in behavior in response to controlled stimulation, included precise protocols for stimulating experimental animals. It occurred to me that the paradigms they described – habituation, sensitization, classical conditioning, and operant conditioning – could readily be adapted to experiments with an isolated *Aplysia* ganglion using artificial electrical rather than natural sensory stimuli. While recording the behavior of a single cell in a ganglion, one nerve axon pathway to the ganglion could be stimulated weakly electrically as a conditioned stimulus, while another pathway was stimulated as an unconditioned stimulus, following the exact protocol used for classical conditioning with natural stimuli in intact animals. One could then see whether synapses changed systematically in response to these patterns of stimulation, and, if so, whether the synaptic changes in any way paralleled changes in the overt behavior of intact animals, which classical psychologists had described. It thus dawned on me that in this way one could begin to take an initial step toward the study of learning in the intact animal by analyzing what I soon began to call *analogs of learning* – higher-order stimulus sequences based on patterns of stimulation used in learning experiments in intact behaving organisms, but applied directly to a neuronal system.Paris, Aplysia, and neural analogs of learning: chemical synapses prove to be remarkably plastic Based on this idea, I wrote a successful application for an NINCDS postdoctoral fellowship for work to be done in Tauc’s laboratory. And in September 1962, about a year after our son Paul was born, the three of us took off for Paris. Tauc proved an excellent person to work with; both our interests and our areas of competence complemented each other. He was, of course, completely at home with *Aplysia*, but he also had a strong background in physics and biophysics, which I lacked. Born in Czechoslovakia, Tauc had originally studied the electrical properties of plant cells. As a result, he had no experience with behavior and had up to this point thought little about the problems of neuronal integration that dominated thinking about the mammalian brain – problems that Alden and I had discussed incessantly. Tauc was quite enthusiastic about my approach, which proved even more effective than anticipated. In my cellular studies of analogs of habituation, sensitization, and classical conditioning in *Aplysia*, I found synaptic changes that paralleled the behavioral changes seen in experiments on intact animals. This encouraged us to write in our 1965 paper in the *British Journal of Physiology*:“The fact that the EPSPs (excitatory postsynaptic potentials) can be facilitated for over half-an-hour with an input pattern scheme designed to simulate a behavioral conditioning paradigm, also suggests that the concomitant changes in the efficacy of synaptic transmission may underlie certain simple forms of information storage in the intact animal.”A brief return to the Harvard Medical School Upon completing a very productive 16-month stay in Tauc’s laboratory, I returned to Harvard in November 1963. More than a year and a half later, in July of 1965, our daughter Minouche was born, completing our family – one boy, one girl – exactly what we had hoped for.During this period I struggled with three choices that were to have a profound effect on my subsequent career. First, I realized that to do effective science I could not combine basic research and a clinical practice in psychoanalysis, as I had earlier hoped. I therefore decided not to apply to the Boston Psychoanalytic Institute, a decision which meant that I would not attempt to become a psychoanalyst but devote myself full-time to science. It was my strong sense that one of the problems within academic psychiatry, a problem that has become only worse with time, is that young people take on much more than they can handle effectively. I concluded that I could not and would not do that.The second choice arose a few months later when Dr. Ewalt and Dr. Howard Hiatt, then chairmen of the Department of Medicine at the Beth Israel Hospital at Harvard, suggested that I take on the newly vacated chairmanship of the Department of Psychiatry at the Beth Israel Hospital. For a moment I was forced to rethink my decision to focus full time on science. The person who had just left that position, Grete Bibring, was a leading psychoanalyst who had been a colleague of Marianne and Ernst Kris in Vienna. Earlier in my life achieving this position would have represented my highest aspiration. But by 1965, my thinking had moved in a very different direction, and I decided against it with Denise’s strong encouragement. (Denise summarized it simply: ‘What?” she said, “throw your scientific career away?”) Instead, I made my third decision. I decided to leave Harvard and accept an invitation to start a small neurophysiology group focused specifically on the neurobiology of behavior in the Departments of Physiology and Psychiatry at the New York University Medical School.Harvard was quite wonderful, and it was not easy to leave that intellectually heady neurobiology environment. My interaction with Kuffler had increased after my return from Paris and, until his death in 1980, Kuffler proved a marvelous friend and counselor. Moreover, my interactions during this period with members of Kuffler’s group – Hubel, Wiesel, Furshpan, Potter, and Ed Kravitz, a biochemist who joined them later – were extensive and I learned much from them. Many years later, at a small meeting at the Marine Biological Laboratory in Woods Hole in honor of Steve Kuffler, I was surrounded by Steve’s Harvard entourage, some of whom were struggling with the decision of whether to leave Harvard for attractive positions elsewhere. I could not resist beginning my lecture with the remark, “I am here as living proof that there is life after Harvard.”New York University and a focus on the behavior of Aplysia The position at N.Y.U. had several great attractions that, in the long run, proved critical. First, it brought us back to New York and closer to my parents and to Denise’s mother, all of whom were having medical problems that benefited from our being nearby. Second, N.Y.U. gave me the opportunity to recruit an additional senior neurophysiologist, and Alden Spencer agreed to move to N.Y.U. from the University of Oregon Medical School where he had returned after his stay at the NIH, and to occupy the laboratory next to mine. Although Alden and I never collaborated experimentally again, we talked daily not only about our science – the neurobiology of behavior – but also about almost everything else, until his untimely early death at age 46 from amyotrophic lateral sclerosis in 1977, when we had already moved to Columbia University. During the period he was alive, no one influenced my thinking on matters of science as much as Alden. I still think about him frequently.Alden and I arrived at N.Y.U. together in the winter of 1965. Within a year we were joined by a biochemist, James H. Schwartz, whom I had first met in the summer of 1951 at Harvard summer school and who was now a member of the Department of Microbiology at N.Y.U. and was becoming interested in behavior. The three of us formed the nucleus of the Division of Neurobiology and Behavior at N.Y.U.With several important decisions behind me, I made a strong effort to focus on whole-animal behavior. In France I had found that chemical synapses are remarkably plastic; they could readily undergo long-lasting changes in strength. But I had no evidence that these analogs of learning were in fact behaviorally meaningful. I had no reason to believe that these are the sorts of changes that actually occur when an animal learns something. Although during my last few weeks in France I had begun to replicate my results by substituting natural stimuli for electrical stimulation of nerves, I still had not shown that synaptic plasticity actually occurred during behavioral learning. As a first step I thought it essential to show that *Aplysia* was capable of learning. With this in mind, I set about recruiting a postdoctoral fellow with a specific interest in behavioral learning. I was fortunate to recruit, first to Harvard and then to N.Y.U., Irving Kupfermann, an extremely critical and thoughtful student of behavior. We were later joined by another learning psychologist, Harold Pinsker, and together we set about delineating a very simple behavior that we could study: the gill-withdrawal reflex. We quickly found that this simple reflex could readily be modified by two forms of learning: habituation and sensitization.As we explored the two forms of learning, we focused on short-term memory. In 1971, we were joined by another experienced behavioral psychologist, Tom Carew, who brought a new level of energy and insight to our behavioral studies. He arrived as Pinsker was leaving, and soon after we shifted from working with restrained to unrestrained animals, thus opening up the study of long-term memory. Tom found that spaced repetition converted the memory for short-term habituation and sensitization to longer-lasting memories. In 1981, after several unsuccessful attempts, Carew, Terry Walters, Tom Abrams, and Robert Hawkins finally were able to define the conditions for reliably producing classical conditioning in *Aplysia*. This was a particularly exciting period; Carew, Walters, Hawkins, and I met regularly to discuss how to explore whether a simple reflex, in a simple invertebrate, could show the higher-order cognitive features of classical conditioning recently demonstrated in mammals by Leo Kamin and somewhat later by Robert Rescorla and Alan Wagner. Soon, Hawkins indeed was able to demonstrate that the gill-withdrawal reflex can undergo second-order conditioning, blocking, overshadowing and other cognitive aspects of associative learning, features that were surprising to uncover in such a simple behavior.We thus were able to describe a rather rich repertory of learning in *Aplysia*. But long before this inventory of the animal’s behavior was complete, we returned to our initial concerns. What happens in the brain of an animal when it actually learns a task? How does it remember? We proceeded, first with Kupfermann and Vincent Castellucci and then with Jack Byrne and Hawkins, to work out most of the neural circuit of the gill-withdrawal reflex. We identified specific sensory neurons and motor cells that produced movements of the gill. Next, we found that the sensory neurons made direct connections to the motor neurons as well as indirect connections through interneurons, both excitatory and inhibitory. The aversive tail stimuli that produced sensitization of the gill-withdrawal reflex activated modulatory interneurons that acted on terminals of the sensory neurons. We now could turn to think about how learning might occur in this reflex.Cellular mechanisms of learning At the end of the 19th century Ramón y Cajal introduced the principle of connection specificity, according to which, during development, a neuron will form connections only with certain neurons and not with others. Kupfermann, Castellucci, and I saw in the circuitry of the gill-withdrawal reflex of *Aplysia* this remarkable regularity of connections that Cajal referred to and we saw, in exquisite detail, that specific identified cells made invariant connections to one another. But this invariant organization of neurons posed deep questions. How could we reconcile hardwired circuits in the nervous system and the specificity of connections with the animal’s capability for learning? Once acquired, where or how is learned information retained in the nervous system?One solution was proposed by Ramón y Cajal in his Croonian Lecture to the Royal Society of London in 1894 when he suggested that “… mental exercise facilitates a greater development of the protoplasmic apparatus and of the nervous collaterals in the part of the brain in use. In this way, pre-existing connections between groups of cells could be reinforced by multiplication of the terminal branches of protoplasmic appendices and nervous collaterals.”This remarkably prescient idea was by no means generally accepted. On the contrary, different theories of learning at various times held the attention of neural scientists. Two decades after Ramón y Cajal’s proposal, the physiologist Alexander Forbes suggested that memory is sustained not by changes in synaptic strength of the sort suggested by Ramón y Cajal, but by dynamic changes resulting from reverberating activity within a closed loop of self-exciting neurons. This idea was elaborated by Ramón y Cajal’s student, Rafael Lorente de Nó, who found in his own and in Ramón y Cajal’s analyses of neural circuitry neurons that were interconnected in closed pathways and could thereby sustain reverberatory activity, thus providing a dynamic mechanism for information storage. In his influential book *The Organization of Behavior* (1949), D.O. Hebb proposed that a “coincident activity” initiated the growth of new synaptic connections as part of long-term memory storage. But for short-term memory, Hebb invoked a reverberatory circuit:“To account for permanence, some structural change seems necessary, but structural growth presumably would require an appreciable time. If some way can be found of supposing that a reverberatory trace might cooperate with the structural change, and carry the memory until the growth change is made, we should be able to recognize the theoretical value of the trace, which is an activity only without having to ascribe all memory to it. The conception of a transient, unstable reverberatory trace is therefore useful. It is possible to suppose also some more permanent structural change reinforces it.”Similarly, in *The Mammalian Cerebral Cortex*, an influential book of 1958, B. Deslisle Burns challenged the relevance of synaptic plasticity to memory.“The mechanisms of synaptic facilitation which have been offered as candidates for an explanation of memory … have proven disappointing. Before any of them can be accepted as the cellular changes accompanying conditioned reflex formation, one would have to extend considerably the scale of time on which they have been observed to operate. The persistent failure of synaptic facilitation to explain memory makes one wonder whether neurophysiologists have not been looking for the wrong kind of mechanisms.”Indeed, some scholars even minimized the importance of specific neuronal connections in the brain, advocating instead mechanisms of learning that were partially or even totally independent of “pre-established” conduction pathways. This view was held by Wolfgang Kohler and the famous Gestalt psychologists, and subsequently by the neurophysiologists Ross Adey and Frank Morrell. Thus, in 1965, Adey wrote:“No neuron in natural or artificial isolation from other neurons has been shown capable of storing information in the usual notion of memory. … In particular, the possibility exists that extraneuronal compartments may participate importantly in the modulation of the wave process that characterize the intracellular records, and that these wave processes may rank at least equivalently with neuronal firing in the transaction of information and even more importantly in its deposition and recall.”Finally, there were memory macromolecular notions advocated by Holger Hyden, based upon his finding of changes in the nucleotide composition of RNA. He proposed that learning gave rise to a specific pattern of instructional neural activity that altered the stability of RNA molecules, so that one base can exchange for another. In this way, new RNA molecules are formed with new base sequences that are specific to the instructing pattern of neural activity induced by learning. Hyden’s hypothesis thus implied that the patterns of stimulation activated by learning could introduce changes in RNA.We were now therefore in a position to test experimentally which, if any, of these ideas had merit. Using the gill-withdrawal reflex, we quickly established that memory in the *Aplysia* nervous system is not represented in self-exciting loops of neurons but in changes in synaptic strength. We found that all three simple forms of learning – habituation, sensitization, and classical conditioning – lead to changes in the synaptic strength of specific sensory pathways, and that these changes parallel the time course of the memory process. These findings, which had been fully anticipated by our earlier studies of analogs of learning, gave rise to one of the major themes in our thinking about the molecular mechanisms of memory storage. Even though the anatomical connections between neurons develop according to a definite plan, the strength and effectiveness of those connections is not fully determined developmentally and can be altered by experience.We therefore concluded the third of our 1970 series of consecutive papers in Science on the cellular mechanisms of learning with the following comments:“… the data indicate that habituation and dishabituation (sensitization) both involve a change in the functional effectiveness of previously existing excitatory connections. Thus, at least in the simple cases, it seems unnecessary to explain the behavioral modifications by invoking electrical and chemical fields or a unique statistical distribution in a neural aggregate. The capability for behavioral modification seems to be built directly into the neural architecture of the behavioral reflex.Finally, these studies strengthen the assumption … that a prerequisite for studying behavioral modification is the analysis of the wiring diagram underlying the behavior. We have, indeed, found that once the wiring diagram of the behavior is known, the analysis of its modification becomes greatly simplified. Thus, although this analysis pertains to only relatively simple and short-term behavioral modifications, a similar approach may perhaps also be applied to more complex as well as longer lasting learning processes.”A beginning molecular analysis of memory storage Having defined a critical site of plasticity, the situation became ripe for a molecular analysis. Here again I could not have been more fortunate. As I mentioned earlier, soon after I arrived at N.Y.U. I ran into James Schwartz. Jimmy had attended N.Y.U. Medical School two years behind me, but we had not really talked since I left N.Y.U. in 1956. After medical school Jimmy obtained a Ph.D. with Fritz Lipmann at the Rockefeller University, studying enzyme mechanisms and protein translation in cell-free bacteria extracts. As he and I began to talk again, he mentioned that he was thinking of moving from *E. coli* to the brain. *Aplysia* seemed ideal for biochemical study of individual nerve cells, so in 1966, Schwartz and I joined forces to carry out biochemical studies on individual identified nerve cells of *Aplysia*.Jimmy soon showed that each nerve cell in *Aplysia* had a specific transmitter biochemistry. Cells that we had presumed on pharmacological grounds to be cholinergic did in fact synthesize and release acetylcholine. With time, Jimmy became interested in the molecular mechanisms of synaptic plasticity, and together we began to examine the role of protein synthesis in memory storage. We knew from the work of Louis Flexner and Bernard Agranoff in the mid 1960s that long-term memory in vertebrates required protein synthesis whereas short-term memory did not. In our first study together in 1971, we found that blocking protein synthesis for 24 hours did not prevent the short-term synaptic changes associated with habituation and sensitization. That finding made us think that short-term changes representing memory storage might involve activation of a second-messenger pathway, for example, the cyclic AMP (cAMP) cascade, whose actions might persist for periods longer than the millisecond duration of conventional synaptic actions.In the discussion of our 1971 paper on the role of protein synthesis and synaptic plasticity, we wrote:“Alterations in molecular configuration would not be expected to persist for long periods of time, although molecular changes lasting for several minutes have been observed. … Most likely, the biochemical mechanisms underlying these short-term plastic changes are composed of a series of sequential reactions which result in a new distribution of transmitter substance. Mechanisms involving cyclic 3′,5’AMP might serve as one example of a series of reactions which result in transient enhancement in the activity of a critical enzyme system. A pathway of this kind might trigger the mobilization of transmitter from one component (a long term store) to another (an immediately releasable store).… If our conclusion is correct, … rapidly synthesized RNA cannot immediately play a role in neuronal functions; it might however, be important for long-term neuronal processes.”Sutherland and Rall had already shown in brain slices that several neurotransmitters known to exist in the brain could increase the concentrations of cAMP by activating the enzyme adenylyl cyclase that converted ATP to cAMP. We appreciated that we had a particularly good experimental preparation for examining, on the cellular level, the role of second-messenger pathways in synaptic transmission, synaptic plasticity, and memory storage. In 1972, Schwartz, Howard Cedar, and I found that stimulation of the pathway involved in sensitization increased the level of cAMP in the entire abdominal ganglion. Schwartz and Cedar next found that the transmitter serotonin could also increase cAMP, providing the initial evidence that serotonin might activate an adenylyl cyclase in *Aplysia*.Columbia University and the molecular analysis of short-term memory It was at this time that I was invited to move from N.Y.U. to the Columbia University College of Physicians and Surgeons to become the founding director of the Center for Neurobiology and Behavior. I was able to persuade James Schwartz, Alden Spencer, and Irving Kupfermann (who was by then an Associate Professor, having established an independent research program concerned with feeding and motivational state in *Aplysia*) to join me. This move was attractive to me for several reasons. Historically, Columbia has had a strong tradition in neurology and psychiatry, and a friend and former clinical teacher, Lewis Rowland, was about to assume the chairmanship of the Department of Neurology. In addition, I had my first experience in neurobiology at Columbia with Harry Grundfest who was now retiring and I was being recruited to replace him. Finally, Denise was on the Columbia faculty and our house in Riverdale was near Columbia, thereby greatly simplifying our lives.In 1974, just after arriving at Columbia, Castellucci and I went back to the elementary circuit of the gill-withdrawal reflex to determine the exact site of the synaptic change produced by short-term sensitization. We wanted to know which component of the synapse changes. Is it, as we suspected, based on indirect evidence, the presynaptic element of the synapse where chemical transmitter is released, or is it the postsynaptic site which contains the receptors which bind and respond to the transmitter? Using a quantal analysis, we found that the synaptic facilitation characteristic of sensitization is presynaptic and that inhibitors of serotonin block this presynaptic facilitation. Later, Hawkins and I found that tail stimuli that initiate sensitization activate a set of modulatory interneurons, the most important of which are serotonergic. The serotonergic and other modulatory interneurons all acted on the sensory neurons and on their presynaptic terminals to enhance transmitter release from their presynaptic terminals. We could now ask for the first time: Was cAMP directly involved in facilitation? In 1976, Marcello Brunelli could take advantage of the size of the *Aplysia* neurons and inject cAMP directly into the presynaptic sensory cell and thereby find a clear enhancement of synaptic transmission. This cAMP-induced enhancement paralleled the enhancement produced by serotonin or tail stimulation.I now began to interact with Paul Greengard, who was demonstrating that cAMP produced its actions in the brain through the cAMP-dependent protein kinase, or PKA. In 1980, Schwartz, Castellucci, and I collaborated with Greengard. We injected a purified catalytic subunit of bovine PKA into presynaptic sensory neurons and found that it simulated the actions of cAMP or serotonin. Moreover, we could block the actions of serotonin by injecting into the sensory neuron the specific peptide inhibitor of PKA, protein kinase inhibitor PKI. With Steven Siegelbaum we next began to define some of the targets of PKA and focused on one target, a novel K+ channel. Steve showed that this channel is closed by serotonin and by PKA and that this closure is achieved in a manner consistent with the channel being phosphorylated directly by PKA.The Howard Hughes Medical Institute and the molecular analysis of long-term memory Just before I arrived at Columbia, Arnold Kriegstein, an M.D.-Ph.D. student, succeeded in culturing embryonic *Aplysia* in the N.Y.U. laboratory, a quest which had intrigued biologists and eluded their efforts for almost a century. Most of us who were there will not readily forget Kriegstein’s extraordinary in-house seminar in December, 1973 when he first described his discovery that the red seaweed *Laurencia pacifica* is required to trigger metamorphosis from a free-swimming veliger larva to a small crawling snail, a discovery that allowed him to show the first pictures of the beautiful tiny post-metamorphic juvenile *Aplysia*. I remember saying to myself. “Babies are always so beautiful!” Kriegstein’s work opened up the study of development and cell culture in *Aplysia*.Because we now had young animals at all stages of development, we at last had the essential requirements for the generation of dissociated cell culture. This was taken on by Sam Schacher and Eric Proshansky. With the help of Steven Rayport (another M.D.-Ph.D. student at Columbia University), Schacher soon succeeded in culturing the individual sensory neurons, motor neurons, and serotonergic neurons of the gill-withdrawal reflex. The development of the culture system coincided with two other events that allowed me to begin studying the molecular mechanisms of long-term memory storage. The first was my encounter with [Richard Axel](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2004/index.html) and my collaboration in 1979, with him and with Richard Scheller, who became a joint post-doctoral fellow. The second was my being recruited to become a senior investigator at the Howard Hughes Medical Institute.Axel and Scheller’s success in 1982 in cloning the gene encoding the egglaying hormone in *Aplysia* seeded Axel’s long-term interest in neurobiology and gave me not only a wonderful friend but also an exposure to the methods of recombinant DNA and modern molecular biology. The very next year, in 1983, Donald Fredrickson, the newly appointed President of the Howard Hughes Medical Research Institute, asked Schwartz, Axel, and me to form the nucleus of a Howard Hughes Medical Research Institute at Columbia devoted to molecular neural science. The Howard Hughes Medical Research Institute gave us the opportunity to recruit from Harvard both Tom Jessell and Gary Struhl, as well as to keep Steven Siegelbaum at Columbia.My first goal on becoming a Highes Investigator was to examine the molecular mechanisms underlying the synaptic changes that parallel long-term memory storage. In 1885, Herman Ebbinghaus transformed speculation about memory into a laboratory science by having subjects memorize lists of nonsense syllables. In this way Ebbinghaus generated two basic principles about memory storage. First, he found that the transition from short-term memory to long-term memory is graded; practice makes perfect. Second, he anticipated the existence of a fundamental distinction between short- and long-term memory.What, then, was the molecular basis for this fundamental distinction between short- and long-term memory? As we have seen, in the mid-1960s Flexner and Agranoff examined this distinction biochemically and found that inhibitors of protein synthesis disrupt long-term memory without adversely affecting learning, or short-term memory. We found that long-term sensitization in *Aplysia* is similarly dependent on protein synthesis, whereas short-term sensitization is not. These findings illustrated the generality of the distinction between short-term and long-term memory processes for both invertebrates and vertebrates. In each case spaced repetition of the learning stimulus acts to transform a transient memory into a more stable (long-term) form by means of a process that depends on new protein synthesis. But how this occurred was a mystery.We had earlier found in *Aplysia* that long-term sensitization involved a persistent increase in the strength of the same synaptic connection altered by the shortterm process – the connections between the sensory and motor neurons of the gill-withdrawal reflex. To study this process more effectively we turned to dissociated cell culture and found that we could reconstitute both short- and long-term synaptic facilitation in a culture consisting of only a single sensory neuron and a single motor neuron. We did this together with Sam Schacher, Philip Goelet, and Pier Giorgio Montarolo by applying either one or five brief spaced pulses of serotonin to the sensory neuron and motor neuron in the culture dish. Much like behavioral long-term memory, the long-term synaptic changes required new protein synthesis while the short-term changes did not. Thus, we had trapped the protein synthesis-dependent component of memory storage in the elementary synaptic connection between two identified cells. We now could address directly the question: Why is protein synthesis required for long-term and not short-term facilitation? What are the molecular steps that switch on long-term facilitation and, once switched on, how is it maintained?We next found that steps for new proteins are activated by a cascade of genes initiated by the cAMP-dependent protein kinase. With repeated application of serotonin, PKA translocates to the nucleus and in so doing activates the MAP kinase (mitogen activated protein kinase), another kinase often recruited for growth. Thus, one of the functions of repeated stimulation was to cause both kinases to move into the nucleus. Pramod Dash and Binyamin Hochner and later Cristina Alberini, Mirella Ghirardi, and Dusan Bartsch provided the first evidence that in the nucleus, these kinases act on a gene regulator called CREB-1 (the cAMP response element binding proteins) to initiate a cascade of gene actions. With David Glanzman and Craig Bailey, we found that the CREB-mediated gene cascade which triggers the synthesis of new protein is required for the growth of new synaptic connections and it is the formation of these new synapses that sustains the long-term change.The requirement for transcription in long-term facilitation explained why long-term memory requires the synthesis of new proteins. However, this requirement now posed a cell-biological puzzle: if long-term synaptic change relies on the activation of genes in the nucleus, that means there is ready communication between the nucleus and the synapse. If that is so, must all such long-lasting changes in the signaling ability of the neuron be cell-wide? Or can long-term synaptic changes be restricted to individual synapses. Experiments by Kelsey Martin, based on a beautiful new cell culture system she developed, revealed that individual synapses or groups of synapses within a cell can be modified independently.A return to the hippocampus: genetically modified mice and the study of complex spatial memory storage In our studies in *Aplysia* we focused on the simplest forms of memory, called implicit (or procedural) memory. These memories are concerned with the unconscious recall of perceptual and motor skills and do not require a hippocampus. The hippocampus is involved in explicit (or declarative) memory, memory for people, objects, or places, memories that require conscious participation for recall. For years I tried to encourage people who left my lab to turn their attention to the hippocampus, but to no avail. Finally in 1990, when I reached my 60th birthday, I returned to the study of the hippocampus myself. I was emboldened to do so in great part because of the development of methods for inserting and for knocking out individual genes in mice. This work made it clear to me that mice offered a superb genetic system for examining the role of individual genes in synaptic modification on the one hand, and intact behavior – explicit memory storage – on the other. Mice have a well developed medial temporal lobe and hippocampus, and these are important for explicit memory of objects and space. Moreover, in 1972, Tim Bliss and Terje Lomo in Per Andersen’s laboratory in Oslo, had discovered that electrically stimulating any one of the three major pathways in the hippocampus gives rise to a synaptic facilitation, called long-term potentiation or LTP. We were interested in two questions: (1) What are the molecular signaling pathways that are important for LTP? (2) Is LTP important for explicit memory storage? In the move to genetically modified mice, the contributions of Seth Grant and Mark Mayford were particularly influential.Grant was the driving force in our first studies, in which we showed a role for nonreceptor tyrosine kinases in long-term potentiation, and in spatial memory in the hippocampus. Mayford’s critical thinking became important somewhat later, as we began to realize the limitations in the first generation of genetically modified mice. The limitations stimulated Mayford to develop regionally restricted promoters that limited the expression of genes to only certain regions of the brain, and methods for controlling the timing of gene expression. Those two technical advances by Mayford proved important in allowing us, and Susumu Tonegawa (whose laboratory was now also focusing on studying memory in genetically modified mice), to generate mice whose phenotypes were more specific and in whom a genetic defect could be more readily interpreted than in the first generation of genetically modified mice because the defect could be related, somewhat more directly to specific synaptic changes and to behavior. Over the next few years Mayford, Ted Abel, Mark Barad, Isabelle Mansuy, Chris Pittenger, Amy Chen, and Angel Barco created a number of regionally restricted and regulated transgenic animals that allowed us to examine the role of the PKA- CREB-1 and CREB-2 and the protein synthesis-dependent transcriptional switch within the hippocampus, and to find that it was quite similar in principle to what we had encountered in *Aplysia*. Our lab and those of Alcino Silva and Dan Storm found that the cAMP, PKA, and CREB switch were required for long-term forms of synaptic plasticity in the hippocampus, was also required for spatial memory.A molecular approach to the cognitive map of space in the hippocampus: steps toward a molecular biology of attention With this background information about genes, LTP, and spatial memory, we now could ask a deeper question: How does an animal learn about extrapersonal space? Why does spatial memory go awry with defects in PKA signaling? What is the function of the transcriptional switch? To address these questions, we turned to studying how space is represented in the hippocampus.One of the key insights to emerge from the study of higher cognitive functions is that each perceptual or motor act has an internal or neural representation in the brain. These representations can be either simple or complex. The simplest internal representations are those evident in the sensory systems where the afferent fibers are arranged as topographic maps of the receptor surface. These are the representations which Wade Marshall, my former mentor at the NIH, had discovered in the 1930s and early 1940s. Marshall showed that this map is most clearly evident in the neural representation of *personal space*, the representation of touch. The neural representation of the space surrounding the body, the *extrapersonal space*, is far more complex. Here the representation is not topographical but encoded in the pattern of firing of cells that do not have any specific topographic relation to one another with respect to the receptor surface. Thus, adjacent cells need not encode adjacent regions of extrapersonal space.This representation was discovered in 1971, by [John O’Keefe](https://www.nobelprize.org/nobel_prizes/medicine/laureates/2014/okeefe-facts.html) at University College London, who made the brilliant observation that the hippocampus has a cognitive map – a complete representation of extrapersonal space. O’Keefe discovered that all the pyramidal cells in the hippocampus, the very same cells that are used to study long-term potentiation have, as a natural function in the intact animal, the ability to encode space. He found that when an animal moves around in a familiar environment, different pyramidal cells in the hippocampus fire as the animal traverses different regions of the environment. This tendency is so marked that O’Keefe referred to the pyramidal cells as *place cells*. Some place cells may fire only when the animal’s head enters one position in a given space. Other pyramidal cells will fire when the animal’s head enters another position in the same space. Thus, a mouse’s brain breaks up the space in which it walks into many small overlapping fields, and each field is assigned to specific cells in the hippocampus, forming a spatial map of the animal’s surroundings. When the animal enters a new environment, a new place map is formed within minutes.These observations have given rise to the idea that the hippocampus contains a map-like representation of the animal’s current extrapersonal environment, and that the firing of place cells in the hippocampus signals the animal’s moment-to-moment location within the environment. This spatial map is the best-understood example of a complex internal representation in the brain, a true cognitive map. It differs in several ways from the classical sensory maps found by Wade Marshall for touch, vision, or hearing. Unlike sensory maps, the map of space is not topographic, that is, neighboring cells in the hippocampus do not represent neighboring regions in the environment. Furthermore, a place cell will fire in the same place regardless of what the animal is looking at. Moreover, the firing of place cells can persist after pertinent sensory cues are removed and even in the dark. Thus, although the activity of a place cell can be modulated by sensory input, it is not determined by sensory input as is the case for the activity of neurons in a sensory system. It appears that the place cells do not map the current sensory input, but the location where the animal thinks it is in space.Place fields are formed in minutes, and once formed the map to which they contribute can remain stable for weeks. It struck me in 1995 that formation of this internal representation – this cognitive map of space – was a learning process and that synaptic plasticity related to LTP might have a role in stabilizing this cognitive representation.Although place cells have been studied since 1971, nothing was known about the cellular or molecular mechanisms whereby new place fields are formed, and specifically no one had attempted to relate the biology of place cells to the molecular mechanisms of LTP or hippocampal-based memory. To explore this problem, I was fortunate to start a collaboration with Robert Muller at Downstate Medical Center in Brooklyn, who had pioneered the systematic study of place cells. This problem was taken on by Cliff Kentros, a postdoctoral fellow in my lab, by Naveen Agnihotri, a graduate student, and by Alex Rotenberg, a joint student with Muller and myself. Using a combination of pharmacological and genetic approaches, we demonstrated a link between recruitment of PKA and protein synthesis on the one hand, and on the other, the long-term, but *not* short-term stability of the hippocampal representation of space. Thus, PKA and protein synthesis are required for longterm memories of extrapersonal space because that memory is based on a learned internal representation of space whose long-term stability requires PKA and new protein synthesis.This raised a final question: Explicit memory in humans differs from implicit memory in requiring conscious attention for recall. How does conscious attention come to bear on explicit memory? Indeed, how can one study consciousness in the mouse? In the course of our work on place fields, Kentros, Agnihotri, Hawkins, and I found that the long-term stability of the place field map correlated strongly with the degree to which the animal was required to attend to its environment. This demonstrates that, rather than being an implicit, automatic, process, the long-term recall of a stably formed place cell map requires the mouse to attend to its environment, as would be expected for explicit memory in human beings. The finding that attention, the recruitment of PKA, and new protein synthesis are required to form and recall a stable map in the mouse has opened up a molecular biological approach to an attentional process.From psychoanalysis to Aplysia to the role of attention in the cognitive representation of extrapersonal space During the past 10 years my career has begun to come full circle. From an initial interest in the complex cognitive problems of psychoanalysis and memory storage, my research on memory led me first to the mammalian hippocampus, which proved too difficult as a first step and forced me to take a more reductionist approach and study initially the simplest forms of memory in *Aplysia*, and then, only much later, the more complex forms of memory in mice. I found that despite important differences in detail, simple implicit and explicit memories have a similar short- and long-term storage form. In each form, short-term storage requires covalent modification of pre-existing proteins leading to the alteration of pre-existing synaptic connections, whereas long-term memory storage requires gene activation, new protein synthesis, and the growth of new synaptic connections.In the course of this work we began to explore how explicit memory storage for space affects the internal representation of space. We found that on the level of internal representation the storage mechanisms for explicit memory are similar to those in human beings in requiring attention. Attention is a component of conscious response, perhaps the great challenge of all research on mental processes. It thus seems likely that in future decades, the study of memory, perhaps even in mice, is likely to allow molecular insights into even the deepest problems of human behavior.A personal perspective Although doing research on *Aplysia* and the hippocampus and discussing science with colleagues in my lab have given me the greatest intellectual satisfactions, I have loved teaching and have learned a great deal from lecturing to medical and graduate students. It was in the context of the neural science course at Columbia that the idea arose of doing a textbook, *Principles of Neural Science*. In college and medical school I was never a good note-taker. I always preferred sitting back, enjoying the lecture, and just scribbling down a few words here and there. When I came to Columbia to develop the neural science course, I was struck by how much energy students were devoting to writing out every single word of lectures, and I wanted to help them get over that. I therefore encouraged the faculty to provide a syllabus for each lecture, and with time I edited the syllabus, added figures to it and improved it. Then Jimmy Schwartz and I decided that the syllabus was becoming sufficiently useful that we might make a textbook out of it. Our textbook was the first attempt to bridge cell and molecular biology to neural science and neural science to behavior and clinical states. The response to the first edition was so gratifying that we made an effort to make the book better and more complete. With the second edition, not only students but also scientists began to regard our textbook as useful. With the help of Tom Jessell, we further improved the third and fourth editions. The widespread reception of this book, both in the United States and abroad, has been a source of deep satisfaction to me and to the other contributors.Outside of our work and our family, Denise and I enjoy the visual arts and classical music, especially opera. Our interest in both of these activities is greatly enriched by having within easy reach of our home the great museums and galleries of Manhattan as well as the Metropolitan Opera. We also are inveterate – I am tempted to say *addicted* – collectors of art and antiques. We have lived for 36 years in a now 150-year-old house in the Riverdale section of the Bronx, with wonderful views of the Hudson River and the Palisades. We collect French art nouveau furniture, vases, and lamps, an interest that originated with Denise and her mother, and graphic art of the Austrian and German Expressionists, an interest which originated with me. As I write this, I am beginning to suspect that our collecting may well be an attempt to recapture a part of our hopelessly lost youth.In the course of my career I have incurred many debts both personal and scientific. First and foremost I owe an enormous personal debt to my parents and my brother Lewis. My parents were able in mid-life to relocate to a foreign country – my father spoke not a word of English when he first arrived in New York – and to create a new life for themselves and their sons. My parents not only succeeded in establishing themselves in their small store in Brooklyn, but were sufficiently successful to support me through college and medical school. They were so occupied with their store that throughout their life in America they did not share in the cultural life of New York, which Lewis and I were beginning to enjoy. Despite their constant labor they were always extremely optimistic and supportive of us, and never tried to dictate decisions about my work or play. Lewis was also an enormous influence on me in my early years, and my interest in classical music and my joy in learning were importantly influenced by him. While a graduate student at Brown University writing his dissertation in linguistics and Middle High German, he was called to service as an intelligence officer in the Korean War. He and his wife, Elise, went first in 1951 to Germany and then in 1953 to Paris, France, where he had a position as a civilian in Air Force Intelligence. He so enjoyed his life in France, that he lost his interest in an academic life and stayed in France for 13 years, where he and Elise raised five children. He eventually returned to the United States and finished his career in a series of administrative positions, in the Health Department of the City of New York. He died in 1979, at age 54 of a recurrence of a cancer of the kidney, which we all thought had been successfully removed when it first presented 10 years earlier.Second, I have been privileged to enjoy a wonderfully supportive, endlessly interesting, and stable family life with Denise, my partner, best friend, and most honest critic for now 45 years. Throughout our life together she has consistently encouraged my love of research and supported my scientific aspirations. Denise is a professor in the Department of Psychiatry and in the School of Public Health at Columbia University, and has pioneered the study of drug abuse in adolescence. Her work on the epidemiology of drug abuse has become the basis of the current understanding of the developmental sequence whereby adolescents become involved in drugs. I am also greatly in debted to our two children, Paul and Minouche, for the joy they gave Denise and me while growing up and the satisfaction they have given us in seeing what principled and interesting people they have become and how thoughtful they are as parents to their own children. Our son Paul majored in economics at Haverford College and graduated from the Columbia Business School. He now manages a set of investment funds at Dreyfus-Mellon. Paul is married to Emily Kaplan, an interior designer; they live in Scarsdale, N.Y. and have two daughters, Allison (born on January 5, 1992) and Libby (born on October 14, 1995). Our daughter Minouche went to Yale College and Harvard Law School. She practices public interest law in San Francisco specializing in women’s rights and family violence. Minouche is married to Rick Sheinfield, also a public interest lawyer, and they have a son, Izak (born on November 10, 1998) and a daughter, Maya (born on March 12, 2001).In retrospect it seems a very long way for me from Vienna to Stockholm. My timely departure from Vienna made for a remarkably fortunate life in the United States. The freedom that I have experienced in America and in its academic institutions made Stockholm possible for me, as it has for many others.Postscripts: a Curriculum Vitae I began my academic career at the Harvard Medical School, where from 1963 to 1965, I was an instructor in the Department of Psychiatry. In 1965, I moved to New York University as associate professor where, together with Alden Spencer and James Schwartz, we developed the first group in the country devoted to both cellular neurobiology and behavior. At the time I was recruited to N.Y.U., Denise was recruited to the Columbia University College of Physicians and Surgeons, where she gradually rose to the rank of professor.In 1974, Harry Grundfest retired and I was recruited to Columbia to replace him. At Columbia I was the founding director of the Center for Neurobiology and Behavior. In 1983, I became a University Professor at Columbia. In 1984, I resigned as director of the Center to become a senior investigator at the newly formed Howard Hughes Medical Research Institute at Columbia.Since 1974, I have been a member of the National Academy of Sciences USA. Later I became a member of the National Science Academies of Germany and France, the American Academy of Arts and Sciences, the American Philosophical Society, the National Institute of Medicine, and most recently, Germany’s Orden Pour Le Mérite für Wissenschaften und Künste. Being invited to join the Orden was for me a particularly great honor. The collection of scholars and scientists in the Orden is extraordinary; as an extra bonus it includes old friends such as the great German historian Fritz Stern, and a sterling group of biologists including [Max Perutz](https://www.nobelprize.org/nobel_prizes/chemistry/laureates/1962/index.html), [Christiane Nüsslein-Volhard](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1995/index.html), [Bert Sakmann](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1991/index.html), [Erwin Neher](https://www.nobelprize.org/nobel_prizes/medicine/laureates/1991/index.html), Walter Gehring, Charles Weissman, and Robert Weinberg.I have been awarded the Lester N. Hofheimer Prize for Research of the American Psychiatric Association (1977), the Karl Spencer Lashley Prize in Neurobiology from the American Philosophical Society (1981), the Dickson Prize in Biology and Medicine from the University of Pittsburgh (1982), the Albert Lasker Award (1983), the Rosenstiel Award of Brandeis University (1984), the Howard Crosby Warren Medal by the Society of Experimental Psychologists (1984), the American Association of Medical Colleges Award for Distinguished Research in the Biomedical Sciences (1985), the Gairdner International Award of Canada for Outstanding Achievement in Medical Science (1987), the National Medal of Science (1988), the J. Murray Luck Award for Scientific Reviewing from the National Academy of Sciences (1988), the American College of Physicians Award in Basic Science (1989), the Robert J. and Claire Pasarow Foundation Award in Neuroscience (1989), the Bristol-Myers Squibb Award for Distinguished Achievement in Neuroscience Research (1991), the Warren Triennial Prize from the Massachusetts General Hospital (1992), the Harvey Prize of the Technion in Haifa (1993), the Stevens Triennial Prize from Columbia University (1995), the Dana Award (1997), the Gerard Prize of the Society of Neuroscience (1997), the Wolf Prize of Israel (1999), and the Dr. A.H. Heineken Prize for Medicine from the Royal Netherlands Academy of Arts and Sciences in Amsterdam (2000).I have received honorary degrees from nine universities, including three European universities: the University of Vienna, Edinburgh, and Turin. Surprisingly, the first honorary degree I received, in 1983, was from the Jewish Theological Seminary in New York. I was thrilled that they would even know of my work. I suspect they learned of that from my colleague Mortimer Ostow, one of the psychoanalysts who first stirred my interest in relating psychoanalysis and the brain. My father had already died but my mother came to the graduation ceremony, and in his introductory remarks Gerson D. Cohen, the chancellor of the seminary, referred to my having received a good Hebrew education at the Yeshiva of Flatbush, an acknowledgement which filled my mother’s Jewish heart with pride. As this recitation makes clear, I also owe a profound intellectual debt to my scientific teachers – Harry Grundfest, Dominick Purpura, Wade Marshall, and Ladislav Tauc – who tolerated my naivete and encouraged my brashness. I also benefited greatly from Steve Kuffler’s sage insight and advice and from Alden Spencer’s generous friendship. I also am indebted to the extraordinary collection of colleagues, fellows, and students that I have had the privilege of interacting and collaborating with and whose individual contributions I describe in more detail in my Nobel Lecture. Finally, I am deeply grateful to Columbia University and the Howard Hughes Medical Research Institute, two great institutions that have created open environments supportive of scholarship and research. |
| Autobiographical |  |
| Podcast |  |
| Telephone  interview |  |
| Interview |  |
| Q41 | So, there is a little discrepancy between you on this one anyhow. But if I rephrase the question and say, will it ever be possible to understand the mechanisms of mind? What is your answer then? |
|  | Arvid Carlsson: To understand there is physiological and physiochemical processes that underlie the mind, that we could perhaps reach. But the actual conversion, how these physical phenomena become consciousness, that is what I think is the real tough thing. |
| Q41 | But if you understand the mechanisms or the things that are changing, you can see them, you can measure them, then you can influence the whole system. |
|  | Arvid Carlsson: That is very true.In that way, if my question contains the possibility of interfere with all aspects of mind, your answer is yes.Arvid Carlsson: Yes.Paul Greengard?Paul Greengard: I think that the history of science indicates that one by one various barriers have disappeared in areas that the human race thought were impossible to resolve. And everything seems to be solvable. And I don’t see why an understanding of how we think and what consciousness is wouldn’t be approachable in the same way. I think it’s going to be a very long time till we understand the nature of consciousness, even today with these imaging techniques you can start finding out precisely which type of cells are active when you do this or this type of thinking. It certainly should be possible to do similar imaging and understand when people are awake and asleep and I don’t think it’s a huge step beyond that to understand the nature of consciousness. |
| Q34 | So you’re only putting more weight to the answer that all the different mechanisms that at the end lead to the consciousness experience, those mechanisms can be known and cleared. Is science limitless? |
|  | Paul Greengard: In certain principles such as the [Heisenberg](https://www.nobelprize.org/prizes/physics/1932/heisenberg/facts/) uncertainty principle I think yes it’s limitless. I didn’t always feel that way, it just seems that if you look what happened in the last 30 years it’s unbelievable what the human mind can achieve. |
| Q34 | Eric Kandel, on the mechanisms of mind, of course you would have to answer yes on that question as well. |
|  | Eric R Kandel: I sort of come down more on Paul’s side. First of all, I think one needs to distinguish between mechanisms of mind, which involves all operations related to mental processes, action, thoughts, memory, perception, and consciousness. There’s lots of perception, mental processes going on of which we’re unconscious for example. You’re shaking your head as we talk, you’re probably not completely aware of the fact that you’re engaged in sort of reflexive autonomic movements as you talk. Those are mental processes but they’re not necessarily conscious ones. And we have made very good progress in understanding aspects of perception and motor action and I’m confident we will continue to do that.The mechanism of consciousness is a fascinating one, and one that is getting a lot of attention. Not necessarily a lot of scientific progress, but a lot of attention. [Francis Crick](https://www.nobelprize.org/prizes/medicine/1962/crick/facts/) has developed a paradigm for looking at attention and consciousness, saying that one ought to look at a simple version of it, which is selective attention. You know, when I sit in this room, I attend to you but I’m also in the background perceiving pictures on the wall and things like this. But there’s a special effort involved in selectively attending to you, so the difference between perceiving something and the heightened selection that goes on with attention, is something he’s been studying in experimental animals with the help of other people. And there is now pretty good understanding of how a monkey, for example, attends to a visual image compared to just looking at the image without attention. So simple cases of conscious awareness are beginning to be analysable. To what degree consciousness of oneself, the most interesting parts of consciousness, become understood is unclear as yet. I sort of agree with Paul that a lot of problems that seemed insoluble became soluble with time. When there’s no add of time, we haven’t reached the limit by any means. It is conceivable that this problem is so difficult that the human mind may not have the computational power to analyse it, but we are far from reaching that particular barrier. |
| Q23 | But you stick to some of the mechanisms to start with, the one that Arvid Carlsson has discovered is dopamine, and I think there is a fascinating correlation between too little dopamine – then you lose control over your body – and too much dopamine – you lose control over your mind. Is that so Arvid Carlsson? |
|  | Arvid Carlsson: As well as the body. |
| Q23 | But is there some sort of relation between the mind and the body in this respect that is basically the same mechanism that in a way controls the material world and the mental world? |
|  | Arvid Carlsson: That’s a very interesting question. Anatomically the wiring that analyse movements and the wiring that analyse mental processes are very similar. The balance between different neurotransmitters involved in either of these two is very similar. And have probably evolved along with each other which, in a way, makes a lot of sense because if one goes ahead of the other you’ll have no use for it. The mind and movement have to evolve in parallel. |
| Q23 | And in this system you have discovered the chemical signal substances between the connection between the nerves, and Paul Greengard your discovery is really what is happening inside the cell. How does your discovery relate to how we react and how we are, how we experience the world? Are there any connections that you have thought of? |
|  | Paul Greengard: The work that we did elucidates how these chemicals, the neurotransmitters which are the mechanism by which the nerve cells communicate with each other, how they produce their responses in the target cells on which they act. |
| Q23 | And they are related to what sort of mental phenomena? |
|  | Paul Greengard: All mental phenomena, memory, consciousness and everything else, is all attributable to the behaviour of nerve cells and what the three of us are doing is trying to understand how one nerve cell communicates with another. It’s through the release of a chemical, a neurotransmitter which activates the second nerve cell and then what happens in the second nerve cell once the neurotransmitter activates it and then how that in turn sends a neurotransmitter to the third nerve cell. What we’re doing at this present level, all three of us, is to understand these biological systems going on, these biochemical molecular systems. Other types of neuroscientists, brain scientists, will take the kind of things that we’re doing and try to relate them to the higher order of behaviour in the nervous system. |
| Q23 | But if Arvid Carlsson has done something in between the synapses where the signals are changing the connections between them, you’re only working with molecules inside the cell and how molecules are changing their shape and their effectiveness, what they do, the proteins we are talking about. |
|  | Paul Greengard: What we’ve done is to take these neurotransmitters that Arvid Carlsson had been studying and study exactly how they produce chemical and electrical changes in the nerve cells, working out what those biochemical steps are. |
| Q23 | And they are related to memory in what way? |
|  | Paul Greengard: That remains to be understood to a large extent. Except Eric Kandel’s work addresses that and maybe he’d like to speak to that. |
| Q23 | So, memory and changes inside the nerve cells, Eric Kandel. What is the concept or idea? |
|  | Eric R Kandel: Let me pick up what Paul Greengard was saying. One way to conceive of the contribution the three of us have made is to think of two sets of processes in the brain – mediating and modulating. That there are vast synoptic connections that are responsible for mediating many of the actions, for example motor actions, sensory perception. But the wonderful thing about the brain is that it can regulate the strength of connections. And my colleagues and I have shown that this occurs during learning, that the strength of connections are not fixed, but that inputs such as serotonergic input or dopaminergic input can modulate the strength of synoptic connections. And it does so by activating processes similar to the kind that Paul Greengard has described. In *Aplysia* one can show … |
| Q23 | *Aplysia*, that is the sea snake that you have been working with? |
|  | Yes, one can show that in fact that a very simple withdrawal reflex, like the withdrawal of a hand from a hot object, can be dramatically amplified by an aversive stimulus. And that amplification involves activation of one of these modular choice systems, the serotonergic system that activates a signalling system within the cell. And activation of that signalling system causes strengthening of the synoptic connection, which is responsible for the enhanced withdrawal.That means that there is a physical change of the size, so memories are actually made of these changes.Eric R Kandel: Anatomical changes. That’s right.This is somewhat exciting that the fast reactions, that is electricity and the somewhat slower …Eric R Kandel: The fast, and not simply electricity, the faster also chemical transmitters but they act on different receptors.But long term things are also represented by long term changes.Eric R Kandel: That’s right. |
| Q14 | You have all been part of a dramatic shift in paradigm when it comes to looking at the brain because all electrophysiology before and when you entered this stage you changed the picture totally into biochemistry. Arvid Carlsson, why did you choose to go contrary and against everyone else? |
|  | Arvid Carlsson: I think it depended to some extent on ignorance. I was not so well read in the field of brain physiology, so I could look at the facts in a simple, straight forward way, whereas those people who were burdened by a lot of knowledge, they had to think in other terms. They were, so to speak, fixed in the dogma. I was outside, just because of my ignorance, I think. |
| Q11 | Eric Kandel and Paul Greengard, what makes someone want to go towards the conventional wisdom of the time? |
|  | Paul Greengard: In the case of the study of the brain at the time that Arvid, Eric and I did our work, there were two approaches to understanding brain function. There were physiologists who worked in physiology departments and studied the electrical properties of nerve cells. And there were biochemists working in biochemistry laboratories who took a brain or a liver or a muscle and threw it into a homogeniser and studied the chemicals in the brain. And the two groups did not interact. The people sitting biochemistry were only interested in the biochemistry of the brain. The people doing physiology were only interested in the electrical property of the brain. In one sense we were not going against dogma. There was very little prior art out there. In my own case, my work was guided by the hypothesis that a particular mechanism that had been shown to work in the endocrine system, in which hormone released from one cell activates a target cell, that that system might be analogous to how two nerve cells communicate with each other. And that is through a chemical mechanism, that hypothesis turned out to be correct. |
| Q11 | Eric Kandel, you started off as being a psychoanalyst interested in psychoanalysis and everyone thought that was the gateway to the brain at that time. How come that you didn’t believe it? |
|  | Eric R Kandel: I did at the beginning and I still find the psychoanalytic view a rich and nuance view of the mind. I just became disappointed as I continued my medical education with how much empirical evidence there was to support it and how devoid it was in thinking about the brain. I became a little bit interested in the brain and as I got more deeply involved I became fascinated with it. And it struck me that memory is the central question in psychoanalysis. And in the 1950s when I began, the dominant view of the brain was that of Karl Lashley at Harvard, who showed that memory was not localisable. That you could remove many regions of the brain and not interfere with memory. What Lashley did not realise is that animals are very smart and if you remove a part of the brain, for example, let’s just say they’re doing a spatial task, if you remove the visual part of the brain, they will use tactile stimuli to find the way, or smell. They have lots of different strategies they can use. I thought one needed to take an extremely simple animal, an extremely simple reflex, where there would be no question about localizability. |
| Q22 | Excuse me for interrupting, but I got so curious, but this is true that you have all entered a new way of looking at things that were contrary to the conventional views of the time. And still the question I am really curious about is how is your mental set up to want to go against this? |
|  | Eric R Kandel: I think each of the three of us gave a somewhat similar answer, in the sense that we did not think of ourselves as revolutionaries at the barricades. We were working along and we thought that one way of moving in the field was the sound one, it’s almost an intuition that this is the right way to go. It turned out be in opposition to what other people were thinking, but one wants to think in original ways, you try to tackle a problem you think is interesting and approach it in the way that you think is most profound.Paul Greengard: To amplify what Eric said, it’s not that we were going against conventional wisdom, we were following our own instinct. This must be the way it works. And then more conservative folks would say we were disagreeing with them, but we weren’t, we were just looking at things in a different way.So in a way it was a very unconscious way of …Eric R Kandel: That’s right. I think that’s absolutely right.Paul Greengard: No, I don’t understand what you mean, an unconscious way?You didn’t really think about going against what was the convention, you just did what you thought was working.Paul Greengard: It was nothing that they had done was wrong, we were exploring an area that other people hadn’t explored, I would say.Do you agree Arvid Carlsson?Arvid Carlsson: No. I was taken by surprise, I must say, when we reported on our data and all the big figures in the field said, no this can’t be true.Paul Greengard: But that’s true for all three of us.Arvid Carlsson: I mean, I was right and they were wrong. I mean that is how I experienced it. I wouldn’t like to give them any sort of excuse that we were right, all of us, after all. I don’t agree.Paul Greengard: Maybe add a certain limited truth, we said, look we think that there are other things going on than what you’ve been studying and there’s all this and this. And then we’d say, yes, there’s all this and this. And then we’d show it and they’d say, no, you’re wrong. We were never saying they were wrong, I don’t think. They were saying we were wrong.Arvid Carlsson: They were wrong, in my opinion.Eric R Kandel: I must say that Roy Spencer and I wrote an article in 1968, when we first began to realise that learning could be localised to specific synopses. And we pointed out that Lashley’s view, which was the dominant view, had misled the field. |
| Q34 | But if we look then in the future, this is not the last time where things are going to be turned upside down. Have you seen anything in the current science that indicates that there will be maybe a totally new model coming up of how the brain is working? Maybe adding some fundamental new knowledge to the function of the brain? |
|  | Paul Greengard: It’s exactly what I’m saying. There will be totally new ways of looking that will not necessarily be contradictory to what we did. What we’re doing is eliminating truths just like the people before us had even more eliminating truths, and the next people add on to that. And they’re not going to prove that the work that we did was incorrect, they’re going to show a new dimension.Eric R Kandel: It’s almost probabilistic in a sense. The views that we have ended up supporting existed before, just to a minor degree, so people had seen in the endocrine system the kinds of things that Paul discovered in the nervous system. Kajal had spoken about the fact that synopsis could be the site of memory storage. But at the time that we were working those views were rare, very few people held that. Most people held the opposing point of view. For example, many people felt that [Bernhard Katz](https://www.nobelprize.org/prizes/medicine/1970/katz/facts/) and [Eccles](https://www.nobelprize.org/prizes/medicine/1963/eccles/facts/) had described synoptic transmission in the nervous system, it was fast synoptic transmission. So they thought all synoptic transmission in the brain was fast. When Paul and I began to study slow synoptic transmission, they thought there’s something unusual about this and people were initially sceptical that this could be of importance. |
| Q35 | But when the two models that has exchanged for each other, the electrophysiological model, the biochemistry model, what do you think about the future, Arvid Carlsson, are there totally new things coming up? |
|  | Arvid Carlsson: I guess there will be paradigm shifts in the future. But I think it’s inherent in the definition of dogma that we cannot identify it. As soon as we identify it as a dogma, it’s no more a dogma. |
| Q35 | But before there’s a thunderstorm coming up you can always see a little glimpse of the lightening coming, do you see any glimpse here? |
|  | Eric R Kandel: We certainly see that. For example, we thought that the nervous system by the time a child is four or five years old, does not generate any more nerve cells. We thought that the number of nerve cells in the brain are limited – if you lose nerve cells as a result of disease, stroke, Alzheimer’s disease, there’s no way of replenishing those nerve cells from the cells in the brain. There’s now increasing evidence that there is a primitive population of cells that stays around in the brain and they can be the source of additional cells later on. That could be the basis of a new development that would enrich our understanding. So I think that’s a very important development. |
| Q35 | And what would be the conceptual change of that idea? |
|  | Paul Greengard: Right now it’s thought that the brain has very little ability to repair itself. And with these new ideas that’s not the case. I would like to go back and correct something that I said, refer to something Arvid said on this. The people who are our predecessors, what they did was not wrong, their interpretation was wrong. For example, in his case, they said no, this molecule dopamine cannot be a neurotransmitter, so in that sense they were wrong. The experimental work they had done was correct, their interpretation was not correct. This is, in my case, they said these slow biochemical reactions cannot be involved in mediating communication between nerve cells, they were wrong about that. |
| Q24 | But then finally, Arvid Carlsson, do you agree with Eric Kandel that there may be a totally new way of looking on the dynamics of the brain, which is really at the heart of his statements? |
|  | Arvid Carlsson: One direction that I think will become very important is the understanding of the interaction between the different neurotransmitters in complex neuro-circuitries. And there are new possibilities to approach these complex problems. And that deals with something that we can call pattern analysis. You can collect enormous number of data and feed into computers and the computers will feed back to you pictures of the data, that actually are patterns of very, very complex processes in the brain, by means of which you can come closer to these very, very complex mechanisms that deal with the mind, feelings and cognition and so forth.And maybe even get a picture of the conscious experience then on the screen.Arvid Carlsson: Yes, and also to distinguish between different personalities. By means of imaging you will tell this is a happy fellow and this other fellow here has a short fuse, that kind of thing.Eric R Kandel: I also think that the human genome is going to enlighten our understanding of mental processes. One of the deep questions that is a confronted analysis of the mind, has been to what degree is the mind built on the base of genetic information? What is nature versus nurture? What do you inherit versus what do you acquire? And most personality traits are quite complex, so they’re not attributable to one or two genes, so they’ve been very hard to decipher. But now that we will have the whole human genome, we’ll be able to look at patterns of genes and we’ll see to what degree any of our behavioural patterns derive from familial traits versus acquired or learned traits. I think that’s going to be a very rich area for investigation.Paul Greengard: I would like to go back to your original question and ask you and my two colleagues whether there is any reason to think that we won’t be able to understand the nature of consciousness or any other aspect of the brain. What reason is there for pessimism, given the history of the last decade?Eric R Kandel: I think it’s hard to know what the limitations of knowledge are. I think it is hard to know at this particular point whether the optimism that we all share, that science can solve all problems in the universe, is in fact true. We’ve solved many problems so far, but there is the possibility that there are limitations to human understanding which we and the computers that we develop will not be able to solve.Paul Greengard: At the moment we have not reached that point.Eric R Kandel: We have not reached that point. |