FRED SANGER – DOUBLE NOBEL LAUREATE
A BIOGRAPHY

Considered 'the father of genomics', Fred Sanger (1918–2013) paved the way for the modern revolution in our understanding of biology. His pioneering methods for sequencing proteins, RNA and, eventually, DNA earned him two Nobel Prizes. He remains one of only four scientists (and the only British scientist) ever to have achieved that distinction.

In this first full biography of Fred Sanger to be published, Brownlee traces Sanger's life from his birth in rural Gloucestershire to his retirement in 1983 from the Medical Research Council's Laboratory of Molecular Biology in Cambridge. Along the way, he highlights the remarkable extent of Sanger's scientific achievements and provides a real portrait of the modest man behind them. Including an extensive transcript of a rare interview with Sanger by the author, this biography also considers the wider legacy of Sanger's work, including his impact on the Human Genome Project and beyond.

George G. Brownlee is Emeritus Professor of Chemical Pathology at the Sir William Dunn School of Pathology, University of Oxford, and a Fellow of Lincoln College, Oxford. He studied under Fred Sanger at the MRC Laboratory of Molecular Biology, Cambridge, where he later became an independent researcher. He is a recipient of the Biochemical Society's Colworth and Wellcome Trust Medals, a Fellow of the Royal Society and the Academy of Medical Sciences and is an EMBO Member. He received the Haemophilia Medal (France) and gave the Owren Lecture (Norway) for his pioneering work on haemophilia. He retired in 2008 to write this biography.

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EDWARD GEORGE BROWNLEE (1973–1995)
He helped me prepare for my interview of Fred Sanger

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Foreword

In the 1950s, biology was seen as such a soft science that it was not taught in the boys' grammar school that I attended. Boys who wanted to study biology had to suffer the taunts of fellow pupils as they crossed the road for lessons at the high school for girls. That it is now a subject with a cutting edge (and fit for boys!) is due in large part to the scientific contributions of Fred Sanger. That such a modest, self-effacing man whose childhood nickname was 'Mouse' could have such a profound impact needed some explanation. In this biography, George Brownlee gives us that explanation.

When Fred Sanger joined the Laboratory of Molecular Biology (LMB) in Cambridge in 1962, he had already won a Nobel Prize for his work on the structure of insulin. This Nobel Prize was, appropriately, for chemistry, since he showed that proteins were proper chemicals, with a defined structure, and not some ill-defined mixture as thought by some. It was a discovery that opened up the chemistry of macromolecules, and created a new subject, distinct from the biochemistry of those days, that demanded a new name: molecular biology. In the LMB he turned his attention to the nucleic acids, no doubt influenced by the presence of Francis Crick's Division of Molecular Genetics. While the molecular geneticists treated their central subject as a coding problem – how does the information in DNA end up as a sequence of amino acids – and used clever genetic tools to crack the problem, Sanger carried on with his chemist's approach and developed powerful ways to sequence first RNA and then DNA. Along the way, as Brownlee describes, he made a number of important discoveries. And he introduced the notion that it was important to sequence entire genomes and then ask what the sequence told about the biology – an approach that is now called hypothesis-free discovery, carried out on a massive scale. But his work was not appreciated by all his colleagues. I once overheard Francis Crick remark: 'The trouble with Fred is that he has developed all these powerful methods, but we can't persuade him to do anything interesting with them.'

Crick's disdain echoed an attitude to technology development common in those days. It was seen as a poor second to what was done

by those using technology to make discoveries or test ideas; perhaps because technology is ephemeral while discoveries endure.

But Sanger didn't just want to apply his methods to answer questions, he wanted to develop new methods to tackle ever more difficult molecules – that was his thing; as popular parlance would have it, it was in his DNA. Wisely, Brownlee avoids the question of whether it was really in his DNA, whether his intelligence and inventiveness were genetically programmed, and seeks the explanation in his character, as shaped by his upbringing in a Quaker family. What qualities are needed to be an outstanding inventor? What we see in Brownlee's description of Sanger are imagination and exceptional boldness, determination to the point of doggedness, and strong self-belief. Once he had decided on a problem, Sanger went to extraordinary lengths in his drive to achieve his objectives. I learned one of his RNA sequencing techniques from Ken Murray, who had worked with Sanger. Among many other steps, the method involved electrophoresis on large sheets of DEAE paper, at 2000 V, in tanks holding gallons of highly flammable white spirit – to the list of qualities, we should add almost reckless courage!

Whatever the source of his qualities, he certainly needed them when, in 1970, he came to tackle the problem of sequencing DNA: 'the ultimate challenge'. It is a remarkable story, fully described in Brownlee's account. We see it unfold over a period of six or seven years with Sanger slowly edging forward in significant steps: building on his experience of separation methods that he developed in his work with RNA; adopting advances made by others, such as the application of chain extension by polymerase; and, ultimately, finding the solution by combining chain terminating precursors, which he had to synthesise himself, with gel electrophoresis.

Sanger himself doesn't attribute his successes to any personal quality. When Brownlee asks, 'What do you think are the most important things, in general, that allowed you to make these huge advances in molecular biology. . .?' Sanger replies, '. . . being at the right place at the right time . . . I certainly have been lucky in being able to be independent . . . Maybe I've had a few ideas but I never know where they come from . . . they may come from talking to other people around the lab.' This may be one occasion on which we catch the great man being less than fully truthful.

FOREWORD

The enormous impact of Sanger's sequencing method is so wide in its scope that it is impossible to capture in a short biography. Brownlee illustrates it with three telling examples. First, the sequencing of the human genome. The success of this enormous project stimulated the second example, the foundation of a DNA sequencing industry with the introduction of automation and high-throughput methods. There are now numerous companies manufacturing and selling machines and reagents and others that offer sequencing services. And finally, the most important impact that DNA sequencing has had on medicine, the discovery of genes and mutations associated with cancer.

Sanger, typical of many successful scientists, is reserved, even shy. So, we are fortunate that he offered to be interviewed by Brownlee and to provide an account which ranges wide over his early life and his scientific career. Brownlee includes a verbatim transcript of this interview. This is a special treat for those of us who knew both men: we can picture this conversation between two colleagues and friends, see their faces and hear their voices. More important, perhaps, is the record it embodies. It will be a priceless source for those researching the broader history of the remarkable period that saw the birth of modern biology. The biography will provide inspiration and encouragement for aspiring inventors, for whom there is still a great need. Above all, it provides lessons for the funders: to find the next Sanger, they must be prepared to give long-term support with strings loosely attached.

Sir Edwin Southern
Professor of Biochemistry (Emeritus) and Fellow, Trinity College,
University of Oxford

Acknowledgements and original sources

The following are major sources in addition to Fred Sanger's own publications (see Bibliography):

1. Biochemical Society video archive (1987). Sanger-sequences [Dr F Sanger interviewed by Mr H Judson, 13 Nov 1987].
2. Biochemical Society video archive (1992). A life of research in the sequences of proteins and nucleic acids: Dr F Sanger OM, CH, FRS interview with Professor George Brownlee FRS, 9 Oct 1992.
3. Finch J (2008). *A Nobel Fellow on Every Floor*. Cambridge: Icon Books.
4. Silverstein A, Silverstein E (1969). *Frederick Sanger: The Man Who Mapped Out a Chemical of Life*. New York: John Day.
5. Wellcome Archive, Euston Road, London. Fred Sanger's laboratory notebooks form part of the Biochemical Society collection held at the Wellcome Archive (SA/BIO/P/1).
6. Wellcome Beit Archive, Euston Road, London. Fred Sanger's Beit Fellowship archive (SA/BMF/A/2/231).

Original sources

Fred Sanger encouraged me to write his biography when I first asked him in 2008. A year later he told me to 'get a move on', if it were to be published before he died (I did not succeed in this). His wife, Joan (deceased 2012) told Sue, my wife, in 2010 to 'make Fred's biography interesting'. Fred himself, who died in 2013, was not well enough to be able to check the manuscript for me, although it was written before he died. His son, Peter Sanger, read the section dealing with the family history and has given me significant help and encouragement by lending me original images from the family archive, and some letters and drafts of speeches that Fred Sanger gave after his retirement in 1983. Peter Sanger also allowed me to interview him about Fred as a father and a family man.

I have also had generous help from Mary (May) Willford, *née* Sanger, Fred Sanger's younger sister, and her sons Noel and Julian Willford. May has given me information about Fred as a person, helped me understand the Sanger family tree and lent me Cicely Sanger's (Fred's mother's) diary [or children's book] from 1918 to 1937. I had access to a visitors' book (held by May Willford) originally kept by the Sangers' parents (Frederick and Cicely Sanger) covering the period 1918 to 1938 with further entries from 1938 to 2001. May Willford and her sons Noel and Julian also brought the Svenhonger Diary, second volume, 1941, 1942, 1943 (a private publication by Clyde Sanger, about 2000) to my attention. These are the diaries of Gerald Sanger, Fred Sanger's cousin, son of Fred's Uncle William. May Willford also lent me a DVD of an interview Fred Sanger gave at his old school, Bryanston, in 2007, when he opened the new school Sanger Building.

Fred Sanger's laboratory notebooks from 1940 to 1983 and limited additional material are archived for the Biochemical Society at the Wellcome Library, Euston Road, London and I thank the archivists for access to this archive. I also accessed part of the Beit/Sanger archive, also held at the Wellcome Library (courtesy of the archivist).

I thank numerous scientists whom I interviewed in connection with this biography, namely Jerry Adams, (the late) Richard Ambler, Elizabeth Blackburn, Alan Coulson, Ted Friedmann, Brian Hartley, Celia Milstein, (the late) Sir Kenneth Murray, George Petersen, Julia Porter and John Sedat. I corresponded with John Donelson to clarify his role in the development of the gel 'read-off' methods in the period 1971–3 when he was a postdoctoral fellow in Fred's laboratory. All their individual recollections have given me many insights into Fred Sanger's character and personality. I thank my wife, Sue Brownlee, for help at my interviews of scientists, since she knew many of them in her own right, but also for all the help and patience she has shown while I was writing this biography. Her memory of events often complemented mine and has added significantly to this biography.

I interviewed Hagen Bayley, University of Oxford and David R. Bentley, Illumina, Cambridge, in connection with Chapter 7 on post-Sanger sequencing. I particularly thank David Bentley and Larry McReynolds, who critically reviewed Chapter 7. Sir Michael Stratton, Dr Lisa Walker and Sir Ed Southern suggested corrections and improvements to Chapter 8. I am most grateful to Ed Southern for writing a

Foreword to this biography. I thank Paul Berg, Elizabeth Blackburn, Sir John Sulston, David Bentley and Sir Paul Nurse for providing illuminating commentaries. I am grateful to the author Colin Tudge for his encouragement while I was writing this biography.

The archivist, Annette Faux, at the Medical Research Council Laboratory of Molecular Biology, Cambridge, has generously provided me with original images from their archives (copyright 'MRC Laboratory of Molecular Biology'). Dr John Lagnardo, as the Biochemical Society archivist, has given me significant help and permission to reproduce images published in their Biochemical Society video archive of Sanger in 1992 (The Biochemical Society, with permission). In many but not all cases, I have had access to the original image used for this video, courtesy of Peter Sanger, and have used original images in this biography where possible, because of their higher resolution. I thank the librarian, Joanna McManus, *née* Hopkins, at the Royal Society London, and Michael Gurr, Hans Tuppy, (the late) Ted Thompson and Stephen Burch who have helped me with individual images. Every effort has been made to track down original copyright owners. I would be grateful for information on any omissions, so that corrections can be included in any future biography or reprinting.

Only limited correspondence between Fred Sanger and his scientific colleagues survives. What is available is thanks to George Petersen and the late Sir Kenneth Murray who made their correspondence with Sanger available to me. I have not been able to trace Sanger's known extensive scientific correspondence between 1962 and 1983 during his period at the Laboratory of Molecular Biology, or any of his correspondence while in the Biochemistry Laboratory at the University of Cambridge between 1940 and 1962. I would be grateful for any information that might help locate this missing correspondence.

Brief chronology

1918	Born in Rendcomb, Gloucestershire, 13 August, second son of Frederick Sanger, MD and Cicely Sanger, *née* Crewdson.
1927	Entered Downs Preparatory School, Malvern, as a boarder. This was a Quaker school.
1932	Entered Bryanston School, Dorset – a liberal, public (fee-paying) school as a boarder.
1936	Went up to St John's College, Cambridge, to read Natural Sciences. He took four years overall, because he needed an extra year for Part I. He specialised in biochemistry in his fourth year. Father, Frederick, died in 1937; mother, Cicely, died in 1938.
1940	Started PhD in Department of Biochemistry, Cambridge, supervised initially by Bill Pirie, then by Albert Neuberger. Self-funded. Married Joan Howe in December 1940.
1943	Submitted PhD thesis, University of Cambridge: 'The metabolism of the amino acid lysine in the animal body'.
1944–55	Sequence of insulin, supported by a Beit Memorial Fellowship from 1944 to 1951, and by the Medical Research Council from 1951 onwards.
1958	First Nobel Prize in Chemistry.
1962	Moved to Medical Research Council's Laboratory of Molecular Biology, Cambridge.
1962–70	RNA sequencing.
1970–80	DNA sequencing.
1980	Second Nobel Prize in Chemistry, jointly with Paul Berg and Walter Gilbert.
1983	Retires aged 65.
1983–2013	Retirement: gardening, boating, reading, seeing grandchildren.
2012	Joan Sanger, Fred's wife, dies.
2013	Fred Sanger dies.

Honours

Civic

1963	Commander of the Order of the British Empire (CBE)
1981	Companion of Honour (CH)
1986	Order of Merit (OM)

Scientific

1951	Corday–Morgan Medal and Prize, Chemical Society
1954	Fellow of King's College, Cambridge; 1983, Honorary Fellow
1954	Fellow of Royal Society
1958	Foreign Honorary Member of American Academy of Arts and Sciences
1958	Nobel Prize in Chemistry
1961	Honorary Member of American Society of Biological Chemists
1961	Member of the Academy of Science of Argentina
1961	Member of the Academy of Science of Brazil
1961	Honorary Member of the Japanese Biochemical Society
1961	Corresponding Member of the Asociación Química of Argentina
1962	Member of the World Academy of Art and Science
1966	Alfred Benson Prize, Denmark
1966	Honorary Fellow National Institute of Sciences of India
1967	Foreign Associate of US National Academy of Sciences
1968	Honorary DSc, Leicester University
1969	Royal Medal, Royal Society
1970	Honorary DSc, University of Oxford
1970	Honorary DSc, Strasbourg University
1971	Sir Frederick Gowland Hopkins Memorial Medal, Biochemical Society

HONOURS

1971	Gairdner Foundation Annual Award, Canada
1976	William Bate Hardy Prize, Cambridge Philosophical Society
1976	Hanbury Memorial Medal, Pharmaceutical Society of Great Britain
1976	Fellow of the Royal Society of Edinburgh
1977	Copley Medal, Royal Society
1978	G. W. Wheland Medal, Chicago University
1979	Louise Gross Horwitz Prize, Columbia University
1979	Albert Laskey Award, New York
1979	Gairdner Foundation Annual Award, Canada
1980	Biochemical Analysis Prize, German Society of Clinical Chemists
1980	Nobel Prize in Chemistry
1981	Foreign Associate, French Academy of Sciences
1982	Corresponding Member, Australian Academy of Sciences
1983	Gold Medal, Royal Society of Medicine
1983	Honorary DSc, University of Cambridge
1994	Association of Biomolecular Resource Facilities Award
2010	Honorary Fellow, St John's College, Cambridge
2013	Fellow, American Association for Cancer Research Academy

Introduction

Fred Sanger asked me to interview him for the Biochemical Society archives in October 1992. He never told me why he chose me as an interviewer rather than one of his many colleagues and friends in Cambridge. I had worked with Fred in Cambridge from 1963 to 1980 but by 1992 had moved to the Sir William Dunn School of Pathology at the University of Oxford. Naturally I was honoured and accepted. In that interview Fred Sanger gave a full and frank account of his life and provided some insight into what qualities he thought were needed to be a successful scientist. This biography is, in part, based on that interview.

Fred had an unusual upbringing and it may surprise many readers to learn that he was not initially committed to research. As a young man he had a strict Quaker upbringing. He was ambivalent about studying medicine, changing his mind to study biochemistry rather than medical subjects at Cambridge because his father, a doctor in general practice, was always rushing around attending to patients and 'could not really concentrate on anything'. Both his parents died when he was an undergraduate, leaving him vulnerable. He doubted he was good enough to do research and applied at the last minute to study for a higher degree, a PhD, in biochemistry at Cambridge only after he learnt he had been awarded, to his surprise, a first class degree. Sanger was a conscientious objector in the Second World War. He learned to do research rather than killing the enemy.

In spite of this uncertain beginning to his career, he quickly showed aptitude for research. He seemed to have the ability to succeed in solving 'impossible research problems' where others had feared to tread. He was a 'hands-on' researcher doing research himself with the help of a trusted technical assistant right up to the end of his career. Many of his critical research findings were the result of his own findings carried out personally. This did not mean he was not a good leader. In fact he was a consummate team leader and early on attracted others to his research team because of his achievements and the great personal effort he made. This personal commitment to research inspired confidence in his many collaborators, including me. He was also unusual in stressing the contribution of the whole of his research team. In particular,

he emphasised the role of his two technicians, Bart Barrell and Alan Coulson, as much as the effort of his more academically qualified collaborators. Fred Sanger did not allow himself to be distracted by teaching or scientific administration. He was 100% committed to research.

A modest man, Fred Sanger's name deserves to be better known for inventing methods for sequencing proteins, for sequencing RNA and especially for the Sanger method of sequencing DNA – the genetic basis of life. More or less by chance he made many other highly significant and surprising discoveries in molecular biology, for which he was justly proud. He was the first to directly confirm the genetic code, the first to discover the unexpected phenomenon of 'overlapping genes' and the first to show that the genetic code could vary in different organisms. The Sanger 'dideoxy' method was used to unravel the human genome sequence in 2000. It is difficult to think of a contribution to modern biology that is more significant.

I was fortunate to work in Fred Sanger's laboratory in Cambridge from 1963 to 1980, first as his PhD student and later as an independent researcher. At the interview for my PhD Fred asked me if 'I wanted to sequence proteins or RNA'. I replied that I wanted to sequence RNA. My decision was wise as progress was rapid in the subsequent decade in developing new methods for sequencing RNA. This RNA sequencing phase – perhaps the least well-known period of Fred's research – was a transition period after Fred had worked out how to sequence proteins but before he had developed rapid methods for sequencing DNA. Fred had chosen RNA rather than DNA because the only known small nucleic acids available were RNA. DNA was too long and completely out of range at that time in the early 1960s.

This biography traces Fred's life from his birth in 1918 in a remote village in Gloucestershire to his retirement from the justly famous Laboratory of Molecular Biology in Cambridge in 1983. Fred spent his whole scientific career in Cambridge and must be one of Cambridge's best-known sons. I describe Fred Sanger's upbringing and scientific achievements in Chapters 1–3 followed in Chapters 4–6 by a slightly edited transcript of my interview with him in 1992. Unusually for a biography I include two further chapters to illustrate the ongoing impact of Fred's DNA sequencing method that he described in 1977. Chapter 7 – post-Sanger automated sequencing – describes the development of his method that others used to unravel the human genome

sequence of nearly 3×10^9 bases (or 3 000 000 000 bases) in the year 2000. Chapter 7 brings sequencing up to date, describing current newer sequencing methods using massively parallel DNA sequencing. Sanger always wanted to make an impact in medical research. Chapter 8 describes results of one current medical-research-based sequencing project to identify the genetic basis of breast cancer. In my opinion these rapid-sequencing methods of cancers – still in part based on Sanger's method – describing the genes that are actually mutated in cancers will be the main driver for new drugs specifically targeted to individual genes in cancers. Finally, Chapter 9 includes commentaries by five eminent molecular biologists describing, each in their own way, Fred Sanger's legacy to science.

My hope is that his main scientific achievements are adequately described in a way that is understandable by the interested general reader. I include endnotes and a full list of Sanger's scientific papers for readers who want more details, but my overriding aim is to try to answer the question as to why Fred was able to contribute so much to molecular biology in one lifetime. How was he able to work out how to sequence a protein, insulin, from 1944 to 1955 when the problem of protein sequencing was regarded as impossible by other scientists at the time? How did he have the foresight to take on the challenge of sequencing RNA in 1962 and then to succeed in developing a rapid method for DNA sequencing by 1977? Was it his upbringing at home and the influence of his medical father? Was it his training at the well-known public school Bryanston, or as an undergraduate in Cambridge? Was it the influence of the Cambridge biochemistry department where he did his PhD under Albert Neuberger, and where he would have met other visionary scientists? Was it his interpersonal skills perhaps based on his upbringing as a Quaker? Was it perhaps in his DNA?

Fred is amongst only a handful of people ever to have ever been awarded two Nobel Prizes. Such prizes are awarded by the Swedish Academy of Sciences annually to people who have made outstanding contributions to knowledge, or to peace in the case of the Nobel Peace Prize, and are widely considered to be the ultimate accolade. To gain one Nobel Prize might be considered by critics to be lucky or because the person was in the right place at the right time. To gain two such prizes cannot be attributed to chance.