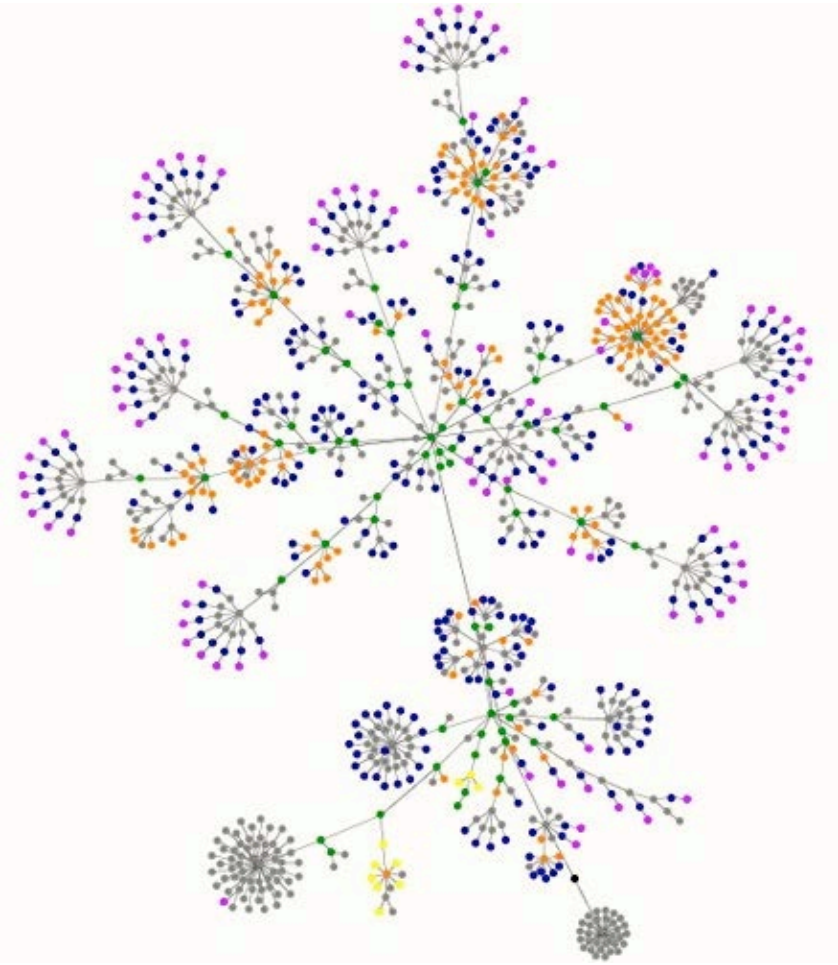
ENCOUNTER WITH

MOLECULAR BIOLOGY



Sarah Harrison and Alan Macfarlane

Contents

Preface to the series

There have been many autobiographical accounts of the creative process. These tend to concentrate on one level, and within that one aspect, the cerebral, intellectual working of a single thinker or artist's mind. Yet if we are really to understand what the conditions are for a really creative and fulfilling life we need to understand the process at five levels.

At the widest, there is the level of civilizations, some of which encourage personal creativity, while others dampen it. Then there are institutions such as a university, which encourage the individual or stifle him or her. Then there are personal networks; all thinkers work with others whether they acknowledge it or not. Then there is the level of the individual, his or her character and mind. Finally there is an element of chance or random variation.

I have long been interested in these inter-acting levels and since 1982 I have been filming people talking about their life and work. In these interviews, characteristically lasting one to two hours, I have paid particular attention to the family life, childhood, education and friendships which influence us. I have let people tell their own stories without a set of explicit questions to answer. This has led them to reflect on what it was in their lives which led them to be able to do their most interesting and rewarding work. They reveal the complex chains which sometimes lead to that moment when they discovered or made something new in the world.

I started for some years mainly in the disciplines I knew, anthropology, history and sociology. But after 2006 I broadened the project out to cover almost all fields of intellectual and artistic work. I have now made over 200 interviews, all of them available on the web. Future volumes based on these interviews are outlined at the end of this volume.

How to view the films

The films are up on the Internet, currently in three places.

Alan Macfarlane's website, www.alanmacfarlane.com

The Streaming Media Service in Cambridge:

http://sms.cam.ac.uk/collection/1092396

On both of these, the full summary of the interviews are available.

Most of the interviews are also up on the 'Ayabaya' channel of Youtube.

The films can be seen from within a PDF version of this book by pressing on the image. You will need to download an Adobe Acrobat PDF reader (free) from the web if you do not have it. If you right click on the image, further choices open up.

Technical information

Unless otherwise specified, all the interviewing and filming was done by Alan Macfarlane, mostly in his rooms in King's College, Cambridge.

The detailed summaries, with time codes to make it easier to find roughly where a passage of special interest is to be found, were made by Sarah Harrison, who also edited and prepared the films for the web.

The cameras improved with time, but there are occasions when both the early cameras and microphones were less than satisfactory. We have had to wait for the technology to catch up. It is hoped one day to improve this if funding and technology allow.

Introduction

When I came to Cambridge in 1971 I was hardly aware of the break-through in 1953 when the helical structure of DNA was discovered and Crick, Watson and Wilkins received the Nobel Prize for perhaps the most significant discovery of the twentieth century. Crick and Watson had worked in Cambridge, and those who surrounded them there, and who later continued in the exploration of the implications of their discovery, were all round me when I arrived at King's College.

In my first years on the Fellowship Electors of the College, Sydney Brenner, whose interview is below, was one of the most active members and I would listen to him with amazement quite frequently. Brenner shared the Nobel Prize in 2003 with John Sulston, who directed the team which first sequenced the whole of the human genome, and whose interview is also below.

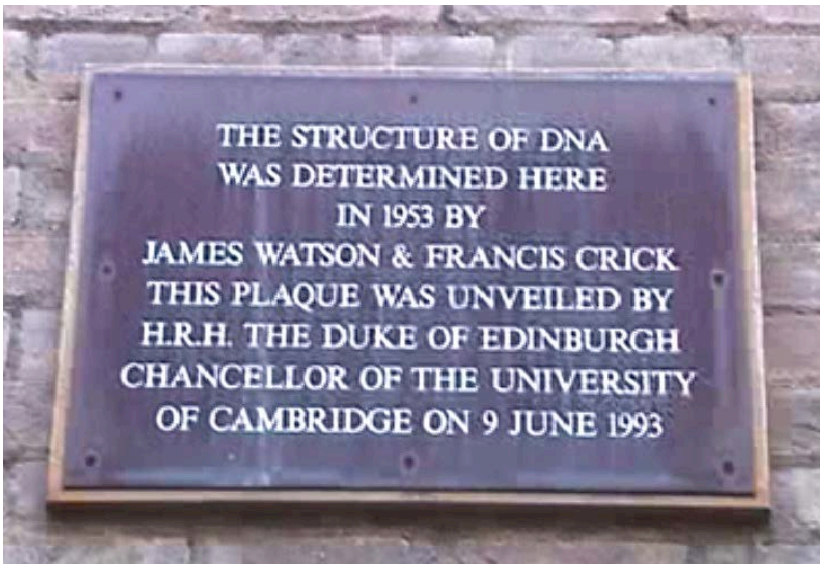
Another Fellowship Elector was Dan Brown, whom I later learnt was a central, if somewhat unrecognized, key player in the developments through his work on RNA. Dan became a friend and I was honoured to give the memorial address in the Chapel on his death, which is reproduced below.

From time to time people would point out to me the presence at dinners of another Fellow of King's, Fred Sanger, until his recent death the only living double Nobel Prize winner. The two prizes were won for being the first person to sequence the whole genome of a non-living and then a living organism.

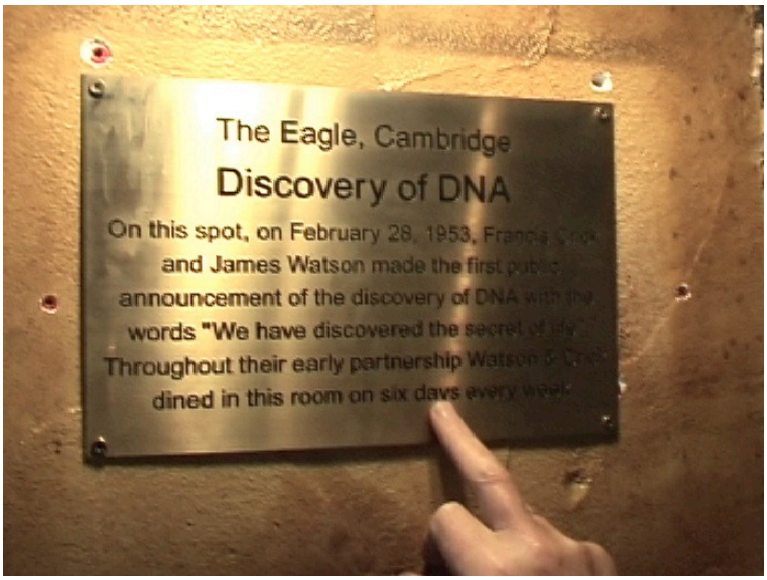
Most of these figures had been closely associated with the M.R.C. Laboratory of Molecular Biology, which had been the home of over a dozen Nobel laureates. One of these, and sometime Director, was Aaron Klug. I had heard of his formidable achievements, including his work with Rosalind Franklin (who had provided the key to the work of Crick and Watson). I interviewed him in his laboratory near the Addenbrooke's Hospital.

Finally, I was advised to interview John Gurdon, whose work on stem cells had also transformed our world. I did so shortly before he received his Nobel Prize for this work.

It is clearly a great privilege to have been able to interview six important figures who, between them, won six Nobel prizes.



Alan Macfarlane in the Eagle Pub in Cambridge with the plaque commemorating the announcement that 'We have discovered the secret of life'



http://downloads.sms.cam.ac.uk/1290463/1290468.mp4

Sydney Brenner

23 August 2007

http://downloads.sms.cam.ac.uk/1139457/1139464.mp4

Sydney Brenner with Lewis Wolpert, *My Life in Science* (2001)

Extracted from Wikipedia – 21 August 2014

Sydney Brenner, CH FRS (born 13 January 1927) is a South African biologist and a 2002 Nobel prize in Physiology or Medicine laureate, shared with H. Robert Horvitz and John Sulston.

Brenner made significant contributions to work on the genetic code, and other areas of molecular biology while working in the Medical Research Council Unit in Cambridge, England.

He established the roundworm *Caenorhabditis elegans* as a model organism for the investigation of developmental biology, and founded the Molecular Sciences Institute in Berkeley, California, U.S..

Brenner made several seminal contributions to the emerging field of molecular biology in the 1960s. The first was proving that all overlapping genetic coding sequences were impossible. This insight separated the coding function from structural constraints as proposed in a clever code by George Gamov. This led Francis Crick to propose the concept of the adaptor or as it is now known "transfer RNA (tRNA)". The physical separation between the anticodon and the amino acid on a tRNA is the basis for the unidirectional flow of information in coded biological systems. This is commonly known as the central dogma of molecular biology i.e. that information flows from nucleic acid to protein and never from protein to nucleic acid. Following this adaptor insight, Brenner proposed the concept of a messenger RNA, based on correctly interpreting the work of Elliot "Ken" Volkin and Larry Astrachan. Then, with Francis Crick, Leslie Barnett and Richard J. Watts-Tobin, Brenner genetically demonstrated the triplet nature of the code of protein translation through the Crick, Brenner, Barnett, Watts-Tobin et al. experiment of 1961, which discovered frameshift mutations. This insight provided early elucidation of the nature of the genetic code. Leslie Barnett also helped set up Sydney Brenner's laboratory in Singapore, many years later.

Brenner, with George Pieczenik, created the first computer matrix analysis of nucleic acids using TRAC, which Brenner continues to use. Crick, Brenner, Klug and Pieczenik returned to their early work on deciphering the genetic code with a pioneering paper on

the origin of protein synthesis, where constraints on mRNA and tRNA co-evolved allowing for a five-base interaction with a flip of the anticodon loop, and thereby creating a triplet code translating system without requiring a ribosome. This model requires a partially overlapping code. This is the only published paper in scientific history with three independent Nobel laureates collaborating as authors.

Brenner then focused on establishing *Caenorhabditis elegans* as a model organism for the investigation of animal development including neural development. Brenner chose this 1 millimeter-long soil roundworm mainly because it is simple, is easy to grow in bulk populations, and turned out to be quite convenient for genetic analysis. For this work, he shared the 2002 Nobel Prize in Physiology or Medicine with H. Robert Horvitz and John Sulston. The title of his Nobel lecture on December 2002, "Nature's Gift to Science," is a homage to this modest nematode; in it, he considered that having chosen the right organism turned out to be as important as having addressed the right problems to work on. In 2002, he won the Dan David Prize (that was directed by Professor Gad Barzilai) and the March of Dimes Prize in Developmental Biology. In recognition of his pioneering role in starting what is now a global research community that work on *C. elegans*, another closely related nematode was given the scientific name *Caenorhabditis brenneri*.

INTERVIEW SUMMARY

Sydney Brenner interviewed by Alan Macfarlane 23rd August 2007

0:09:07 Born in Germiston near Johannesburg 13th January 1927; father emigrated from Lithuania to South Africa where he had a brother in about 1911; mother came from Latvia and she emigrated in 1922 and had lived through the revolution; father repaired shoes and we lived initially in rooms at the back of his shop; mother has ambitions for her children; father was illiterate but had a gift for languages; mother encouraged me to read which I learnt to do from newspapers; went to a kindergarten run by a customer of my father's who had found me there reading a newspaper on the floor; did first three years of primary school in one year; went directly into standard 2 at the government primary school aged six; meant I was always about two years younger than the rest of the class which was not helpful

5:12:10 After High School matriculated when under fifteen; had won a scholarship to university to study medicine; had a lab of my own in a garage; can't remember being influenced by any teacher at the school and got most of my education in the public library; as a child interested in nature and took flies apart and wondered how you could put them back together again; went to University of Witwatersrand aged fifteen; commuted every day, by bicycle, train, then walking; tough regime with lectures or laboratory sessions every day including Saturday morning from 8am; enjoyed it as there did meet interesting people; a man in the botany department working on chromatography let me work in his lab; we did four subject - botany, zoology, chemistry and physics; after the first year moved to the medical school where I did anatomy and physiology; discovered that I couldn't qualify as a doctor as I would be under twenty-one so I was able to take a year out to do a Bachelor of Science degree in anatomy and physiology; took out three years and did a B.Sc., B.Sc. Hons. then Master of Science by which time I was already doing scientific research; realized I was not a good medical student but did complete another four years to qualify for the sake of a safe job; finished at the end of 1950 and I did go abroad in 1952; had been at Witwatersrand for almost nine years;

had become a lecturer while still a medical student teaching physiology; became an expert on calorie intake

13:58:22 At Witwatersrand a most important influence was Raymond Dart the Professor of Anatomy but more so was a man called Joseph Gillman who was a lecturer in histology and later Professor of Physiology; working in the laboratory was a tremendous experience; nothing there so had to make amino acid for an experiment, for example; also built an ultracentrifuge and used it; parents supportive throughout although mother would have been much happier to see me as a specialist doctor; was interested in molecular biology which had not yet been invented; Waddington came out to South Africa for a time and encouraged me to apply to Cambridge which I did; they never replied to my letter; I won a rare scholarship linked to the 1851 exhibition in 1950; Principal recommended me to go to work with Cyril Hinshelwood, Professor of Physical Chemistry at Oxford; accepted to do a DPhil in physical chemistry and went in 1952

19:06:04 In South Africa made films with a group and had made one on Dylan Thomas; had to imagine what England was like from reading but it was a shock when I came here; arrived during the time of food rationing and for two years just dreamt of food; married after a term in Oxford; May was in London doing a PhD; settled in Oxford and both finished in two years; I won a travelling scholarship from the Carnegie Foundation to go to America for four months; had a very good friend in Oxford called Jack Dunitz; had come to Oxford with the idea that I could determine the structure of DNA; heard about Crick and Watson and went to Cambridge to see them in April 1953 with Jack and Leslie Orgel; they had already discovered the structure of DNA which we saw and the implications were just blindingly clear; immediately saw the problems or coding and copying and the work that needed to be done

25:00:21 On that day Francis wouldn't stop talking but Jim gave me the impression of an irritated bird; they had made a breakthrough but no notice was taken of it for quite a time except for a tiny band of people who saw that this had reformulated major questions in biology; at Oxford there was a club called the Alembic Club of

chemists and Fred Sanger came to talk in 1953 as he had just assembled insulin; Robert Robinson said it was remarkable because Sanger had proved that proteins actually had a chemical structure; Sanger was an unique scientist as he saw that determining how the sequence was arranged is important; he devised simple techniques to achieve this; he liked to work in the lab and when he retired he put down his pipette and said "That's it" and walked out

33:47:19 John Griffith's role in the discovery of DNA; after D.Phil went to America for four months but in the meantime started to discuss with Francis about coming back to join him in the MRC unit; had to go back to South Africa to fulfill obligations attached to my scholarship but two years later, at the end of 1956, I came to Cambridge; had a three year job at £1100 a year and three children; beginning of an incredibly exciting time in science; Francis read all the time and when he left Cambridge the entire room was full of books on the brain; value of conversation with Crick resulting in productive thoughts; I would try them out in the lab to see if they were right; value of guessing; correct theories and true theories; science similar to a medieval guild with journeymen and master; blinding flashes of illumination; work with Francois Jacob

SECOND PART

0:09:07 Became a fellow of King's in 1959; Noel Annan had wanted to get Crick as a fellow earlier but not successful; wanted someone from molecular biology and John Kendrew suggested me; was offered a fellowship at Churchill but preferred to try for King's and was elected; quite often had tea with Morgan Foster as a benefit of the college was to have friends outside science; other friends at King's included Francis Haskell, Michael Jaffe, and Dadie Rylands; Bernard Williams and Robert Bolgar; Edmund Leach, Meyer Fortes - always been fascinated by anthropology; did archaeology and paleontology as a hobby; interested in creating a new anthropology which would include biology and the place of man in the animal world, the natural world and the world of our own creation; we may have the genome of Neanderthal man pretty soon

11:57:10 Originally we were housed in the Cavendish Laboratory; Crick very good at getting extra space and at the end of our time there we were in seven buildings on the site; prior to this the MRC had decided they might have a building somewhere but we did not want to be in a large place with everyone; got agreement for an MRC laboratory of molecular biology and joined up with Fred Sanger who was in urgent need of space; Hugh Huxley and Aaron Klug joined us; I officially became the director in 1979 before which Max Perutz was chairman; retired from the directorship at sixty and got my own small unit to return to science; on final retirement from the MRC managed to raise enough money to continue the lab for some time

19:54:22 Work on nematode worms; genes build the nervous system which then performs the behaviour; needed to determine the structure of the nervous system, it should be a small nervous system so could be finite and that we could make mutations and see how it altered behaviour; then we would hope to see what changes in the nervous system the mutations would produce and then would be able to map those onto the altered behaviour; that program has been partly carried out but effectively it involved doing the anatomy, the full embryology; big advantage of nematodes is according to the literature they had stereotype nervous system, constant number of cells and, it was thought, the same for every nematode of the same genetic composition; could ask under what conditions do you build a nervous system with the same genetic program; nematode ideal as easy to keep in the lab and easy for anyone to work on

29:48:12 Nobel prize awarded to me with John Sulston and Robert Horvitz; 'don't worry' hypothesis described; the virtue of ignorance

38:20:05 Went to Singapore in 1984 and encouraged them to set up a graduate department of molecular biology; from 1999 a huge surge forward and I have been involved in setting up a gigantic operation there but have just retired; advice to a young scientist would be to go to a lab where there is a good mentor; big challenge that interests me is how to reconstruct the past from what we now

know; science is a way of solving problems and for a young person, find a good problem and try to solve it though getting into the whole apparatus of science, which is difficult

Fred Sanger

24 July 2007

http://downloads.sms.cam.ac.uk/1130236/1130243.mp4

Fred Sanger, "Sequences, sequences, and sequences", *Annual Review of Biochemistry,* 57:1-28 (1988)

Extracted from Wikipedia 21 August 2014

Frederick Sanger, OM, CH, CBE, FRS, FAA (13 August 1918 – 19 November 2013) was a British biochemist who won the Nobel Prize for Chemistry twice, one of only two people to have done so in the same category (the other is John Bardeen in Physics), the fourth person overall with two Nobel Prizes, and the third person overall with two Nobel Prizes in the sciences. In 1958, he was awarded a Nobel Prize in chemistry "for his work on the structure of proteins, especially that of insulin". In 1980, Walter Gilbert and Sanger shared half of the chemistry prize "for their contributions concerning the determination of base sequences in nucleic acids". The other half was awarded to Paul Berg "for his fundamental studies of the biochemistry of nucleic acids, with particular regard to recombinant DNA".

Sequencing insulin

Neuberger moved to the National Institute for Medical Research in London, but Sanger stayed in Cambridge and in 1943 joined the group of Charles Chibnall, a protein chemist who had recently taken up the chair in the Department of Biochemistry. Chibnall had already done some work on the amino acid composition of bovine insulin and suggested that Sanger look at the amino groups in the protein. Insulin could be purchased from the pharmacy chain Boots and was one of the very few proteins that were available in a pure form. Up to this time Sanger had been funding himself. In Chibnall's group he was initially supported by the Medical Research Council and then from 1944 until 1951 by a Beit Memorial Fellowship for Medical Research.

Sanger's first triumph was to determine the complete amino acid sequence of the two polypeptide chains of bovine insulin, A and B, in 1952 and 1951, respectively. Prior to this it was widely assumed that proteins were somewhat amorphous. In determining these sequences, Sanger proved that proteins have a defined chemical composition. For this purpose he used the "Sanger Reagent", fluorodinitrobenzene (FDNB), to react with the exposed amino groups in the protein and in particular with the N-terminal amino group at one end of the polypeptide chain. He then partially hydrolysed the insulin into short peptides, either with hydrochloric

acid or using an enzyme such as trypsin. The mixture of peptides was fractionated in two dimensions on a sheet of filter paper, first by electrophoresis in one dimension and then, perpendicular to that, by chromatography in the other. The different peptide fragments of insulin, detected with ninhydrin, moved to different positions on the paper, creating a distinct pattern that Sanger called "fingerprints". The peptide from the N-terminus could be recognised by the yellow colour imparted by the FDNB label and the identity of the labeled amino acid at the end of the peptide determined by complete acid hydrolysis and discovering which dinitrophenyl-amino acid was there. By repeating this type of procedure Sanger was able to determine the sequences of the many peptides generated using different methods for the initial partial hydrolysis. These could then be assembled into the longer sequences to deduce the complete structure of insulin. Finally, because the A and B chains are physiologically inactive without the three linking disulfide bonds (two interchain, one intrachain on A), Sanger and coworkers determined their assignments in 1955. Sanger's principal conclusion was that the two polypeptide chains of the protein insulin had precise amino acid sequences and, by extension, that every protein had a unique sequence. It was this achievement that earned him his first Nobel Prize in Chemistry in 1958. This discovery was crucial for the later sequence hypothesis of Crick for developing ideas of how DNA codes for proteins.

Sequencing RNA

From 1951 Sanger was a member of the external staff of the Medical Research Council and when they opened the Laboratory of Molecular Biology in 1962, he moved from his laboratories in the Biochemistry Department of the university to the top floor of the new building. He became head of the Protein Chemistry division. Soon after his move he started looking at the possibility of sequencing RNA molecules and began developing methods for separating ribonucleotide fragments generated with specific nucleases. One of the problems was to obtain a pure piece of RNA to sequence. In the course of this he discovered in 1964, with Kjeld Marcker, the formylmethionine tRNA which initiates protein synthesis in bacteria. He was beaten in the race to be the first to sequence a tRNA molecule by a group led by Robert Holley from Cornell University, who published the sequence of the 77

ribonucleotides of alanine tRNA from *Saccharomyces cerevisiae* in 1965. By 1967 Sanger's group had determined the nucleotide sequence of the 5S ribosomal RNA from *Escherichia coli*, a small RNA of 120 nucleotides.

Sequencing DNA

He then turned to sequencing DNA, which would require an entirely different approach. He looked at different ways of using DNA polymerase I from *E. coli* to copy single stranded DNA. In 1975 together with Alan Coulson he published a sequencing procedure using DNA polymerase with radiolabelled nucleotides that he called the "Plus and Minus" technique. This involved two closely related methods that generated short oligonucleotides with defined 3' termini. These could be fractionated by electrophoresis on a polyacrylamide gel and visualised using autoradiography. The procedure could sequence up to 80 nucleotides in one go and was a big improvement on what had gone before, but was still very laborious. Nevertheless, his group were able to sequence most of the 5,386 nucleotides of the single-stranded bacteriophage φX174. This was the first fully sequenced DNA-based genome. To their surprise they discovered that the coding regions of some of the genes overlapped with one another.

In 1977 Sanger and colleagues introduced the "dideoxy" chain-termination method for sequencing DNA molecules, also known as the "Sanger method". This was a major breakthrough and allowed long stretches of DNA to be rapidly and accurately sequenced. It earned him his second Nobel prize in Chemistry in 1980, which he shared with Walter Gilbert and Paul Berg. The new method was used by Sanger and colleagues to sequence human mitochondrial DNA (16,569 base pairs) and bacteriophage λ (48,502 base pairs). The dideoxy method was eventually used to sequence the entire human genome.

INTERVIEW SUMMARY

Frederick Sanger interviewed by Alan Macfarlane 24th August 2007

0:09:07 Born 1918 at Rendcombe in the Cotswolds where father was a doctor who had previously been a missionary in China; think that he came back as he contracted TB; he became a Quaker later on and my brother and I used to go to Friends Meetings; brother was a year older and an extrovert; I was more bookish and interested in using my hands; did a lot of carpentry and also had a little forge; mother came from a fairly wealthy family; grandfather was in the cotton trade in Manchester

7:34:00 First school was in Colwall near Malvern, a Quaker boarding school, where I went at the age of nine where brother had preceded me; went on to Bryanston which I enjoyed much more for its freedom and common sense; remember the chemistry teacher, Mr Ordish, particularly; during my last year I had already qualified for Cambridge and I was allowed to go to the lab and experiment which was my first real taste of chemistry; started at Cambridge doing physics as well as chemistry but gave up physics in second year and did physiology instead as my maths was not good enough

11:04:07 Chose St John's Cambridge because my father had been there; Baldwin was my supervisor, an enthusiastic teacher if not that brilliant as a scientist; no great role models in chemistry at the time; came up just before the war and stayed on in Cambridge as a conscientious objector; when I went to Cambridge still going to Quaker meetings though never actually joined; had no musical skills but played squash a little; got a 2:1; stayed on a fourth year and did biochemistry where I got a first; my initial supervisor was Albert Neuberger who was interested in proteins; department rather neglected, Hopkins was the Professor but was old; towards the end of the War Professor Chibnall came who was also interested in proteins; my first paper was on nitrogen of the potato

20:59:23 I was starting on a research degree at that stage and worked with Neuberger for a year or two and when he left, taken on by Chibnall who suggested work on insulin, protein chemistry which turned out to be very successful; without him I would have continued metabolic work which would not have come to much; Chibnall had been working on amino acid analysis of protein; something a bit odd about insulin which was about the only protein that could be obtained in a pure form; Chibnall had found there were more free amino groups in it than you would have expected from the concentration of lysine which is the one amino acid that has free amino groups and asked me to look into it; that was really where my work started as I did find there were extra amino groups which were at the end of the protein chains; I was able to develop a chemical method for identifying the end terminals of the amino groups and showing that insulin was composed of two chains and identifying the amino acids at the ends; at that time all that was known was that proteins were chains of amino acids and no one had any idea of what order they were in or how they were arranged; I was able to identify two amino acids at the end of the insulin chain which was quite a breakthrough as it was the first time that any amino acid was identified in a particular position in a protein; from then on that was my main interest in determining the amino acids' composition and structure of proteins; in the initial bit when looking for the amino groups you had a reagent and made a DNP compound, a nitrophenyl, and could isolate those bits; later on did more random digestion, breaking them into little bits and fractionating them; that developed in parallel with the new techniques for separating compounds; later on you could just cut it up like a jigsaw puzzle, look at the different bits and then put them together; I did not actually design methods but methods of fractionation came along and I was quick to use them; my work has centred on separating compounds

27:56:16 Work mainly alone with a technical assistant and sometimes with a colleague; the first was Hans Tuppy, an Austrian, an enthusiast with whom I did the whole chain of insulin which was quite a breakthrough and contributed to getting first Nobel prize; originally in St John's but invited to become a Fellow of King's, probably in the late 1950's; never became a real college man

31:27:09 Worked in the biochemistry department firstly in the basement with Tuppy; when Young became the Professor he was interested in me working with him on physiological matters; I did not want to do that but to get on with my studies on insulin; Chibnall had retired but had the protein hut which was outside; I was supposed to work in the main building; had two students, one was Hal Dixon, who was more interested in hormones, and the other was Ted Thompson who was working with me on the sequence of insulin; Ted was put in the protein hut but I spent most of my time there finishing off the sequencing rather than working in the main building where I had been assigned; later moved out to the MRC unit run by Max Perutz; he was a very fair, kind, man and devoted to science; he did not influence me as he was more of a physical chemist but he was very supportive of me

37:17:15 Work on phage followed on from the sequencing of insulin; people had got interested in nucleic acids, RNA and DNA; when I started they didn't know what nucleic acids were doing but it became clearer just how important they were; I switched first to RNA and did some sequence work; the techniques were different; with proteins have twenty different amino acids and the protein size is a few hundred amino acids long whereas in nucleic acids you have four components and they are much longer so it needed quite a change in technology; luckily I was not in the position where I had to produce papers at speed and Max was sympathetic to my going into the nucleic acid field; I had quite a time before I made any progress but eventually we developed methods; first sequenced RNA but as it became more obvious of the function of DNA I switched to it; difficult to get pure DNA; got it from small organisms, essentially viruses; a phage is a virus in a micro-organism, a bacteria, and this is what was sequenced

43:16:13 Thoughts on Crick and Watson; John Griffiths an extremely bright person who came to the labs and could always tell us what was happening but didn't do experiments at all; Archie Martin also very good on the theoretical side; he and Synge had a famous paper at the beginning of sequencing and he came up with marvelous techniques; sadly got Alzheimer's when still young and

faded out; most of the fractionation techniques that I used were devised by Martin

48:21:05 Remained in Cambridge but did go for a couple of months to North Western University and they were anxious for me to stay on; found Cambridge a good environment for research and I like England; very lucky not to have to do any administration; did give a few lectures in the biochemistry lab but don't enjoy lecturing; do not enjoy writing either; now I don't read at all, my memory is hopeless; when I retired I really retired; I'd got the sequencing work going pretty well on DNA and had done a bacteriophage phi X 174 and had got to the stage of mass production of sequencing to get the human genome; was by then sixty-five and not interested in continuing as it would not have been much fun; feel that the sequencing of DNA was the thing I was most satisfied by because it is fundamental to know who we really are

Aaron Klug

11 December 2007

http://downloads.sms.cam.ac.uk/1124232/1124239.mp4

Sir Aaron Klug, Brian Heap and Jennifer Kent, *Towards Sustainable Consumption: a European Perspective* (2000)

Extracted from Wikipedia 21 August 2014

Sir Aaron Klug, OM, PRS (born 11 August 1926) is a Lithuanian-born British chemist and biophysicist, and winner of the 1982 Nobel Prize in Chemistry for his development of crystallographic electron microscopy and his structural elucidation of biologically important nucleic acid-protein complexes. His scientific biography is currently being written by former colleague Kenneth Holmes.

Klug was born in Želva, Lithuania to Jewish parents Lazar, a cattleman, and Bella (née Silin) Klug with whom he moved to South Africa at the age of two. He later graduated with a degree in science at the University of Witwatersrand and studied crystallography at the University of Cape Town before he was awarded an 1851 Research Fellowship from the Royal Commission for the Exhibition of 1851, which enabled him to move to England, completing his doctorate at Trinity College, Cambridge in 1953.

He moved to Birkbeck College in the University of London in late 1953, and started working with Rosalind Franklin in John Bernal's lab. This experience aroused a lifelong interest in the study of viruses, and during his time there he made discoveries in the structure of the tobacco mosaic virus. In 1962 he moved to the newly built MRC Laboratory of Molecular Biology in Cambridge. Over the following decade Klug used methods from X-ray diffraction, microscopy and structural modelling to develop crystallographic electron microscopy in which a sequence of two-dimensional images of crystals taken from different angles are combined to produce three-dimensional images of the target.

He was awarded the Louisa Gross Horwitz Prize from Columbia University in 1981. Between 1986 and 1996 he was director of the Laboratory of Molecular Biology in Cambridge, and was knighted by Elizabeth II in 1988. He was elected President of the Royal Society, and served from 1995–2000. He was appointed OM in 1995 – as is customary for Presidents of the Royal Society. He is also a member of the Board of Scientific Governors at The Scripps Research Institute.

INTERVIEW SUMMARY

Aaron Klug interviewed by Alan Macfarlane 11th December 2007

0:09:07 Born in Lithuania in 1926; father's father was a cattle dealer and had a farm which was unusual for a Jew; father was trained as a saddler but went back to the farm to help his father as a cattle dealer; realized there was not much future in Lithuania and moved to South Africa in 1929; mother's family had emigrated there in 1900 (her family name was Gevisser) and had established a business in Durban so that is where we went; learnt English early; have an elder brother; father employed in the Gevisser firm as a hide merchant; he had gone ahead to Durban and found a place to live and the family followed; father's brother later emigrated to Johannesburg; father much concerned with making a good living and had been regarded as clever; he would go to the synagogue and was interested in the Talmud and when he retired he went for weekly study; when I married in England he sent extracts by post; mother died when I was about six of pneumonia; mother's younger sister had come with us and later married my father; told that one of the older Gevisser cousins had said it was her duty to marry my father and help bring us up; we still continued to call her aunt though later realized she was our mother and changed to mum

8:36:12 Went to a primary school; lived near the bush; Durban had a white population of 100,000, mainly of English origin who thought of England as home; Britain had taken Natal from the Dutch and in 1870 there was a large emigration to Durban; on our first holiday in England we went to Swanage and noticed that the beach huts there had been copied in Durban, so had the post boxes; as a child knew a lot about England so when I came here knew exactly where I was; later moved to Durban High School where the philosophy was that if you were bright you went into the Latin class (Greek had been abandoned as we had to do Afrikaans as a second language); if you were middling you went into the science class, and the rest made do with geography; I was very good at school and always came first and my brother, second; he was in the same class although two years older; I had been pushed up but he was my protector; we did do one science subject; was very good at Latin; also brother and I went to Hebrew classes and I was pretty

fluent in Afrikaans; later when I began collecting ancient coins could read the inscriptions; later when one of my sons started doing Latin at school got an interlingua text but found the Latin word order had been changed to fit the English so threw it away in disgust

15:56:08 Thing that mattered most at Durban High School was sport which occupied four afternoons a week; had cadets on the fifth day; brother was a good cricketer; I was not good at sport and later when undergoing an army medical found that I had an optic atrophy in my right eye; brother keen on music and I began to listen to serious music in last few years at school; in primary school I couldn't sing in tune; my wife is musical so I do listen; she ran the Cambridge University modern dance group at some time and experimented with Stockhausen and electronic music

19:46:13 No particular inspirational teacher at school; was good at all subjects; at one time became seriously interested in Egyptology and tried to teach myself hieroglyphics and learnt a good deal on the origins of the alphabet; at school read a book by Paul de Kruif called 'Microbe Hunters' which turns out to have influenced many people; he was a Dutch science writer and in this book he told the stories of Pasteur and Koch; made me think I should become a microbiologist; at fifteen went to university to do medicine (as did Sidney Brenner) as two years ahead of my age group; no medical school in Durban so went to University of Witwatersrand in Johannesburg; sailed through my first year; stayed in my father's brother's house; had won a scholarship so did not have any fees; in my second year started doing anatomy, physiology and physiological chemistry; enjoyed dissection to begin with and found physiology and biochemistry much more interesting so decided I should learn some chemistry and give up medicine; went to see the Dean of Science who agreed that I should do a range of subjects - chemistry, physiology, histology, physics and maths; did a four year course instead of three; got firsts in every subject

25:56:05 No particularly inspiring teachers but a man who gave a popular talk on the Schrodinger wave equation had inspired me to do physics; I had intellectual curiosity and found everything interesting; always read history and have continued to do so; where

I got inspired was in Cape Town where they were offering a master's degree in physics; kept myself by teaching practical classes which gave me enough to live on; lived simply in a room in the old slave quarters; parents sent me money but I returned it as wanted to be independent; the Professor was R.W. James and he was an inspiration, not only because of himself but where he had been; he had gone with Shackleton on his polar expedition and been marooned on Elephant Island; he was recruited by Shackleton when just out of Cambridge; was a contemporary of Lawrence Bragg; Shackleton asked him if he could sing as they had to supply their own entertainment; I did apply to the South African Antarctic Survey but they wouldn't take me as I wore glasses; met my future wife, Liebe, in Cape Town; she was a music student at the University and later went to modern dance school; fell in love and was absorbed in the wider culture of a beautiful old city; Durban was provincial in comparison although it had a good library

31:56:03 James had worked with Bragg and in 1937 emigrated to Cape Town to take the Chair; Bragg moved to Cambridge in 1938 when Rutherford died; it is possible that when I came to Cambridge they wanted me to do crystallography as I'd started in X-ray crystallography in Cape Town as James had done; James represented to me the modern Cambridge position; I did the two year M.Sc. course in one year and actually solved the crystal structure of an organic molecule by a new method using Fourier transforms; on the strength of this James thought I should go to Cambridge; I had toyed with the idea of going to London as the crystal structure I had solved was rather unusual and I had taught myself quantum chemistry so when I came to Cambridge I wanted to do something unusual in X-ray crystallography; had heard of the MRC unit doing work on haemoglobin and myoglobin; went to see Bragg on arrival who told me the unit was full; don't believe that was true but one of my predecessors from Cape Town had been a lady, Virginia Martin, who proved to be very clever but hopeless at research; asked Bragg what I should do who said there was an interesting problem in order disorder in silicates; I now find them fascinating but didn't think so at the time; boat took two weeks from Cape Town and for the first two months in Cambridge still had no supervisor; was at Trinity where my tutor was William Hamilton who was not much help; originally thought I might do a

Part II but he thought I knew enough for a PhD; finally taken on by D.R. Hartree, Professor of Mathematical Physics, to work on a problem left over from the war on the cooling of steel; in the end I had learnt a lot of metallurgy and worked out a model of phase transition to account for the dissipation of heat; I modeled this on a computer; never published my PhD thesis; Hartree was not a good supervisor; he was a train addict, but not inspiring; enjoyed my time going to mathematical lectures and learnt group theory, which later stood me in good stead

40:53:01 Married very young and wife went off to live in London to study at the Joos-Leeder School of Modern Dance; the school had been housed by Alice Roughton in Adams Road, Cambridge, during the war but had moved by the time we arrived in Cambridge; my wife kept herself by teaching in a Secondary Modern school; never worked with Bragg; now realize that he may have thought me odd as I only wanted to do things that interested me; however, when I worked on the assembly of tobacco mosaic virus people were trying to understand how the virus assembled and they mixed protein and the RNA and waited twenty-four hours; I managed to do it in two to three hours using the model of nucleational growth that I had developed for my Ph.D. thesis to understand my experiments on tobacco mosaic virus (description)

46:05:14 Spent a year with F.J.W. Roughton, the husband of Alice; worked with him solving the mathematics required for the problem of the combination of oxygen with haemoglobin where both simultaneous diffusion and chemical reaction occur at the same time; used the mathematics developed for PhD; went back to crystallography in London but continued doing things for Roughton; memory of Roughton household in Adams Road; saw advertisement for a Nuffield Fellowship at Birkbeck College where J.D. Bernal was; he was an amazing man who never carried anything through to completion as always interested in the next problem; went to work on protein crystallography with Harry Carlisle who Bernal had recruited from Dorothy Hodgkin; he was trying to solve a protein by some method that didn't work and he refused to see it; I was banished but still had my Nuffield Fellowship and I found myself in a room next to Rosalind Franklin; I had been there for four months already but had not met

her before; she showed me her pictures of tobacco mosaic virus; she changed my life as she introduced me to an important and difficult problem that would take years; I worked with her from 1955 to 1958 when she died; she had come from King's College to work on the tobacco mosaic virus, work which Bernal had started in the 1930's but which was interrupted by the war; as a person she was brisk, to the point, and not at all the person painted in Watson's book 'The Double Helix'; she was a rationalist; I got on with her quite well and she treated me as an equal; when she died I took over her three post-graduate assistants including Kenneth Holmes and John Finch who later moved with me to Cambridge; we managed to get a grant from the United States National Institute for Health as we were the only group working on virus structure; in 1958 after her death I took up the problem of polio virus structure which she had started; through the introduction of a new kind of glass managed to solve polio in 1959; showed Bernal the first X-ray picture of polio virus crystals and he said that the picture was worth £10,000; I had not realized that Bernal had to keep raising money to fund his lab; Rosalind Franklin had been hired to work on coals and carbons not on plant viruses; Bernal's idea was to raise money from applied research to fund pure research; [shows the model of RNA on the staircase of the MRC unit in Cambridge]

Second part

0:09:07 Bernal was a Communist in those days and I didn't get on with him; in 1956 when the Soviet Union invaded Hungary there was a meeting of University College, Birkbeck and the Fabian Society; Bernal spoke about knowledge of the purges only since Khrushchev's speech in June that year; later got to understand him and to realize that he looked with the long eye of history where revolutions move things on; Rosalind Franklin never complained about not having recognition for the important part she played in Crick and Watson's discovery; blamed herself for not noticing the two fold axis of symmetry in her photograph; she did not know enough crystallography; when at King's she had worked out the A and B forms of crystal symmetry of DNA; she knew the B form was helical and said so but the A form eluded her; Watson recognised the relationship between the two forms and they got hold of her report which had been sent to all MRC units and he

and Crick used her data; had she lived, she should have shared their Nobel prize but there was also Wilkins; he was shy and he and Franklin would never have got on; he was clever and had chosen DNA as a problem but had no punch to go ahead; Franklin had been brought in by Randall, the Professor at King's, to put more muscle into the DNA effort; irony was that Wilkins, Stokes and Franklin had all attended Bernal's courses in Cambridge in the 1930's in crystallography and had all learnt about space groups; none of them twigged to it except Crick; only came out later when he and Watson wrote their paper in 1954, on their route to the discovery of the double helix

6:55:14 John Griffiths' part in the DNA saga not relevant but Franklin's work was the key but she had nobody to talk to; if I had been there a bit earlier I would have seen it; [article: 'The Discovery of the DNA Double Helix' amended and signed]; Maurice Wilkins was slow and careful whereas Rosalind was quick and decisive, sometimes brusque, so they would never have got on, it was not because she was a woman; worked at Birkbeck 1954-58 and during that time worked out the overall structure of the tobacco mosaic virus and I also developed analytical methods for turning the X-ray data into a map; wrote papers, one with Crick, on how you do this; after Franklin died her students, Finch and Holmes, came with me to Cambridge in 1962 and continued the work; Holmes went off to be Professor of Crystallography at Heidelberg and John Finch stayed with me; Holmes gradually worked out the three-dimensional structure of tobacco mosaic virus but we had an outline of the structure as early as 1958 which is the model on the stairs [see end of film]

13:03:12 In October 1962 I came to Peterhouse as a teaching fellow; John Kendrew was the Director of Studies and I later succeeded him; at Peterhouse I taught a number of subjects as there were not many teaching fellows including crystallography, microspectroscopy and chemistry, and always taught physics; I was later a Nobel prize winner in chemistry, worked in a biological lab. and taught physics; I enjoyed physics and was quite a good teacher; Ken Holmes had been taught by Fred Hoyle and Abdus Salam but never learnt anything as they would just dash off a problem; I was a good teacher as I had to work my way through it; physics stood me

in good stead as before I developed three-dimensional image reconstruction I did various optical experiments which I wouldn't have done if I had not been teaching optics; I occasionally lectured for the University in place of Perutz; later when I introduced three-dimension electron microscopy I was asked to give some lectures; awarded a Nobel prize in 1982 but went on teaching until about 1984 when Hugh Dacre, the Master, said I should become a supernumerary fellow with no teaching duties; accepted but still continued teaching for a few years until I became more involved with the zinc finger work; in 1986 became head of the lab after becoming President of the Royal Society in 1985

16:34:10 Was President for five years; had turned it down five years before and found that I was the only person to have refused it since Faraday, but I had just started a new division at the Lab and I thought that being head of the MRC Lab was just as prestigious; I introduced a department of neuroscience here which we had not had before; as President of the Royal Society had to deal with a lot of issues such as genetically modified organisms which, by the way, with zinc fingers we can do much better now; this is producing what has been called a game change in plant agriculture; zinc fingers are used to modify genes and you can put genes into a specified place; had to deal with privatization from Mrs Thatcher as she wanted to sell off all our laboratories; also started on global warming; every year in my anniversary address I, like the elder Cato, would bring up the subject; started work here with John Sulston on the human genome; Sydney Brenner and others were going round the world creating the Human Genome Organization; John Sulston started out using any sequencing facilities that there were and made huge progress; Brenner had wanted him to work on the products of the genes, the proteins produced by the genes, and to sequence those, or rather to sequence the RNA which is the intermediate between the DNA; I, in contrast, encouraged Sulston to do the whole genome because there you get not just the products of the genes but, probably equally important, the DNA sequences for binding the regulatory machinery; now, ironically, I am working on zinc fingers which are the most powerful weapon for intervening in gene regulation; after turning down the Presidency I did not think they would ask me again at the age of sixty-nine but Alex Todd had been the same age so there was a precedent; my wife enjoyed the

challenge and we opened up the place by having lunches and improving the menu; we had a flat in London and I had thought we'd go to theatres and galleries, but was too busy as it also overlapped with being head of the lab

23:10:20 Started in the Lab in 1962 and had my own group, but did spend time working with Crick on chromatin; we published very few things together; had a very good post-doc., Roger Kornberg, who got a Nobel prize last year, and together investigated the sub-structure of chromatin; he discovered working on the chemical analysis of chromatin samples that the histones which are used for packaging the DNA on their own form aggregates; the psychological breakthrough was that the proteins form a globular aggregate like haemoglobin and here could not be sitting in the grooves of the DNA as people like Wilkins had assumed; Kornberg discovered the nucleosome; I did not put my name on the paper though might have done; got him to see not "beads on a string" but string of DNA on beads; I also started work on tRNA; also started an Alzheimer group which is flourishing as I thought we should be doing something that is relevant to medical research; had not realized that Alzheimer's disease was specific to certain areas of the brain; realized that it must be caused by a malfunction; work had been in the hands of neurophysiologists and they had been cutting sections of Alzheimer brains; I said we must get the material out as had been done with chromatin; introduced chemical separation methods which we'd used on chromatin, chopping up the material with enzymes etc. so we discovered the filaments; work continues but I moved on to zinc fingers

27:43:04 Max Perutz was head of the Lab when I came here as a group leader; John Kendrew was the head of one of the divisions in the lab called Protein Crystallography; Hugh Huxley was working on the structure of muscle; I was working on viruses; Perutz and Kendrew were working on single proteins; we worked on biological assemblies using both X-rays and electron microscopy; Hugh Huxley was the best electron microscopist of his time, a mystery why he did not get a Nobel prize for his work on muscle; Max was single-minded and determined; wasn't very learned but as he went along he learnt; not highly imaginative but solved, over a period of years, the structures of haemoglobin both in the oxygenated form

and the deoxygenated form and shown the structural transition between them; John Kendrew was very different; a marvelous staff officer, very well organized with a meticulous filing system using a form of punch card; when I told Max how tobacco mosaic virus assembles [shows figures from Nobel Prize lecture] he didn't believe it; own work on spherical viruses described; collaboration with Donald Caspar [shows model of a spherical virus]; in 1966 Max gave an interview for 'Science' and spoke about all the successes of the lab - Nobel prize for Crick and Watson in 1962, and himself and Kendrew, Sydney Brenner's work on the messenger RNA, and "Klug's work is very satisfying" but was "very far fetched"; his gift as Director was to let me get on with my work without believing in it; Crick understood it immediately and I know that he put me up for the Nobel Prize; spherical viruses and Buckminster Fuller geodesic domes

40:06:05 Electron microscopy takes a two-dimensional image; 3D image construction allows you to combine all the 2D views mathematically using a computer and producing and three-dimensional image which is the basis of the X-ray CAT scanner; some thought I should have got a Nobel Prize for this work but Hounsfield patented the machine not the technique; felt a bit sore in 1979 when he got the Nobel Prize because he knew my papers and referred to them and I'd exhibited with him at the Royal Society [shows images of electron micrographs of virus particles and describes use of tilting experiments using computer methods leading on to the method for the CAT scanner]; my paper came out in January 1968 and in August Hounsfield took out a patent for building a machine at EMI; to begin with it produced nonsense as he did not collect enough views for the detail he was looking for; however, in 1982 I got the Nobel Prize on my own for chemistry; earlier tried to interest radiologists to take up computer automated tomography based on image construction techniques but they thought it would be too harmful to take a series of X-ray photographs

51:22:18 Work on zinc fingers; became interested in active chromatin which has become susceptible to enzymes which will attack the open DNA which correlated with genes which were going to be activated; began looking for a source of active

chromatin in large quantities; found that the gene of ëXenopus Leavis, the South African frog or toad, which was present in large amounts; colleague Hugh Pelham had actually worked on it; decided to work on the 5S RNA genes which in this case gets incorporated into ribosomes which are protein synthesis factories; had a new post-doc, Jonathan Miller, and uncovered by purely biochemical experiments over a number of years that this had a repeating structure [shows diagram and the amino acid sequence that came out]; went on from strength to strength [shows number of zinc finger genes from simple forms to human] a marvellous modular system where each finger has a different amino acid sequence which can recognise a short sequence of DNA; so suggested to me a tool for making synthetic fingers having access to genes; now a big technology; with my colleague Yen Choo who formed a company call Gendaq; MRC hold the patents; in the lab started to make libraries of zinc fingers and began to work out the rules of recognition; Gendaq was bought out by an astute American who created a biotech business called Sangamo which may be successful and make some money; now the method of choice, 'game-changing' technology; know I've been noted for another Nobel Prize for it; I didn't set out to be a benefactor of mankind but just out of curiosity which is the driving force; its not only thinking but also doing; we used to make fingers in the lab chemically so I had to learn how to synthesise these things; the first paper on zinc fingers appeared 1985; when I wrote it, I thought it was unlikely to be confined to a lowly gene in a lowly animal; needs not just intelligence but also imaginative powers of the "what if" kind; also need some technical expertise unlike Linus Pauling who often proposed things that were unrealizable as he didn't have enough technical understanding; the truth is in the detail...

Dan Brown

10 January 2008

http://downloads.sms.cam.ac.uk/1114102/1114109.mp4

J Baddiley & D M Brown, 'Alexander Todd: a new direction in organic chemistry'. In *The 1702 Chair of Chemistry at Cambridge*, Archer, M.D., Haley, C.D. Eds. (2005), 210-236.

Extracted from the Memorial Address by Alan Macfarlane in King's College Chapel

Daniel McGillivray Brown

(February 3 1923 – April 24, 2012)

I knew Dan from the early 1970's when we were both Fellowship Electors. Around the table sat a number of distinguished figures, including Dan's good friend, the late and much lamented Gabriel Horn. Dan became one of the Fellows I most enjoyed meeting in King's; always cheerful, always full of wry comments, open and egalitarian. He was a perfect companion at a meal or over coffee, always interested in ideas and what people outside his branch of science were doing. Yet, in the way of Colleges, our friendship never took us behind stage, into each other's inner lives. I knew nothing much about either his life or his work. People told me that his achievements had not been fully recognized, despite his SCD and FRS, but that was all.

Not being a chemist, I have to rely on others for an overview of his work. A summary of the early years is provided by Phil Davison (15 May, 2012, Herald, Scotland), and Mike Gait at the MRC-Laboratory of Molecular Biology in Cambridge also provided some insights into the chemistry.

As a postdoctoral fellow in Todd's laboratory, Dan Brown focused on RNA (ribonucleic acid, the single strand version of DNA). He was able to throw light on how the adjacent nucleotides in RNA (and by analogy in DNA) were joined together. This research into the chemical structure of RNA, which at that time was only partially established, was important in guiding Watson and Crick to their DNA breakthrough on the double helical structure of DNA. His role in this work was little known, except among fellow researchers. In fact the importance of this work is shown in an anecdote described by Thomas Lindahl in a chapter on the history of DNA.

'In 1993, I had the pleasure of attending Dan Brown's 70th birthday party in Cambridge. The guest of honour, besides Dan himself, was the 86-year-old Lord Todd, who was awarded the Nobel Prize in chemistry in 1957. During a group conversation, a misguided molecular biologist chimed in, "Isn't it wonderful that

this year is the 40-year jubilee of the structure of DNA"! Lord Todd magisterially corrected him in his strong Scottish accent: "Dan Brown and I discovered the *structure* of DNA. Crick and Watson worked on the *conformation*. But we didn't realize its biological implications."

Subsequently, as a young lecturer in the Chemistry department, Dan became interested in how certain chemicals could act as mutagenic agents by chemically altering one of the bases in DNA and thereby changing the way it pairs with the opposing base in the complementary DNA strand. During his later research life at the LMB, Dan built upon this work and devised improved mutagenic bases (agents?).

Dan was awarded the Sc.D. (Cantab) in 1968 and became a Fellow of the Royal Society in 1982.

INTERVIEW SUMMARY

Dan Brown interviewed by Alan Macfarlane 10th January 2008
[added notes by Dan Brown on the summary in square brackets]

0:09:07 Born at Giffnock near Glasgow in 1923; father was a restaurateur in Glasgow, taking on his father's business when his elder brother was killed in the First World War; Daniel Brown Ltd. dated from the mid-nineteenth century but neither my brother nor myself ever seriously thought of going into the business; my father had been an engineer on the Clyde during the First World War; he was an intelligent man and interested in my progress at school, particularly maths; mother had been a teacher for a short time and helped with English; did not have a large library of books but father did give me 'The World of Science' by Sherwood Taylor; my interest in chemistry evident when I went to Glasgow Academy; the chemistry teacher suggested that I might sit for a scholarship to Cambridge; that implied staying at school for an extra two years and learning some Latin; rumours of war ended this idea and I went to Glasgow University

6:44:05 Never had any particular hobbies while at school though I have become interested in music since; started at Glasgow University at seventeen; war started but the system at that time was that if you were doing well you could stay and were not called up; for some reason I had not joined the O.T.C. at Glasgow Academy though I don't remember being in any sense a pacifist although I think my father was in a non-active sense; father had no religious affiliations though I sometimes went to church with my mother; I retain from that time a liking for a good philosophical sermon; however I have always been an atheist but one has a liking for some of the ritual and music

12:19:19 Don't remember any really inspiring teachers at university but they were good; one lived one's life in the Lab and lecturers had to pass through it which allowed one to talk to them; there was no supervision beyond that; became clear to me when I arrived in Cambridge that the supervision system, at least in the sciences, did not expect much reading; I did join what is now the Royal Chemical Society in 1942 and, as a student, learned much chemistry from the Journal; at that time papers were

comprehensible to students at our level which is no longer the case; head of the department, J.W. Cook, was a good chemist and he had been associated with the Chester Beatty Research Institute in London and had been involved in the chemistry of carcinogens from coal tar and soot from which were extracted several pure crystalline compounds which when rubbed on the back of a mouse created a tumour; on his suggestion I later became a research student there; the Director was E.L. Kennaway, a strong rationalist, with whom I got on well; I was involved then with the man who, with Cook, had done the important thing that started cancer chemotherapy, an understanding of carcinogenesis by finding a pure organic compound in nature; this had been known for two centuries and discussed by Percival Pott, called chimney sweep's cancer; I learnt quite a lot there although I thought the Ph.D. thesis that I wrote was dreadful; I read it again a few weeks ago and realized that I had become aware among other things, that the genetic material which was the thing that was clearly going wrong in carcinogenesis was probably DNA and not proteins, at least not directly; that was a view that was coming through just at that time

20:59:16 While in Glasgow, my friends and I were reading Sartre, Mauriac, Gide and Duhamel's 'The Pasquier Chronicles', all in translation; felt French writing had an intellectual content which I did not find in English works of the time; did enjoy Shakespeare's sonnets and Keats, Shelley, Coleridge and Tennyson; read C.P. Snow but realized that his characters were like cardboard figures with no depth; only book of his that I felt for later was 'The Search' which was about his own failure as a physical chemist although disguised as a crystallographer who was obviously Max Perutz, and another character (Leo Constantine) who was clearly J.D. Bernal; got a feeling for Cambridge at that time through this book;

[I must add here, that all my time in Cambridge I have been increasingly appreciative of music. More importantly, I have read and collected poetry, specifically the products of the period of the Scottish Literary Renaissance from around 1920-1960. Just as important to me was my continuing interest in Western art and its history, rather specifically, that of the twentieth century. It almost became a practical hobby.]

26:33:10 Stayed at the Chester Beatty for a further year and read a lot; got interested in certain aspects of nucleic acid chemistry; the subject was in confusion; the head of Chester Beatty said I should go to Cambridge for a while and learn some nucleic acid chemistry with Alexander Todd; Todd had made a meteoric rise and had worked at Oxford with Sir Robert Robinson and had spent a year or two in Edinburgh with a man called George Barger, whom I found had been a Fellow of King's; he was learning to work on things which were very difficult as only present in minute amounts in living tissues, in fact the vitamins and coenzymes that derived from them; Todd came to Cambridge in 1944 and I came in 1948 and started working with Todd and Basil Lythgoe, a teaching fellow in King's; I joined Christ's College as a graduate student intending to do a better thesis; I came to Cambridge never having seen it and having no concept of the place; I arrived at Christ's with my friend Hugh Forrest who had come from Glasgow [now in Austin, Texas] and maybe he adapted faster as he played rugger; I found it a terrible institution akin to a finishing school for public school students; however, I had joined an exciting Lab which was going strongly with people coming from all over the world; I turned up at and interesting time; nucleic acids were not discussed much because of concentration on coenzyme synthesis (eg. RTP) and phosphorylation, the thing that Todd had started which got him the Nobel Prize; some of the structures as parts of the coenzymes were the same as those present in RNA although my reading of the literature showed that RNA structural understanding overall was quite chaotic; how the bits [the nucleoside phosphates or nucleotides] were joined together to make any reasonably large structure was just not understood; it was not understood for one reason; RNA was at least thought to be a chain and as with DNA it kept getting bigger as methods were developed to measure its size; and RNA was much less stable and more or less degraded, and the results that other people were getting were not telling them very much; when you have a chain you expect to be able to find the linkage points between one nucleoside phosphate and the next; the curious thing was that for fifteen years everyone believed, erroneously, there was just one position when you broke RNA down ñ the 3í- phosphate [there are four nucleosides in RNA with positions 2í-, 3í- and 5í- which can carry a phosphate group]; amazingly Waldo Cohn found that the methods used to separate

metals in the atomic energy field could be used to separate the nucleotides from RNA hydrolysates; found that you got two kinds of phosphates for each of the four different kinds of nucleosides; sent Todd a pair of them and as I was at that moment the only one in the Lab he asked me to investigate;

[it should have been a simple project ñ the 5í- compounds were known, the 2í- ones had been synthesised in the lab but it took me a year to show that the latter were not what they were claimed to be; however, Waldoís were the 2í- and 3í- compounds, but which was which, and what did they say about RNA structure; as it transpired in synthesising them I obtained their benzyl esters [nucleoside ñ phosphate ñ benzyl] and suddenly realized that they represented simple models of the so-called internucletide linkage in RNA; they behaved exactly like RNA on hydrolysis; put shortly, it showed that a simple model compound and an understanding of the chemical mechanism of its hydrolysis gave an understanding of the real RNA structure; in fact Roy Markham and John Smith working in a nearby lab, (the Molteno Institute), on viral RNA enzymology, and our results fitted exactly; RNA then ended up as a 3í- to 5í- linked polymer]

1950-1956 was a great period and for that reason; I was supposed to be going back to the Chester Beatty but Todd offered me a job as an ADR, Assistant Director of Research, which meant I could carry on working without teaching or demonstrating and I thus got a huge amount of work done; it had the unfortunate effect that I didn't learn to teach at the lower level and I don't enjoy lecturing

45:46:09 When Todd gave me the job Lythgoe left to go to Leeds and I stepped in to become college lecturer in chemistry at King's; this was in 1953; most of my life at the time was spent in the Lab but I did supervise and I quite enjoyed that; I have had some thirty Ph.D. students over the years; I had by that time generally got the RNA structure right and how it hydrolyses and therefore how enzymes hydrolyse; also the general chemical structure of DNA which is basis of the double helical structure described by Crick and Watson; as soon as I had finished working that bit of RNA chemistry the things that other people in the field were then beginning to do were biochemistry and I didn't want to do this; I

looked around for another subject which I called a super-RNA problem which was the phosphoinositides and for a number of years I worked on that but also worked on the hydrolysis of phosphate esters and we derived a lot of interesting chemistry; the theory of organic chemistry up to the time I was learning it at university was almost all carbon chemistry; suddenly people started looking at esters, carbonyl compounds; then when Todd started on the phosphorus chemistry, that was almost another kind of chemistry; I, together with several fine graduate and post-doctoral people, one of whom was Neil Hamer who is now in Trinity, but was then a Research Fellow of King's, discovered quite a lot of interesting things involved with phosphate ester chemistry and phosphorylation methodology; this took me through to my next period

51:35:12 Having got a University job and become a teaching Fellow, Margaret and I decided we would be able to marry; I got to know the Fellows of King's well - Beves, George Salt, Stockdale, Shire, Nicky Kaldor, Lord Kahn; got associated with Kenneth Harrison, a biochemist who did little biochemistry

[However, Harrison and I, with Noel Annan, brought Sydney Brenner to the College. Of course, my colleague Hal Dixon, and my closest friend, Gabriel Horn, were among that early group. I should add that when I became Vice-Provost of King's in 1974, I got to know, and appreciate, all the Fellows, and indeed their wives. My interaction with Edmund Leach was important to me and I enjoyed the position very much.]

gather that if given a choice of college, students would come here though why they might feel the preference I don't know; there is no question that this college is in a real sense different from most others; that derives way back from the period when Shepherd was a young man and Rupert Brooke was here; there was a freedom which was not so in a place like Christ's when I came to Cambridge; women were admitted early and with care not to offend the women's Colleges; however I think that I did better by doing my initial studies in Glasgow rather than here; we taught each other and we read in our subject whereas in Cambridge the relationship between the University and the Colleges were

orthogonal to each other and led to a situation where you finished work at lunchtime and shot over to the College or the Eagle] to eat and shot back again; meanwhile your other colleagues in the Lab did exactly the same; the students that you taught came to supervisions here but you didn't teach people in other Colleges; the College operation in the teaching sense was distinct and the interaction of the students in ones subject was cut apart
[This is too great a simplification, now.]

58:04:14 As far as my work was concerned one very important situation occurred with the appearance in about 1959 of Sydney Brenner; my chemistry had kept moving me away from the centre of chemistry in the Department towards the kind of things that Sidney involved himself in; I got interested in chemistry associated with genetics; that built up and I went back to nucleic acids again and some of my students went and worked in the MRC Molecular Biology Lab and slowly I moved over there so that when I came to have a sabbatical and then retire [early] I went and worked there permanently; I therefore have had two careers, one in chemistry and one in molecular biology although few of the molecular biologists would call me one; that worked very well until a year ago and now I find I can almost drop all that and become more domesticated; of the people that worked with me I would like to mention Srinivasan Varadarajan whose father was a lawyer in Bangalore and a follower of Gandhi's peaceful resistance movement; there were quite a few of similar background in Cambridge at that time, an important generation now disappearing; I have been to India several times; Rajan did incredibly well, a huge amount of work, and took the view that if India was to become industrialized then it had to pull itself up by its own boot-straps; Britain had known since the end of the First World War that it would leave India; it took it too long and was still holding it back; Rajan did that with the petro-chemical engineering business

[Also a variety of biologically-based activities, not to mention the presidencies of the two National Academies of Science. His heroic actions in the Bhopal affair is another chapter in itself. A major justification for Cambridge University, and perhaps the Cambridge Colleges, is to bring such people of ability from other countries into serious contact with each other.]

John Gurdon

20 August 2008

http://downloads.sms.cam.ac.uk/1119934/1119942.mp4

J.B. Gurdon and A. Colman, "The future of cloning", *Nature* 402 (6763), 743-6 (1999)

Sir John Bertrand Gurdon, FRS, FMedSci (born 2 October 1933), is an English developmental biologist. He is best known for his pioneering research in nuclear transplantation and cloning. He was awarded the Lasker Award in 2009. In 2012, he and Shinya Yamanaka were awarded the Nobel Prize for Physiology or Medicine for the discovery that mature cells can be converted to stem cells.

Nuclear transfer

In 1958, Gurdon, then at the University of Oxford, successfully cloned a frog using intact nuclei from the somatic cells of a *Xenopus* tadpole. This work was an important extension of work of Briggs and King in 1952 on transplanting nuclei from embryonic blastula cells and the successful induction of polyploidy in fish Stickleback, *Gasterosteus aculatus*, in 1956 by Har Swarup reported in Nature. However, he could not yet conclusively show that the transplanted nuclei derived from a fully differentiated cell. This was finally shown in 1975 by a group working at the Basel Institute for Immunology in Switzerland. They transplanted a nucleus from an antibody-producing lymphocyte (proof that it was fully differentiated) into an enucleated egg and obtained living tadpoles.

Gurdon's experiments captured the attention of the scientific community and the tools and techniques he developed for nuclear transfer are still used today. The term clone (from the ancient Greek word *κλών* (klōn, "twig")) had already been in use since the beginning of the 20th century in reference to plants. In 1963 the British biologist J. B. S. Haldane, in describing Gurdon's results, became one of the first to use the word "clone" in reference to animals.

Messenger RNA expression

Gurdon and colleagues also pioneered the use of *Xenopus* (genus of highly aquatic frog) eggs and oocytes to translate microinjected messenger RNA molecules, a technique which has been widely used to identify the proteins encoded and to study their function.

INTERVIEW SUMMARY

John Gurdon interviewed by Alan Macfarlane 20th August 2008

0:09:07 Born 1933; our family goes back reliably to 1199 and was well established in a large house in Assington, Suffolk; my grandfather ran out of money as he rented out farming land; the repeal of the corn laws meant that farmers couldn't sell their produce so could not pay the rent; my grandfather had to sell up in 1894; father worked in India and Burma for a while but was then paid a pension by his father to come back and marry and continue the family line; I was brought up on the Surrey-Hampshire border; there is no evidence of any scientific inclination in the family, they were mostly politicians and such like; father was a retiring, meticulous man, and in his later years read an enormous amount and became very good at financial matters which really re-established the family in a relatively comfortable state; my mother encouraged him to do something when he left India and he took up brail transcription of heavy legal textbooks; he had had a rather distinguished war period and was awarded a DCM for gallantry; he was just over age by the Second World War so he was air raid chief warden for the village; he took part in village activities and did quite a bit of voluntary work with my mother; she was born of a Yorkshire farming family and was unusually go-ahead for the time and decided to take a teaching job in America for a time; came back and married; she was very energetic and ran anything that could be run locally; she was extremely supportive of anything so when I took an interest in insects at an early age she would encourage that; by that time my parents had enough money to send me to a private school, Eton; I did one term of science at fifteen and am still amused by the report that the master wrote saying that Gurdon was the worst pupil that it had been his lot to teach, and some talk of Gurdon wanting to be a scientist which would be a total waste of time both from his point of view and those whose job it would be to teach him; I was put onto Greek and Latin which was quite interesting; my real interest has always been in insects and things like that

6:18:14 My interest in insects was probably from the age of eight; I had an aunt who used to catch me butterflies and I liked to set them and find out what they were; for leisure reading in my mid teens I bought a textbook of entomology; my kind mother decided that I really was a scientist at heart so through family connections she arranged an interview with a professor of zoology in Oxford, Alistair Hardy, and somehow persuaded him that I should be allowed to switch from classics to zoology if I did an intervening year in a crammer to get through the 'O' level science; it was a risk as I might not have taken to the subject; having paid my school fees they then had to pay for another year of private tuition in elementary science to be allowed to start at Oxford; that was again a piece of luck because the Admissions Tutor for Christ Church was Trevor-Roper who had more important things on his mind; I got a letter saying that they would accept me under two conditions, one that I came into residence almost immediately and that I should not read the subject in which I had taken the entrance; later I got to know him quite well and he admitted that it had been embarrassing and they had got the numbers wrong and suddenly found they were short of places so anyone who had applied and they had not done much about and could get hold of got in; a back door arrangement that would not be possible now; very fortunate, and thanks to parents for seeing what one's interests really were and to recover for a really bad teacher at school

8:38:12 First school I went to was Frensham Heights, a curious school; remember doing an intelligence test aged eight; remember being asked to draw an orange but I drew it with a stalk which was deemed wrong as what was wanted was a circle; parents received a message that there were difficulties and I would need special education; they then sent me to another school in the village of Edgeborough where we lived; teachers at this school became personal friends; the Headmaster was Charles Mitchell, his deputy Bob Hardy, and the Latin master was Norman Stone, and I remember all of them; a lovely school; during my time at Eton I became interested in squash, partly because you could play it whenever you wanted; I ended up being captain of the school team; I was a keen skier and got into the second University team for that; again, didn't feel I had any particular ability but it was just

hard work and practice; I also became secretary of the Natural History Society at Eton; I was never keen on music; I am not very arty, I don't go to theatres or spend much time watching or listening to other people performing

12:03:17 I have a younger sister who became a nurse and then married a farmer who has a big estate in Lincolnshire; I keep up with her very well, being a lifetime friend; at Christ Church, the idea was to do zoology; I was told that I would have to pass the Prelim exams in one year, which was tough; I started by getting rid of chemistry which was really just learning formulae after one term, the physics was very elementary, and that left biology for the summer term; I got through these tests which then meant I could start as an undergraduate after one year, so I was given four years not three; in the second year started to read zoology; Alistair Hardy was the Head of Department, a wonderful man, who became a personal friend; it was a remarkable department; among the eminent people there was Nico Tinbergen; it was rather a boring course, three days of the week we did the animal kingdom, including palaeontology; I was doing badly as a student but something persuaded me to look at all the old exam papers for the last ten years; I classified all the questions and then asked each staff member how I would be expected to answer each as I had noticed that the questions were somewhat similar each year; by an amazing piece of luck that got me a good degree which meant I was able to be a Ph.D. student; because of my interest in insects I had gone to the entomology department where fortunately the Professor rejected me as a Ph.D. student; a wonderful man, Michael Fischberg was the embryology teacher and I warmed to him; he offered me a place in his group; that was probably one of the most important steps in my career; he put me onto a rather dull project which I didn't thrive on; then he suggested I try a new thing called nuclear transfer and by an amazing piece of luck it looked like it was working; he then gave me that as a major project; he was immensely supportive and would let me do anything I wanted; so several times I survived the fate that might have overtaken me, like becoming a museum entomologist, or not getting to university at all

17:06:17 A friend from my undergraduate years is Bryan Clarke, who became Professor of Genetics in Nottingham; the best person in the class became Professor of Biology in York, John Curry,

whom I keep up with marginally; Bryan Clarke was a Ph.D. student with me and we used to go out most evenings to eat; did play squash but decided to give up trying to get a blue and concentrate on my work; I took no interest in music, drama or politics; on politics I am middle of the road; one thing I do object to are people who do no work and assume that the state must support them; I have respect for people who put a lot into life and contribute; on religion, my father took us to church every Sunday morning; I support the church; in terms of religious views I would say I am agnostic on the grounds of I don't know; there is no scientific proof either way; I support the ethics of the Church of England; I am anti-Roman Catholic as I think they should let people decide for themselves on contraception; I find myself giving lectures to theology students from time to time; this happened because when Master of Magdalene College I thought the sermons were boring; I suggested to the Chaplain at Magdalene that he occasionally asked Fellows to give an address on anything they would like to talk about; the letter was not responded to but the Bishop of Coventry, Simon Barrington-Ward, came back to Magdalene and I mentioned the idea to him; he thought it a good idea and I was asked to give an address; I chose to take as a theme that you should not be prevented from trying to relieve human suffering by your religious views; rather controversial, and the Chaplain didn't like it at all, (by this time I was Master of the College), he got preferment at Windsor and decided that it was interesting and invited me to give it to the theology students in Windsor Castle; I did so and he was very supportive; we disagree on a number of things but I continue do it; these are priests in service who come for revision classes, sent by their Bishop; after the talk I get them to vote; the first time they voted against the line I was taking; the Chaplain suggested that the next time we have a secret vote and then it came out in favour; I like talking on to what extent religion should interfere in the relief of suffering; a classic case is cystic fibrosis and should you get rid of embryos that are going to have it by in vitro-fertilization, and avoid enormous suffering; as Master of Magdalene never found any difficulty in presiding in Chapel; I don't think an agnostic position is inappropriate; I support what the church does very strongly, but the fact that I can't prove what we believe is a good reason to be called agnostic; Richard Dawkins' views are rather too aggressive

but make him good as a television presenter; he was a graduate student shortly after me and worked under Tinbergen; he does interest people in science and that is good though I wouldn't agree with his views on religion

28:11:07 In the 1950's we did not know whether all cells in the body have the same genome or not; the idea was that as an egg turns into an animal with different kinds of cells, maybe the cells lose the genes they don't need any more; your brain cells wouldn't have muscle or skin genes; a perfectly plausible idea and that would be a fundamental principle of how an egg develops into an organism; the point was to test this by experimental means; the idea was to take a specialized cell, take the nucleus out of that and put it into an egg that has no genes of its own; if you can produce an individual that way from, shall we say, the nucleus of an intestine cell, then that intestine cell must quite clearly have retained its genes for muscle, bone, brain etc.; that was the key question which people had been aware of since the 1890's but there was no good test for doing it; then two Americans, Briggs and King, discovered that you could transplant the nucleus of a cell into an egg which they did very successfully; when they tested it a bit later they found that as soon as the embryo developed these nuclei lost the ability to substitute for the egg and sperm; they reached the conclusion that genes were being lost or permanently inactivated; under my supervisor we started work on another frog called Xenopus and the results were roughly the same, but the key point was they were coming out the other way round; even when you took the nucleus of a specialized cell you still managed to get normal development; we eventually had a paper which showed you could get normal fertile adult animals from the nucleus of an intestine cell; that really convinced me and a fair number of other people at the time the opposite conclusion to Briggs and King, that genes were not lost, hence all cells of the body have the same genome; that has come back into popularity recently with the whole stem cell field; the argument is that if all cells have the same genes, in principle you must be able to create one cell from the nucleus of another cell; if you take a skin or bone marrow cell you can take its nucleus out, send it through an egg and recreate brain or nerve, or anything else, hence you will get the idea of patient-specific cell replacement; by use of own cells there is no immunorejection; that has become very fashionable now thanks to a Japanese man, Yamanaka, who

discovered a much simpler way of making this transition; I am lucky in that the work that we did had a certain fundamental basis to it of a scientific kind; that has become useful to people for purposes of cell replacement

32:32:09 The American results were different because when they used a different kind of American frog, Rana pipiens, in which, for reasons we don't understand, it doesn't work very well; luckily for me it worked rather well on a South African frog; the first successful experiment came in 1958 and we kept the animals and published what was the most important paper at that time in the field on the generation of sexually mature normal adult animals from the nucleus of a specialized cell; published in the early 1960's; the first response was not to believe it; the two Americans were highly respected and I would have drawn the same conclusion from their experiments; there was a natural reluctance to believe some foreign graduate student who challenged these masters and pioneers of the technique; gradually, over time, people concluded that our experiments were right; we had no real difficulty with them working; the key feature of them, thanks to Fischberg, who found a genetic marker; when you do this experiment you transplant a nucleus into an egg and you have to be able to show that the embryo or animal you get back carries the genetic marker of the nucleus you put in rather than the marker of the egg whose own nucleus you hoped you had removed; the marker Fischberg discovered was of crucial importance to our work and came at just the right time; the frog cells are very big so you can do this by very primitive methods; we made most of our own equipment to make the pipettes or needles you use and some of them I still use now; it became more refined and when the work was transferred to mammals they use more sophisticated means of doing everything; the major problem was that the frog egg was almost completely impenetrable which meant that you put a needle in it and it would just push the membrane through the other side; thanks to Fischberg having bought a new microscope with an ultra-violet source it turned out that the ultra-violet light permeabilized the membrane which solved the problem

37:06:19 I was still in my twenties when this work was done; I stayed in Oxford until I was thirty-nine; I had become a Research Fellow at Christ Church, first in a junior research post then senior; I did not have much teaching to do so it was a favoured position; I then became part of the teaching staff of the Department of Zoology; John Pringle took over as Professor from Sir Alistair Hardy and he appointed me; he said he would like me to start off with twenty-four lectures, which was tough; the following year this was reduced to sixteen, and later on, to eight; by the time I left I was down to about four; I had attracted a lot of graduate students but was grateful of being relieved of teaching; I don't really liked undergraduate teaching; I objected in principle that the students could fill in a report form and say whatever they wanted, could be as rude as they liked; I was spared the worst but there were some offensive reports, and they aren't signed

39:50:24 After my Ph.D. I went for a post-doc period to California, again thanks to the good advice of my supervisor; I went to Caltech which was a good place, and got to know a lot of the senior professors; I worked on bacteriophage genetics but couldn't make them work so after that year I went back to embryology, but having learnt a great deal; I did not have a job at the end of my post-doc period so I did look at jobs in America; I was interviewed at Columbia University for an assistant professorship; the Head of Department said they couldn't offer me the job but added that if I could persuade my supervisor at Caltech to go there they would give him a full professorship at any time; I was tempted later by an offer from Stanford, but I have been lucky with jobs in this country

42:35:07 While at Oxford I got a letter from Max Perutz to say they had an appointment and would I be interested in moving to the MRC Laboratory in Cambridge; that was the ultra-famous lab with spectacular people, so it was an enormously attractive career move for someone who hadn't really learnt any molecular biology; I came to talk to Max and other; Max was a wonderful person and very supportive and I was offered the job; there was a whole set of rooms; the Oxford people had been good to me and had got me the offer of an MRC unit with quite a significant amount of research support with four or five positions, but the Head of Department was unable to give me space where I could have a

coherent group, so it was tempting to come here; I accepted the job and then heads of other departments in Oxford, most notably Rodney Porter, the Head of Biochemistry, mounted a counter move to keep me in Oxford; however my Head of Department stuck to his guns; as I had a house and family in Oxford I was very tempted to stay and Max wrote a very nice letter wishing me well but keeping the offer open; when I failed to get the terms I wanted I wrote to Max again, accepted the job and moved into his institute; Max was an amazing person, very mild in character; as head of what I think was the most successful lab in history with fifteen Nobel prizes, he insisted on being chairman rather than director; if one wanted to talk to him one waited until he was in the coffee queue to do so; no appointment made with his secretary, all extremely low key administration; think that this was why he was able to keep this amazing group of people - Fred Sanger, Francis Crick, Cesar Milstein, Aaron Klug - in his institute, some for their whole working life, whereas any one of them could have taken an enormously prestigious job anywhere else in the world; Max somehow kept the whole lot going and I've never really understood how he did it; when we in due course came to start our own institute we set ourselves up with a chairman, not a director to try and emulate Max's style

48:31:12 Cesar Milstein, Max Perutz and I used to go skating in the Fens; Cesar was extremely interesting; have been working a little recently with Aaron Klug on zinc fingers; Aaron's phenomenal memory; Fred Sanger was extremely low key and if you didn't know who he was you could take him for the janitor; when we went to the MRC we were invited to join his research group; Sydney Brenner was undoubtedly too clever for me and I found it difficult to follow what he was saying; Francis Crick was a member of Churchill College where I was too, and I had immense admiration for his mind; I didn't know him socially as well as I did Max Perutz; curiously, those I knew better socially were not particularly close to my field; Sydney would have been nearer in interests but I never had any real scientific conversations with him; knew Hugh Huxley well, and John Walker; can't really understand why the lab was so successful; for instance, Crick and Brenner had to share an office for the whole of their time as there was minimal space; I suspect it

was that the concept of a chairman can be more effective than a director; hard to do when you have to have people who govern a place, but Max did it in a way that displeased no one, except in a trivial way; when I joined it was in its present building in Addenbrookes; it was quite far from the centre so people there were rather divorced from College life; Max, Aaron and Sydney had college fellowships, Francis was at Churchill; Richard Keynes arranged for me to be a Fellow at Churchill which I missed, having had a strong college connection in Oxford; I was a Research Fellow at Churchill for about twenty years which was a benefit I have always appreciated; I hardly ever went in to lunch but I did find dinners very pleasant; I feel I have not done enough to support the college system but I do appreciate it a great deal; my Christ Church days were very different; if you went to high table, anything scientific or technological was inappropriate conversation, whereas now in most of the colleges I have been involved with, more often than not it is because it is interesting; a big change over the years

57:47:07 I got an unexpected letter from an unknown person who said it was his job to appoint the Master of Magdalene College and that he would value an opportunity to discuss this; I took it to mean discussing candidates whom he thought I would know about; I was invited to Lord Braybrookeís place, Audley End, where we had a nice lunch, talking about everything from trains to skiing to holidays; he then asked me if I would be interested in the Mastership; after further conversations and thought, went to Magdalene to be interviewed in a mild and uninvasive manner; later got a call from Lord Braybrooke asking if I would do the job; as I wouldn't have to give up my lab we agreed to do it; they had interviewed my wife too which was very wise; she made a huge contribution to College, more than I was able to do, which was very much appreciated; she gave her whole time to it; we have two children; Jean kept the domestic side of life running when I was extremely busy

Second Part

0:09:07 Fred Sanger's retirement tea party; about 1982 I got a letter from the Vice Chancellor inviting me to be the John Humphrey Plummer Professorship, previously held by Alan Hodgkin; natural inclination was to wonder why one should give up an excellent job in a famous lab to take on teaching and administration; told Max

about the offer and he suggested I should not accept; then I discovered that a close colleague, Ron Laskey, who was an early graduate student and with whom I had worked on and off all my life, had also been offered a professorship in Zoology; Ron suggested we thought further and when we looked we found that our positions at the MRC had been whittled away so that we didn't have staff positions any more; thought that if we moved into Zoology and get a reasonable research grant this would help a great deal; we decided we would move and asked for time to get some funding from the Cancer Campaign; in the course of time we did and that turned out all to be due to Gabriel Horn; a clever manoeuvre to get both of us to move; gave us a floor in his Department, we got the money and moved in; it was a key event because it meant that we started with a medium sized research group; we did our teaching which was nice, it was a lovely Department under Gabriel; the work went rather well and the Cancer Campaign who sponsored us at that time asked if we would be interested in expanding a bit; we thought that would be nice but what Ron and I wanted was a small institute; they said they couldn't produce that much money but could make a contribution; by good fortune, the Wellcome Trust came into money at that time and we had an approach from them; we asked if we could put the two together and they agreed; I most particularly emphasised the pivotal role that Gabriel Horn played in this; we had enough money to build a small institute and many of the barons would have been hostile, but Gabriel thought it a good idea and actually helped it along; he spoke to the Secretary General who would ask the General Board if this was a good idea, who agreed; finally asked the heads of departments; this was how it survived; we got the money for the first addition to this institute; Gabriel was the chairman of our advisory board which was immensely valuable; without him I don't think it would ever have come into existence; it was very good of him as it wasn't obviously helping his department but he could see its value from the University's point of view; the initial operation, which cost £4,000,000, went well and in time we had the opportunity to expand; for this building we got £23,000,000; we have now over two hundred people here and bring in quite a lot of money for the University; although it had been against the advise of Max Perutz he nevertheless remained a very good friend

7:34:10 Feel I know Gabriel very well and have immense admiration for him; he is not only nice but an amazingly interesting person; he really transformed the Zoology Department; when he took it over it was pretty low but by the time he had finished he had fourteen FRS in his Department; he was a highly successful Master of Sidney Sussex; he's a kind of genius at managing things and people; he had also set up a way of getting scientists to advise the Government; I participated in one of these; it was a clever manoeuvre to get the Government to be interested in science; Prill, Gabriel's wife

9:43:20 I was very privileged and enormously lucky to end up at Magdalene; I had been sounded out by other colleges but in retrospect I am glad that I wasn't chosen; Magdalene was wonderful to belong to, very small with a highly experienced Bursar who knew everybody; did not attempt to shake up the College; was advised that if you wanted to do something you would suggest it to someone else, then it would pass to others, and gradually a consensus would emerge which then you would ask the governing body to consider it; I was probably seen as a pretty ineffective Master, nevertheless the College did well and it was a happy place; I was very grateful to them for allowing me to keep on my own lab work so when the time came to stop I still had a lab to go to and be active again in my own field; Magdalene also has a President who is a senior Fellow, and is in many respects more powerful than the Master; he is the head of the Fellowship; the role of College teaching must be done but took the view that every Fellow had a significant research contribution; it worried me seeing younger Fellows having to do terrible jobs like Tutor for Admissions; in my time we survived without damaging the careers of younger Fellows; it is a problem how you get these tiresome jobs done; encouraged the use of secretaries who could take on part of the burden; teaching is very important but for a university like Cambridge which is trying to compete with the rest of the world, we have to have people who are pre-eminent in their field; a good example is that some of my colleagues spent their time marking first year exam papers, not a good use of time in my view

15:13:17 The Institute has always been one third cancer and two thirds developmental biology; this was historically how we got our money and it still works that way; no one is going to solve cancer

overnight because it is multiple different disorders and can only be analysed individually; we are fortunate in having some very good groups in this institute who are working in aspects of cancer; delighted to say that in the last two years we have had two of our home-bred staff members elected to the Royal Society, one on the cancer side the other on the Wellcome side; Stephen Jackson this year's Royal Society appointee, has made real inroads into DNA repair; all the time our genes are being damaged and this is a major cause of cancer; he has been meticulously analysing step by step what goes wrong with a view to trying to see if eventually one can alleviate the process of DNA damage by various chemicals which have favourable effects; he started a company called Kudos which saw the commercial side of this; it was then sold for a large sum recently; when I was chairman here I strongly encouraged the commercial side; these people are not well paid and without this commercial side we would have lost them all; another very successful younger person, Daniel St Johnson, who works on the development biology side analysing how it is that the components of an egg arise because they form the basis of how the whole development occurs; an egg is a template for the rest of life and a key question is how does this amazing cell come to be possessed with these components to enable it to start the next life; those are two good examples of younger people who have thrived in this environment, making successful careers for themselves; Stephen Jackson and Tony Kouzarides both started companies; we are charity funded and you can't do commercial work in a charitable organization; they had their companies in the Science Park or elsewhere and guided the activity; both have now sold them; Tony sponsored a company called Abcam which was very successful in making antibodies, a good Cambridge company; that emerged out of someone in his group and he could see the commercial side of it; it has to be kept separate from us as a charity, but that works fine; for sure it is not easy to balance these two things but it must surely be the way forward for university academics to have a significant commercial interest if possible; Government must want this and it gives employment; the University has not interfered in either of these two cases

23:48:15 Hope that I have mentioned all those who have been instrumental in what has been an amazingly fortuitous career; I have talked about Gabriel Horn, but would like to mention Ron

Laskey who has been crucial in getting this institute going; he is a Professor in the University but works at another institute at the hospital; these two have been particularly supportive; also my great gratitude to Magdalene and Churchill College who are so good to me; I feel a bit parasitic, but feel privileged to have had a career in a place like Cambridge; and of course, to Max Perutz for bringing me here

John Sulston

16 September 2008

http://downloads.sms.cam.ac.uk/1131145/1131152.mp4

John Sulston and Georgina Ferry, *The Common Thread* (2009)

Sir John Edward Sulston FRS (born 27 March 1942) is a British biologist. He is a joint winner of the 2002 Nobel Prize in Physiology or Medicine.

Career

Sidney Brenner persuaded Sulston returned to Cambridge to work on the neurobiology of *Caenorhabditis elegans* at the Medical Research Council Laboratory of Molecular Biology. Sulston soon produced the complete map of the worm's neurons. He continued to work for its DNA and subsequently the whole genome sequencing. In collaboration with the Genome Institute at Washington University the whole genome sequence was published in 1998, so that *C. elegans* became the first animal to have its complete genome sequenced.

Sulston played a central role in both the *C. elegans* and human genome sequencing projects. He had argued successfully for the sequencing of *C. elegans* to show that large-scale genome sequencing projects were feasible. As sequencing of the worm genome proceeded, the project to sequence the human genome began. At this point he was made director of the newly established Sanger Centre (named after Fred Sanger and now the Wellcome Trust Sanger Institute), located in Cambridgeshire, England.

Following completion of the 'working draft' of the human genome sequence in 2000, Sulston retired from his role as director at the Sanger Centre. In 2002 he won the Dan David Prize and the Robert Burns Humanitarian Award. Later, he shared the Nobel Prize in Physiology or Medicine with Sydney Brenner and H. Robert Horvitz, both of whom he had collaborated with at the MRC Laboratory of Molecular Biology (LMB), for their discoveries concerning 'genetic regulation of organ development and programmed cell death'. One of Sulston's most important contributions during his research years at the LMB was to elucidate the precise order in which cells in *C. elegans* divide. In fact, he and his team succeeded in tracing the nematode's entire embryonic cell lineage. Sulston is now a leading campaigner against the patenting of human genetic information.

INTERVIEW SUMMARY

John Sulston interviewed by Alan Macfarlane 16th September 2008

0:09:07 Born in Fulmer, Buckinghamshire, in 1942; during the War we lived at Chesham Bois with my grandmother; father was an Anglican priest and was away in Africa; my mother had been a teacher before my birth; I have had a very particular relationship with my father in the sense that I have diverged totally from him; I was brought up as an Anglican, was a server in the church, and really tried hard to be a believer; it was an important part of our relationship and he was anxious to pass on his philosophy to me; he might well have become an academic but chose to go into the church and he expected me to do well; my memory of our relationship (he died in 1986) is completely coloured by the later part when I had to break away from him; in my teenage years I became agnostic, and before long, atheist, in the Cambridge way - rationalist, humanist, atheism is where I have ended up; he found it distressing that I took this course; when I came up to Cambridge I remember discussing religion with fellow students and found that very few understood how important it was to me to be or not to be religious; for me it was the only thing that mattered, a lesson in how one's own experience colours one's priorities; my father was a middle to high Anglican; he was assistant priest in the local parish at weekends, but during the week worked in London as a secretary at the Society for the Propagation of the Gospel which later merged with the Church Missionary Society; he had little experience himself of missionary work though he did visit mission stations that they ran

4:41:23 Agree with Richard Dawkin's view that the Education Officer of the Royal Society should not be a clergyman; think the appointment of Michael Reiss was ill-advised; it is such a particular position in this age, especially given the situation in America, with the belief in creationism rising in this country; how we deal with that is unclear; Michael Reiss is trying to damp it, but my reasoning on what is going on in America, and the way that the intelligent design people behave, is that you have to make your opposition

rather clearer than he is doing; if someone says that two and two make five you have to say clearly that they don't; I think the fairy stories that all religions wrap round the fact of evolution are wrong so oppose Michael Reiss's tolerance of them, especially as Education Officer; if he were a Fellow it would be alright, but as an Officer he would have to be careful; Martin Rees is a very spiritual man but you don't find him speaking in this fashion; he describes himself as an unbelieving Anglican and this resonates to me as I spent my teenage years in that form; it is a matter of respecting the institution whilst not accepting all its tenets; think it is a tragedy that Anglicanism is declining in this country and that various evangelical sects are becoming more powerful; Anglicanism is one of the great secular religions, and always has been since the Reformation; I would not act as spiritual as Martin does in his statements as I find this conflicting; Tim Hunt has said that whilst in biology we are dealing with very clear facts, cosmologists are touching the void; it drives some of them a little mad and makes others a little spiritual; they are touching things way beyond our comprehension, much more than biology, so you can understand the difference in attitude; I have refused to have this conversation with all the newspapers as I feel it is an internal matter for the Royal Society

11:44:14 Atheism is my position for my lifetime and I also label myself as a Humanist, which does provide the framework to live one's life honestly, morally and joyfully; if you have nothing you have no comfort; Humanism gives me comfort in the knowledge that I have a finite existence, I have very good reasons for acting in a moral fashion and feeling that my life is worthwhile as there will be other lives after it; that is my present framework - I see that we have enormous amounts to discover as a strategy for going forward as human beings; I believe atheism makes coherent sense; all the religions are in conflict with each other; they have different stories, based on insubstantial records, but justify them with saying that there was some direct communication with a deity in the past which has led them to this belief; I find those unconvincing, particularly because of the conflict; this was my main argument in discussions with my father; talking recently on the good that science can bring and the extraordinary advance and enlightenment that has occurred as a result of our discovery process; recent landmarks include the cosmological revolution, the Darwinian revolution, the

discoveries of fundamental physics, which completely change the world view of humanity; I look at that story and say this is the way we should be going forward, these are the exciting things that have happened; science has had to fight established religions of all kinds in order to get them accepted and tolerated, and we are still fighting for the Darwinian one; consequently, I think that atheism is a terrific strategy both for me personally, and for humanity

15:29:16 I am Chair of a new institute at Manchester on ethics and science; the University has a strategy of recruiting existing Nobel prize winners part-time, frankly to bolster their position academically; my particular sphere involves the fulltime Director, John Harris, who is a bioethicist; he holds views on the enhancement of humanity which I partly accept; this is a good partnership; we have the opportunity for expansion though there is an existing group of philosophers and lawyers but I want to expand into social and policy areas; my counterpart there in Economics is Joseph Stiglitz, a humanist economist, and we have a great opportunity to do things together; he has a counterpart called the Brooks World Poverty Institute; I am really looking forward to these collaborations; see it as a platform by which, even in my part-time position, I can have some bearing on research, and maybe influence in policy matters which I think is important

17:50:03 Richard Dawkins is deliberately setting himself against the intelligent design crowd who have seized on the idea that the theory of evolution is uncertain; the fact is that creationism and all other religious doctrines are also theories but they are alleged to be facts; this is purely terminology as I see it; if we find that people are treating our theories, which are actually extremely substantial, as just theories, and their own very insubstantial theories as facts, one has to adjust the terminology; I have not thought enough about how one does that, but I ought to

19:54:18 Did a tiny amount of reading on other religions when I was a student, and did find a certain attraction to Buddhism; in the end I find it insubstantial compared with the extraordinary discoveries we have made by rational scientific approaches; I could come back to it; my atheism is provisional but don't see the comfort and inspiration of the humanist version running out before

the end of my lifetime; the only sense in which I would be strongly evangelical is the responsibility to conduct rational policies that do not endanger the future of humanity; despite speculations, we have no shred of evidence that any other life form exists, certainly no intelligent life form; I think we should treat ourselves collectively as very precious; I am extremely opposed to those evangelical philosophies or policies attributed to the Bush administration who use religion, in some degree, as a cloak for very aggressive and dangerous practices in world policy

22:46:09 My mother was my confidant and my rock as I was growing up; I could come home from school and talk; she had been a teacher of English at Watford Grammar School for Girls; throughout the time I was losing my links with my father over religion, my mother was always the neutral party; although she clearly was a believer and strongly supported my father she never indicated to me that she thought I was going off the rails as he did; she was the go-between; the most extraordinary event was that after her death, among her possessions was a letter to me saying how sad she was that I had lost my faith and her hope that one day I would regain it; it shocked me, it was a second bereavement, as here was this person who I had thought of as being at the unbelieving end of Anglicanism, and I had disappointed her; I have a sister who is four years younger; we never had a strong relationship but a happy childhood; we laugh rather bitterly now that I, as the boy, was sent to fee-paying private schools and she was sent to state schools; I did get scholarships throughout so did not take large chunks of the family income

26:38:21 First went to a preparatory school not far from the house called York House; by then we had moved to Rickmansworth in Hertfordshire, to an area called Mill End; it was not a top flight school but the sort of place that you might succeed on your own; can remember no particular teacher having any influence; strongly suspect that my mother was the most important educator through those years; we were taught to read long before we went to school so was ahead of the game; I was a slightly precocious individual as I was always young for my year; from the time I was able to I took things to pieces, I loved playing with electricity, though my parents had no idea what was going on; my sister was also interested in

experimenting with electricity; I had an aquarium, dipped in the pond, an uncle gave me a little microscope, had a chemistry set and tried to make explosions, and was interested in balloons, cranes and Meccano, everything, from the earliest years; more manipulative than is common except among those who become practical bench scientists; I have been hands on throughout my career; the least manipulative stage was when I was doing the cell lineage of Caenorhabditis; however, simply handling the worms there were a lot of gimmicks and tricks, which is why I was successful; after that was over I came back to biochemistry and started working on genomes and I was just manipulating throughout until I finally stepped away from the bench in about 2003 when we had finished the nematode genome; like John Gurdon who always did the injections himself, I did the same with DNA cloning; I was doing that and was full-time Director of the Sanger Centre at Hinxton and full-time doing the worm cloning, in fact doing two jobs and working that hard; there are professions, particularly bioinformatics, where they are not manipulating except on the computer screen mathematically; one connection which people are pushing quite hard on is experiencing molecules as objects, to the extent of having walk-in rooms; not sure if that is not just a failure of imagination; mathematicians spend their lives visualizing things without such aids; do look with dismay at schools which are junking a lot of the hands-on squishy biology that we all did; I can't see any real justification, and no health and safety issues, provided you take a few elementary precautions

36:12:03 After preparatory school I went to Merchant Taylors School at Sandy Lodge, within cycling distance of home; I went there because I got a scholarship that paid most of the fees; I, like most of the boys, was a day boy, for which I was glad as my world was a private one in my workshop in my bedroom at home; I was always terribly homesick when away on exchange visits, so glad I was not a boarder; it was a good school; they had a linked scholarship to Cambridge to Pembroke College; at school had an absolute loathing of competitive sport and bored by history etc.; all I wanted to do was science; I never had any skill at music; the music in my life now comes from Daphne, my wife, who is quite a good pianist and plays the clarinet; my parents did listen to classical music and I listened to Radio Luxemburg, but I was never a

musician; it does not directly input to my work, but what does is the waking dream; now, though my bench days are behind me, I do wake thinking of ways of expressing something I have to say in a speech which have eluded be before; I keep a pad beside my bed to write thoughts down immediately on waking; drink, in moderation, also releases thoughts; have found walking on a high ridge, alone, also frees thought; I work best in the morning; find it now hard to find time to get away on holiday with Daphne; one advantage with walking is that one can disconnect, go offline, but always have a scrap of paper and pencil

47:00:17 At Merchant Taylors there were some good teachers; one, Lloyd, was particularly inspirational for me; later, at a Sixth Formers' gathering found that other people had the same impression of him; he was a crazy sort of person; on one occasion he started a fire while demonstrating in physics; he opened the cosmos to me by showing how by physical and mathematical thought one could reach out in space and time; other teachers too pushed me hard and tried to challenge me and I challenged them at times; parents were quite keen that I went to Oxbridge; came to Cambridge to read natural sciences; at the time I thought physiology would be interesting but it had not moved into its later more fascinating phase by that time; in the end I found Ian Fleming, my supervisor in organic chemistry, quite inspirational as they were excited by models and predictive theories for what electrons were doing in organic molecules as they reacted; found it very exciting, like Meccano, and organic chemistry is like that; I decided to do organic chemistry in my third year; it turned out well as it is a good foundation, learning about molecules; I have to confess that I did not enjoy being an undergraduate here; I was rather shy and socially distressed, particularly by the lack of girls; more importantly, I just didn't like learning; the thing that carried me through all the way was working with my fingers; there were practicals, but they formed a small part with most of the course learning; for most kids who have been bright at school, coming to Cambridge is a pretty shocking experience because you are no longer the big fish in the little pool; so they were lean years for me with not a lot of comfort, but a few drinking companions; Dean Dewey was my Tutor at Pembroke and a sympathetic man, though I didn't understand him at all; in the first year I coasted; in the

second year I joined the ADC and took up theatre lighting; I was never on stage but it is exciting; Miriam Margolyes was my contemporary, and it was a fantastic period for Cambridge drama; I was in awe of them, but lighting was also creative and enormous fun; unfortunately it took much time and I began to slither down academically and didn't do at all well at the end of my second year; both Dewey and my parents talked to me and I determined to learn enough in my third year and scraped a 2:1 which was enough then to become a graduate student; because of the whole atmosphere I decided to drop out and do VSO; would have gone to Africa, and don't know what might have happened if I had gone, but the money dried up on the scheme and I had nothing to do; wandered along and got an interview with Alexander Todd who had enough space for me; Todd was the Professor of Organic Chemistry and had made his name through the elucidation of nucleotide structure and had set up a school of chemistry and was hugely important behind the discoveries of Crick and Watson in deciphering the structure of DNA; I was assigned a supervisor, Colin Reese, who became my mentor for the next two years on the synthesis of oligonucleotides, linking together, at the most basic level, the individual components of nucleic acid; Dan Brown was his contemporary and I still have a very good friend who worked with Dan at the same bench; Colin and the situation changed my life because suddenly I was put in the situation where I didn't have to do any book learning; I was back in my teenage workshop where I could explore chemical reactions; of course, if you do that you find things; there was also a good discussion group among the research students in the laboratory in Lensfield Road; I was enjoying Cambridge not in the sense of the Colleges but in the sense of the science

Second Part

0:09:07 Leslie Orgel, an ex-Cambridge theoretical chemist, was well known to people here and it was somewhat routine for people to suggest to their graduate students that they might like to do a post-doc. with Leslie in California; the connection with Leslie was that he was working on prebiotic chemistry, on chemical reactions that might have some bearing on the origin of life; fitted perfectly with things that I had been doing so I was hired as a post-doc.; it

was great fun for me as I was now catapulted out of a situation where I was really working for Colin to a place where I was expected to work on my own, but nevertheless treated as a close discussant by Leslie; I got quite a lot of invitations to his house to meet visiting scholars

1:48:02 Did meet Paul Dirac through Daphne and Monica, his daughter; he was quite a retiring figure but I got to know him better because he discovered I could fix radios; he was intellectually in a different world from me; in California, had a wonderful time, my daughter was born there; Leslie was based in the Salk Institute; when Jonas Salk produced the first polio vaccine with charitable money, the success of the vaccine drew in more funds, so an institute was started in his name; it stands on a cliff edge just north of San Diego, a beautiful spot; they then started to appoint Fellows, like Leslie, and visiting scholars like me; Leslie actually encouraged me to apply for a permanent Fellowship there after coming back to Cambridge, but we decided to stay here; Leslie, a friend of Francis Crick and Sydney Brenner, knew that Brenner was looking for staff to expand his work on nematode; Leslie arranged that I should come back to Cambridge for a year or so to learn from Sydney's work; having got here and started to work on this worm, we got settled into Cambridge and found we rather liked it, so never did go back to the Salk; at that time, for family reasons, we felt it would be good to stay in England; our parents were here, and we had a second child; if there had not been opportunities I might have found it tougher to get a job, but the expanding Laboratory of Molecular Biology meant that we were able to stay; later on we did not like the increase in neo-liberal trends in America; ironically, our daughter, having been born in California, is a dual citizen, and she went back to America and was a research student in Berkeley; after getting her Ph.D. she lived in America and has now settled in Vancouver with her husband, out of America again; there is quite a lot of feeling in the family about American politics and where one actually wants to live; a bit silly of course as every country has all sorts of people; fair to say that I am a left-winger, perhaps a reaction to my parents who expected me to help with the Conservative Party; I have moved steadily to the left throughout my life; I have probably been urged in this by Daphne who is a very staunch left-winger; basically Labour Party supporters but we are

both extremely uncomfortable with the Blairite trend of New Labour; as a pragmatic issue we both vote pretty consistently Lib-Dem because there is absolutely zero hope of getting a Labour candidate in South Cambridgeshire where we are; the City is different, but outside is extremely conservative

8:15:41 What really worries me about America is its foreign policy; its role as the leading imperial power has been exacerbated by the end of the Cold War; our comment about New Labour is that it enthusiastically joined in with the most recent adventures, and I regard these as the most dangerous things going on in the world today for the survival of humanity, both directly and indirectly because they make it more difficult to come to agreement over such things as climate change; I think we need to adopt a much more holistic view of international affairs than we do at the moment; America is doing nothing differently from what Britain did in its heyday as an imperial power; there certainly would be additional domestic discomfort in living in parts of America where there are fights over the teaching of evolution in schools; perhaps the most important thing is lifestyle; in this country we still tend to regard people not by how much they earn, or how much they visibly spend; there is still a sense of asceticism here; however, we have lots of friends in America and could have settled there; just an explanation of the way one makes major decisions based on trivial balances of considerations; most of all we regard ourselves as citizens of the world; I went to Japan a few times at the beginning and have been to China a couple of times recently to do with the genome; went to India once; have just agreed to be on the advisory board of a foundation set up by a Thai princess, and have visited there once to give a talk; persuaded to do this by David Weatherall who is also on the board; notice a trend nowadays that people not only ask you directly to do something but find someone they think you might admire to write also; think that China will be increasingly important; the Chinese Academy of Sciences and their funders now understand that it is no good just sending Chinese abroad because if they are bright they will stay there and make careers outside China; what you have to do is to establish centres of excellence within the country and attract them back again, and foreigners also; on my first visit to China where Georgina Ferry and I were launching our book, 'The Common Thread', the story of

events around the human genome, I encouraged this idea; whether or not they continue to fund them in an open way to do seriously new things and get their much craved Nobel prize etc., or whether this will be driven into utilitarian matters, I don't know; think they will probably do both; India is already doing this, though it does not care about equality, and very good research is going on; South Korea is quite desperate to move forward in this way; in Singapore, where Sydney Brenner is involved, already see themselves as a hub in the area; so all sorts of important initiatives which will lead to more high quality work in future

15:04:47 Max Perutz was head of the MRC when I arrived; Sydney was joint head with Francis Crick of the cell biology division which I joined; Sydney was also keen to expand his group working on the nematode worm; there was some scepticism that anything new would come from this work; those working with drosophilae were scornful as they thought they had a very good model already and saw no point introducing another; it was not wholly new; there was a lab in France which was also working on this little worm; just remarkable that when Sydney came to work on it personally with a couple of assistants for five years, he just completely revolutionized what was going on and turned this thing into a powerful model; he began to attract post-docs who were very serious about making big careers; Bob Horvitz, with whom I shared the Nobel prize along with Sydney, was not one of those who would work on anything that was not going to deliver something important in science; I was much more of a casual recruit; I could see there were potentials but was not making such as serious decision as Bob Horvitz; from 1965 when Sydney picked up this almost unknown animal deliberately as a new model for developmental biology, working on the genetics, cutting sections; Nichol Thomson who used to work for Lord Rothschild then moved to work with Sydney as an electron microscopist and Muriel Rigby as his assistant in the genetics lab, just this little group put together this really convincing set of mutations and hints about why these mutations should be important in development; Sydney was hugely charismatic; for a long time I got along fine because I was very low key with no ambition; I was a bench monkey; the people with ambition, like Horvitz, were going off to start their own labs; I was no threat to Sydney and worked along quietly and got things done, though in

the 1970's I increasingly felt that I was not getting enough done; looking back, can see that I was doing a lot, but by the end of the 1970's I was looking elsewhere; I am something of a depressive, I suppose, in scientific life; it has often occurred to me that I am rather unusual in working out of depression, I have achieved most of what I have achieved always out of a pit of despair; that was how I got my 2:1 and the cell lineage of the embryo achieved; why couldn't I do those things and be cheerful at the same time? The down and out syndrome allows you to take the slightly larger step than you thought you were capable of; it is characteristic of relationships with Sydney, whom I admire enormously, that he finds it very hard to let things go; he was hugely supportive and I depended on him very much throughout the 1970's; when it came to doing my own thing, at first it was good but then we began to diverge; my own thing was working on genomes as a whole; it wasn't sequencing because the Fred technique was not automated fast enough at that stage, though later on the very same chemistry did become automated; what I am thinking of was mapping, where you break the genome; in the case of the nematode you have a set of pieces of DNA in total 100,000,000 nucleotides long; these have to be manipulated in some way in order to discover the genes so that you can work on them and find out what their individual bits of sequence are and then go on to do experiments; by the end of the 1970's people were desperate to do these; I had done the lineage work and we had all these lovely mutations, starting with Sydney, but then by lots of other people, all very interesting behaviourally, all affecting things like the cell lineage, the way the muscles work, the way the nervous system hooks up, all sorts of things, and we needed to get at the genes; it did hit me that I was going to work on the genome personally; it hit me at a Gordon Conference with Matt Scott who had done heroic work on the Antennapedia complex in Drosophila; it was fantastic work but all he had was just a little bit but we had a huge genome of other genes; thought that we should not just work on a bit of the genome but map the lot

23:24:00 People thought I was crazy; it turned out that one other person was doing exactly the same thing at the same time; that was Maynard Olson in Washington University, St Louis Missouri, who was thinking exactly the same things about yeast; my tremendous

friend and colleague, Bob Waterston, who had also been a Sydney post-doc, had got a job at St Louis and was coming back from time to time on sabbatical; it so happened that as I began to do the map working with Alan Coulson, who had been liberated to work on this by Fred Sanger's retirement, Bob Waterston came over; he spent his sabbatical in our room and brought together some technology that Maynard Olson's lab had developed which fitted perfectly with what we were doing and allowed us to forge forward with the map; as a result of this connection I got to know Maynard a bit, and we both felt this negativity very much; the fly people thought it was a joke as they had it all sorted anyway; they had these very clever things called polytene chromosomes that actually give you a visual mapping of a barred pattern where genes were active and inactive and allows them to dissect out the genes in a more direct way; what we did was to lay out the nematode genome on a piece of filter paper in spot so that it was exactly equivalent to their polytene chromosomes, so we produced what I call the polytene filters by the end of the 1980's for the nematode; the whole thing was very successful, it really launched the nematode forward, all the genes started to be discovered, and people were absolutely delighted; we were made, we were now a fully-fledged genomic organism; soon after that, when we moved into the sequencing process in the early 1990's that the fly began to get uneasy because it realized that not only had we this powerful worm tool, but we had the spots and you could pick any of them out and manipulate them directly; then we were going ahead and sequencing the whole thing and the fly, in this long-standing competition, was beginning to lose post-docs to the worm because the worm was so powerful, both in the interest of its developmental biology and in the tools to deal with it; eventually Gerry Rubin took the bull by the horns and initiated the genome project for the fly, and the two got sequenced

28:19:53 Interesting to reflect on these little competitions because they are no bad thing; the so called model organisms are modelling two things - the politically incorrect view is that they are modelling the human, and from the medical point of view that is what they are about, but they also model organisms for biology in the sense that these are areas that you can manipulate particular aspects and look at the signals and controls that are being used; there is an important reason for using the word model is that the mechanisms

you discover tend to be applicable far beyond the confines of the particular organism because, of course, we have a tremendous unity of life through the process of evolution, and the way things actually work; interesting to see how the competition between the two models impelled people on to do new things rather than just coasting

29:37:52 So by the early 1990's Bob Waterston and I with our groups were beginning to sequence the nematode which we published in 1998; during that process we became involved with the human genome; in my case it was because we needed space; the Medical Research Council was funding the worm process and was just about able to afford it, though it was a lot of money for them; through Jim Watson I was invited to become Director of a new institute which we eventually called the Sanger Centre, after Fred, which would tackle some or all of the human genome; this was in 1992; I saw this as a Faustian contract; I didn't really want to get involved with the human genome but to continue with worm, but this was the way to get space; partly in parallel with that, Bob Waterston was being expanded by the National Institutes of Health who were his funders in America, also to take an interest in the human genome; this flowed on and during this we became aware of Craig Venter who initially was a colleague who had his own lab at NIH; he got fed up and moved out and started the Institute for Genome Research which was partly industrially and partly state funded; at that point the public/private began to intrude because it turned out that he had some kind of commitment to Smith Kline Beecham via Bill Heseltine's outfit called Human Genome Sciences - it is all very complex, I am just describing a little bit of corporate America, a chain of contracts which meant that Craig was now much more required to give people first refusal; at that stage he was not terribly interested in the large sequencing, and rather decried it as did Sydney; Sydney always said that it was a complete waste of time to sequence whole genomes; what you needed to do was to get hold of the genes through the cDNA process and in that he was in agreement with Venter; this went on for a while but we were all supposed to be colleagues together until suddenly in 1998 Venter announced that he was going to make a run for the human genome in a new company which became Celera, and he was going to outrun the international consortium as it now was, working on

the human genome project; we were substantial stakeholders, slightly larger were the Americans, Bob Waterston and Eric Lander and a number of other labs in America; I thought that having an international consortium on something as philosophically important as the human genome was a really good one; I dislike the idea of even one country working on it let alone one corporation; however Celera was going further, they wanted to make this a paying operation, the money was being invested not coincidentally by the company that made our sequencing machines, which was now called Perkin Elmer which bought the original spinout, Applied Biosystems, who had decided, under the influence of Tony White, that they would invest not only in the machines but in the product that the machines produced; they would get the human genome, patent it in large measure, and run it as a paying database; at this point I go into my standard talk about the scientific social economy and how things ought to work; if you try to put a very important chunk of knowledge, such as the human genome, into a database which is private and can only be accessed for fees, then you have to put a very significant criterion on that in the contract that those who access the database may not redistribute the data; this means that people cannot talk about an extraordinarily important piece of information in any sensible way; the people who propose this sort of technique, and Celara was not unique, would say that for academic purposes they could let you talk, but of course they can't, and in the end it has to be secret otherwise you have no business plan; this to me was a thing to fight; it spilled over into the press and media on both sides of the Atlantic, most incredibly obnoxious things were said; in the end it was resolved by a pact being drawn at a rather high level by the Wellcome Trust and NIH arranging that there would be an agreed draw; we couldn't stop them sequencing and there was very great danger that they would persuade the American tax payers that NIH should not fund the American public domain to sequence any more; of course, they would have a very strong case because American industry should not be competed with by an American government agency; that was my reason for coming out in a much more full-blooded way than I really wanted to, to say why I thought it was so important to keep this data public; in the end it was so tough, it was election year for Clinton, and so our high level diplomats arranged an announcement by Clinton and Blair that the

human genome had been achieved and that Craig should be given his due etc.; Craig Venter and Francis Collins as the head of the international project stood up in the White House and announced that the thing was done; it wasn't done at all, this was a premature conclusion, that part of the strategy of the Venter Celara outfit was that the genome would be done very roughly, just enough to get patent; we had to compete on the same ground otherwise we would have lost the patents to them and so we were drawn into producing what Francis Collins very cleverly called the rough draft of the genome; the actual human genome was finished in the public domain in 2003; it is still not absolutely complete because the bits at the centres of human chromosomes where they join on to the spindle when entering cell division, very repetitive and hard to sequence, are still being worked on but all the rest is done now and joined up; the information is in the public domain and everybody can use it, as is the mouse genome and many others; it is an extraordinarily important tool with which one can do comparative genomics which is the foundations of biology today; it is a huge success story on the public side; rather sadly is the way in which individual pieces of the human genome and other genomes are being patented and protected far too strongly, but that is a battle that will continue to be fought and will gradually fade out as the patents expire, and we move into a more subtle landscape where people are not patenting knowledge but patenting useful processes; it continues to be a most awful abuse of intellectual property in biotechnology today

40:13:50 This was not the work for which I was awarded the Nobel prize; I have argued in public and will continue to do so that this is not an appropriate area for the Nobel prize because there are far too many actors; my prize, along with Sydney and Bob Horvitz, was for the work we did beginning in the 1970's; my contribution is the discovery of the cell lineage, and in particular the study of cell deaths and how to look at them, along with some associated genetic work although most of that went into Bob Horvitz's lab at M.I.T.; they produced the story of the genes that control in this cascade process programmed cell death; it is something that is constantly mystifying to people; later today I am going down to celebrate with some fabric artists from St Martin's School on an M.R.C. funded project on fabrics inspired by our work; my particular connection is

Carol Collet and she has been fascinated by programmed cell death and has made garden furniture that behaves in a similar way; Sydney inspired all of us and first started working on the worm at all

42:27:45 One of the small burdens to bear of a Nobel prize is that people actually write asking how to get a Nobel prize; my message is very simple that they should not think about the prize; you have to think about the science and enjoy it, and do something novel in it; in that way you will win as you will be enjoying your science, and you will be more likely to do good science, worthy of a prize; of course, there is a little bit of hypocrisy in it for me as I know very well that I have made progress very often when I am not enjoying it; but of course, as soon as I began to make progress I did enjoy it, so I suppose it is alright

44:02:55 Agree with the importance of getting things roughly right rather than precisely wrong; at the meeting I was just at I heard Wendy Hall of Southampton talk on her work in information technology, talking about her friend Tim Berners-Lee; she gave him credit for going the right way in inventing the World Wide Web; she said that at the time, she and her group were very involved in producing hyperlinks in a very precise way, all within one computer; Tim Berners-Lee said that it wouldn't work, you needed a scruffy approach where most of the links work, and you just let it scale; then you go round with some sort of search engine to tidy up links afterwards; this applies in all sorts of things; when we had our one and only weekend of management training at the Sanger Centre, the administrator there quite rightly noticed that when the institute grew larger than about fifty people there was tremendous distress among the staff, and by the time it got to one hundred, people were getting seriously upset; I couldn't understand this; my door was always open and I thought they could come and see me if they were upset, but of course they don't; what they want to have is a structure, a set of rules, so what we did to prepare for this was to go on a management training course; we learnt a huge amount in this one weekend from the facilitator; he gave us some sort of personality test and after analysing the results he went round each of us; when he came to me he said that I was the sort of

person who gets there in the end and emerges out of a hedge backwards covered in broken glass; he was right

47:03:49 Pembroke gave me an Honorary Fellowship and I occasionally go there; I have no duties but when I can I go to feasts; Cambridge is a good place to do science but I don't think there is any particular mechanism that counts; bear in mind that all of my good fortune in getting anything done at all has not been in the University but in the Medical Research Council Laboratory of Molecular Biology; that is absolutely part of Cambridge but not part of the University; of course it has all sorts of formal links in terms of teaching; if you take the larger phenomenon, including these satellites, then there is no question that Cambridge is wonderful; it is mostly about critical mass, about the fact that when you have a number of bright people around then will find interesting things in one another's work that will spark off novel things between them; why was the Laboratory of Molecular Biology so successful for so many years, I think our Nobel prizes were about the thirteenth in line, the reason is that they had a bunch of bright people to start with and they attracted other bright people coming through; they had a very strict rule about dead wood from the start so about two-thirds of the staff were transient; many post-docs coming through with their own agendas and eager to learn, so a real hothouse phenomenon; that is too much to take for most of us all our lives; the whole University has something of the same phenomenon with a constant stream of visitors who are attracted to the bright people there; the word for this nowadays is a centre of excellence; in looking to its future, Cambridge should think more about a centre of excellence based on the people and not worry too much about the mechanisms it uses; there is no doubt that the college system is helpful though not essential, but we should preserve it; it is nice to have a diversity of ways in which people can meet and discuss and you need different ways for different people; lots of people are not very social but they have much to contribute; they will probably not do well in the high table stuff but will do well in the chance of one to one meetings; of course, we must be open, and if we want to continue as a great centre of research here in Cambridge and a great country for research in the UK, we must not be excessively grasping and utilitarian about what come out; of course we can have all the

spinouts, there is no problem with that, but don't, as seems to be the trend at the moment, put them first and plan grant proposals around how many patents you hope to get out of it; in the humanities it is easy to say that is nonsense, in science it is a real trap and it is very possible that we will destroy our possible future with respect to places like China and India if we allow ourselves to be seduced down the utilitarian pathway; the important thing is that we are thinking about life, the universe and everything

Other possible volumes
(not necessarily divided in this way)

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Chemistry and biochemistry: Sydney Brenner, Dan Brown, Hal Dixon, Aaron Klug, Frederick Sanger, John Sulston, John Meurig Thomas, John Walker, David King [2 volumes]
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