SYDNEY BRENNER

13 January 1927 — 5 April 2019

Elected FRS 1965

BY JOHN WHITE FRS¹,* and MARK S. BRETSCHER FRS²

¹Emeritus Professor, Center for Quantitative Cell Imaging,
University of Wisconsin Madison, Wisconsin 53706, USA
²Formerly Laboratory of Molecular Biology, Francis Crick Avenue,
Cambridge CB2 0QH, UK

From modest beginnings Sydney became an extraordinarily influential and accomplished molecular biologist. His critical knowledge of, and insights into, key scientific problems were legendary. His irrepressible personality, acerbic wit and ebullient talks inspired a generation of young biologists. He made seminal discoveries in how genetic information is used for protein synthesis, and established Caenorhabditis elegans as one of the foremost model organisms for the study of development and neural function. He also pioneered techniques for genome analysis and was instrumental in establishing several outstanding centres of biological research around the world.

OUT OF AFRICA

Sydney was born of Jewish immigrant parents in what was then the small town of Germiston, South Africa (figure 1, figure 2). His father emigrated from Lithuania in 1910 and married an émigré from Latvia; Sydney was the younger of their two children. Although illiterate, his father mastered several local languages and had a strong sense of humour, an attribute his son inherited. Sydney learned to read from a neighbour and was recognized to be a precocious child, progressing rapidly through school. He took Hebrew lessons and suffered some antisemitic abuse from local Afrikaners. He dates his atheism to a time when he was beaten up and sat in the street uttering a Hebrew prayer, which was left unanswered. He

* Email: jwhite1@wisc.edu
was an intensely curious young boy and became a voracious reader. Fortunately, he had access to a good local library, one of many around the world that had been established by the Carnegie Foundation. Taylor’s *The young chemist* (1934) inspired him to undertake experiments at home. However, it was a book by Wells, Huxley and Wells, *The science of life* (Wells *et al.* 1931), which turned him on to biology. These early experiences provided Sydney with valuable lessons in self-sufficiency, causing him in later life to be rather disdainful of young investigators who expect to go on a training course before embarking on any new venture.

Sydney was awarded a town scholarship, which enabled him to attend Witwatersrand University in Johannesburg (Wits) to study medicine when he was 14. From the beginning, he managed to combine his formal medical studies with time spent working in a laboratory. Many seeds that developed into lifelong scientific pursuits were sown in the course of his bench work. He developed a fascination for methods of staining biological tissue and observing its detailed structure by microscopy. In particular, he was intrigued that he could stain and section cells to visualize chromosomes, which, he had learned from E. B. Wilson’s book *The cell in development and heredity* (1925), were the likely bearers of heredity. Through the friendship of a mathematics undergraduate, Seymour Papert, Sydney became aware of the concepts of information theory and self-replicating automata that were being developed in the nascent field of computer science. In particular, he was very struck by the von Neumann concept

Figure 1. Young Sydney with parents Leah and Morris. (Courtesy of Cold Spring Harbor Laboratory Archives, NY.)
of a machine that reads a linear sequence of stored instructions to execute a process that builds itself and then replicates these instructions. Furthermore, von Neumann presciently had suggested that this could be a paradigm for the genetic material in chromosomes.

Sydney soon became aware that his interests lay in scientific pursuits rather than the practise of medicine. Fortunately, he was able to avail himself of an enlightened scheme initiated by Raymond Dart that offered medical students at Wits the opportunity to take time off from their medical studies to study for a science degree. Sydney obtained an MSc and published a paper on the karyotype of the shrew *Elephantulus edwardii* from his master’s thesis project (1)*. Dart, a distinguished palaeontologist and anthropologist, ignited what became a lifetime interest in these subjects, which kept thoughts of evolution in the forefront of Sydney’s mind throughout his career.

Although Sydney claimed to be apolitical in later life, he nevertheless was actively involved in student politics at Wits, rising to the presidency of the Students’ Representative Council. One of the main concerns of this body was to maintain Wits open to students of all races. Sydney was also an enthusiastic participant in the lively social scene at Wits, where he made several friends including May Covitz, whom he eventually married. He exhibited a remarkable gift for ad lib humour and impersonating foreign accents in skits that were staged by students, characteristics that came to define his personality in later life.

**Graduate studies in Oxford**

Sydney had garnered a considerable reputation for his scientific prowess at Wits and was eager to embark on a career in science. However, he was advised to finish his medical degree

* Numbers in this form refer to the bibliography at the end of the text.
first, which he duly completed in July 1951 (after having to retake his final year of medical school). Humphrey Raikes, the principal of Wits, suggested that Sydney should consider applying to Sir Cyril Hinshelwood, whom he had known when he worked in Oxford, for a graduate research position. Hinshelwood, a physical chemist, was at the time interested in bacteriophage resistance in bacterial cells. Following letters of enthusiastic support from Raikes, Sydney obtained an 1851 Exhibition Scholarship that allowed him to undertake his graduate studies in Oxford. He set out for the UK as soon as his scholarship started, arriving in October 1952. Coincidentally, May Covitz also left South Africa with Jonathan, her young son from a previous marriage, to study for a PhD in psychology at the University of London. Soon after Sydney’s arrival in Oxford he contacted May and they started dating. Theirs was a whirlwind romance, culminating in marriage on 6 December 1952. Stefan, their first child, was born in October 1953 and was followed by Belinda and Carla (figure 3).

Hinshelwood believed that adaptation rather than mutation was the reason that bacteria sometimes exhibit resistance to phage infection. Sydney was sceptical of this, but was delighted to have the opportunity of working with phages. These bacterial viruses were fast becoming powerful genetic tools; by repeating the Luria–Delbrück fluctuation test (Luria & Delbrück 1943), he eventually persuaded Hinshelwood that bacterial resistance to phage infection was either caused by mutation (can’t) or lysogeny (won’t), states referred to by Sydney as impotence or chastity.
While in Oxford Sydney met with the American crystallographer Jack Dunitz and the English theoretical chemist Leslie Orgel. They formed an informal club to discuss molecular structures and genetics, where Sydney learned from Dunitz about Francis Crick’s ideas on helical diffraction and the model of deoxyribonucleic acid (DNA) that he had built with James Watson. In April 1953, Dunitz, Orgel and Sydney visited the Medical Research Council (MRC) Unit for the Study of Molecular Structures in Cambridge to meet Crick and Watson and to see their model, located within the Cavendish Department of Physics. Seeing the double helix was an epiphany for Sydney—he immediately saw that DNA was a repository of information coded in the linear sequence of bases in chromosomes. This had to be the information envisioned by von Neumann that is used to build a machine. Furthermore, the complementary base pairing between the strands showed how this information could be replicated. Sydney’s excitement and immediate appreciation of the significance of the DNA structure was in marked contrast to the gentle ripples that the DNA model generated in the pool of scientific consciousness in the few years following its publication. Sydney made a significant impression on Crick—a feeling that was clearly reciprocated. Their mutual respect was instrumental in their future careers becoming markedly intertwined.

Not long after Sydney returned to Oxford, he heard a talk by Fred Sanger in which he described his discovery—so readily assumed now, quite astonishing then—that the insulin molecule consists of two polypeptide chains, each with a unique amino acid sequence. This, together with the linear nature of DNA, provided the basis for believing that the amino acid sequence of a protein maps directly onto the base sequence of DNA.

Milislav Demerec, the director of the Cold Spring Harbor Laboratory (CSHL, one of the key centres undertaking phage research) visited Hinshelwood’s lab in late 1953. Demerec was impressed by Sydney’s work and encouraged him to visit CSHL before he returned to South Africa. He helped Sydney obtain a grant from the Carnegie Corporation to cover expenses for a four-month sojourn in the USA.

When Sydney finished his graduate studies in the summer of 1954, May returned with Jonathan and Stefan to South Africa, while Sydney set out on a road trip, partly in the company of Jim Watson, that took him across the US from CSHL to Pasadena, a trip that had a significant impact on his career. Along the way he met many of the key members of the phage community, including Seymour Benzer, who became a lifelong friend and collaborator (figure 4). On his way back to South Africa he visited Crick in Cambridge, who offered to try to secure a position for Sydney within the MRC Unit. When this was approved, Sydney and his family moved to Cambridge to start their new life in December 1956.

When Sydney started work on phages in his new lab at the Cavendish, one of the first things he tried was to look at phage particles in the newly installed electron microscope. Using negative staining, he obtained the first detailed images of these beautiful structures (3).

Mutation and the genetic code

The first thoughts on how DNA can encode a polypeptide were posed by the cosmologist George Gamow in 1954: how a nucleic acid sequence made from four different bases can encode a polypeptide sequence made from 20 amino acids. In his ‘diamond’ code he pointed out that at least three bases would be required to specify each amino acid. With little information to restrict the form of a triplet ‘genetic code’, several attempts were made to guess
it: the ‘comma-less’ code, proposed by Crick, John Griffiths and Orgel in 1957 was ingenious, but also wrong. Shortly after this, Sydney showed that the code could not be fully overlapping (2), i.e. it could not have the form in which a nucleic acid sequence such as ATGCA encodes three amino acids (by the triplets ATG, TGC and GCA). By assembling all the then-known dipeptide sequences, he showed that at least 70 different triplets would be required to encode them; as there are only 64 different triplets, fully overlapping codes could not account for the known amino acid sequences. This demonstrated that constraints on the nature of the code could be deduced from existing data.

Understanding mutation

Brenner was fascinated by genetics and what could be learned from mutation. His first contribution came during a sabbatical visit by Benzer in 1957–8. Benzer had devised a new method for ordering very close mutations in the rII gene of phage T4 and thereby to construct a fine structure genetic map of the region. With Ernst Freese, he had shown that the sites at which the mutagen bromouracil (BU) acts are quite restricted. In Cambridge, Benzer and Sydney, with Leslie Barnett (figure 5), chose to analyse a relatively new mutagen, proflavin (PF, an acridine dye), in the rII gene. They found that PF, in contrast to BU, induces mutations which are much more widely distributed. These findings were extended by Alice Orgel and Sydney; they studied the induced reversion of different mutations in the rII region (4). They found that mutants, originally induced by BU, could be reverted by BU but not by PF. The
reverse was also true: mutants induced by PF could be reverted by PF but not by BU. This showed that these two mutagens act at different sites and perhaps act in a different way, a finding that was to have profound consequences.

It was generally agreed that mutagens, such as BU, are incorporated into DNA during replication; this can lead to the alteration of a single base at that site, and thus a new mutant individual. But how did PF act? In ‘The theory of mutagenesis’ (4), Sydney, Barnett, Crick and Alice Orgel suggested that two classes of mutagen exist: base analogue (like BU) and acridine (like PF). They further suggested that acridine mutagens act by effecting the insertion or deletion of a base pair. This idea naturally arose from the finding of Leonard Lerman (Lerman 1961) that acridine dyes intercalate into the DNA helix, extending it in length. If, during replication, an acridine molecule slid into one DNA strand, but not the other, an extra base might be incorporated in one chain. If such a sequence coded for a protein, the addition of a single base might change the reading frame with devastating consequences. Such a mutation could only be reverted by a second (nearby) mutation in which a base is removed, whereby the original reading frame would be restored. This theory set the stage for the most remarkable experiment in genetics.

**Messenger RNA**

Messenger ribonucleic acid (RNA) is a copy of one strand of the DNA helix; it brings the genetic information from the gene in the nucleus to the protein synthetic machinery in the cytoplasm. Its discovery, in 1961, was the most important finding in molecular biology after the structure of DNA according to Crick, and provided the missing link between genes and proteins.

By early 1960, it was known that dense objects seen in a cell’s cytoplasm using an electron microscope—ribosomes—are the sites of protein synthesis. These particles, about 20 nm in
diameter, contain about two-thirds RNA and the rest protein. Naturally, it was assumed that the RNA component contained the information for making a protein. However, this picture did not feel right for several reasons, which came from two quite different directions. First, the RNA in ribosomes comes in just two sizes, yet the proteins for which they were imagined to code come in almost any size; furthermore, its GC/AU ratio is quite different from the GC/AT ratio of the cell’s average DNA.

Second, kinetic studies on the expression of the $\varepsilon$ gene of the lactose operon of *Escherichia coli*, which encodes the enzyme $\beta$-galactosidase, indicated that the synthesis of this enzyme could be switched on and off quite quickly. Thus, Arthur Pardee, François Jacob and Jacques Monod (figure 6) found that when the $\varepsilon$ gene is introduced into a host cell able to express it, enzyme synthesis occurs at its maximum rate within two to three minutes (in the so-called PaJaMo experiment) (Pardee et al. 1959). Similarly, Pardee and Louise Prestidge found that if the gene is switched on by the addition of an inducer, isopropyl $\beta$-d-1-thiogalactopyranoside (IPTG), synthesis starts almost immediately—the first activity is seen after three minutes; when the inducer is removed, new synthesis stops almost immediately (Pardee & Prestidge 1961). These, and other experiments, indicated that synthesis of a protein could be switched on and off surprisingly rapidly. These observations implied that in the flow of information from a gene to the synthesis of its protein, an unstable intermediate might exist.

The nature of this intermediate became clear at an informal gathering in Sydney’s rooms at King’s College, Cambridge, on Good Friday 1960, which included Sydney, Crick, Jacob, Leslie Orgel and Ole Maaloe. As Jacob was being grilled by Crick about some new PaJaMo-type experiments which showed that the elusive intermediate must be unstable, it suddenly became clear that it had already been discovered! In Jacob’s words (Jacob 1988): ‘At this precise point, Francis and Sydney leapt to their feet. Began to gesticulate. To argue at top speed in great agitation. A red-faced Francis. A Sydney with bristling eyebrows. The two talked at once, all but shouting. Each trying to anticipate the other . . . ’
In 1956, Elliot Volkin and Lazarus Astrachan discovered that, after phage T2 infect *E. coli*, an unstable RNA appears with a base composition unlike that of *E. coli* but similar to that of T2 (Volkin & Astrachan 1956). At the time they surmised that this RNA was a precursor of T2 DNA. According to Crick, he and Sydney made the connection between this RNA and the messenger carrying information from the genes to the ribosomes simultaneously—Sydney letting out a yelp! The existence of mRNA had been hiding in plain sight in the literature.

That evening, Sydney and Jacob figured out how they might prove that mRNA existed: they surmised that after phage T2 infects *E. coli*, the putative T2 mRNA might be directing the synthesis of phage proteins on the host’s old, rather than new, ribosomes. To test this, they needed to find a way of separating the ribosome population made before infection from any made after infection to see whether new T2 RNA is associated with old or new ribosomes. In principle, new and old ribosomes could be separated on a density gradient, if the starting bacteria were grown in a dense medium (containing $^{13}$C and $^{15}$N amino acids and sugars). These dense cells could be infected with T2 and immediately shifted to a normal light $^{12}$C and $^{14}$N medium and radiolabelled $^{32}$P phosphate added to mark new RNA molecules. Matthew Meselson, of Caltech, was the only person with these dense isotopes and, coincidentally, both Jacob and Sydney planned to be in Pasadena that summer. There, in a race against time, they performed a series of experiments; the crucial one—on their last day at Caltech—showed that, after T2 infection, the new unstable RNA was found on old ribosomes. When Sydney returned to Cambridge, he repeated and tidied up all the experiments. However, publication of their results (5) was delayed for several months to allow an international group, led by François Gros of Paris, to publish alongside their evidence that an mRNA also exists in uninfected *E. coli* (Gros et al. 1961).

These two papers appeared in May 1961. In June 1961 Jacob and Monod published a famous review on gene expression in which they proposed the existence of an mRNA as the unstable information carrier from genes to ribosomes (Jacob & Monod 1961). This paper was submitted for publication at the very end of 1960 and is often credited with the original proposal for the existence of mRNA. But this is unfair: while members of the MRC Unit in the Cavendish were squeezed into the hut’s entrance for fresh coffee in late 1961, John Kendrew suggested, jokingly, that he should document exactly who thought of what and when, and then deposit this record in a Swiss bank. Alas, his text must be in a secret account!

In contrast with the structure of DNA, the discovery of mRNA was readily accepted by the scientific community. Within a short time, mRNA had been detected in mammalian cells, where it is comparatively stable. By the summer of 1961, Marshall Nirenberg and Heinrich Matthaei made the momentous discovery that when a synthetic mRNA, a homopolyribonucleic acid, is added to a bacterial extract capable of protein synthesis, a polypeptide built from just one type of amino acid is made (Nirenberg & Matthaei 1961). Poly U encoded polyphenylalanine. Within six months of its discovery, mRNA had become history: the way forward to elucidate the genetic code was wide open.

**The general nature of the genetic code**

The idea that acridine acts as a mutagen by the addition of a base suggested that, as the mRNA for such a mutant gene is being translated, the ribosome would enter the wrong reading frame and any polypeptide made after that would have a new abnormal sequence. A combination
of two added bases should also result in similar effect but, as Crick realized, if the mRNA is read in triplets, three mutants might lead to the restoration of the correct reading frame, although the sequence in between the first and third mutation would be not be that of the normal protein. Taking advantage of the detailed map of the rII region of phage T4, Crick, Barnett, Richard Watts-Tobin and Sydney reported their findings at the very end of 1961 (6). First, they found that their PF mutants could be classified into two categories, which they arbitrarily called ‘+’ and ‘−’; in general, any combination of a + with a − gave a wild-type T4 phenotype, consistent with the scheme that the reading frame was being altered, and then corrected. Furthermore, a ++ or −− combination gave mutant phenotypes. Amazingly, +++ or −−− combinations gave wild-type. Thus, in one of the most remarkable papers in biology, they concluded that the mRNA is read sequentially from one end of the mRNA in triplets and that most triplets must be readable—the code is highly degenerate.

The reason these genetic constructs functioned at all was due to the fortunate circumstance that the region of the rII protein in which they were performed is unusually tolerant to changes in its amino acid sequence. There were, however, a few combinations of a + and − that did not give a wild-type phenotype; between them a ‘barrier’ existed in the gene that was phase sensitive: a combination of a − and + across the barrier had a wild-type phenotype. These barriers are now known to be nonsense codons.

**NONSENSE CODONS AND CO-LINEARITY**

In the early 1960s, a variety of ‘conditional’ mutants were found in bacterial genes: these mutations could be suppressed by a second mutation in another part of the genome—by a ‘suppressor gene’. A given suppressor was found to suppress conditional mutants at many different sites, both in bacterial and phage genes. In 1962, Benzer and Sewell Champe provided genetic evidence that in the rII region of phage T4, such conditional mutations are nonsense: they do not code for any amino acid, whereas in the presence of a suppressor (a ‘permissive’ or su+ strain), the nonsense now becomes readable (Benzer & Champe 1962). Thus, the genetic code is read differently in permissive (su+) and non-permissive (su−) strains.

In addition, out of a collection of different conditional mutants in T4 genes, John Wiberg et al. (1962) found that many were suppressed in the same su+ strain. They called these mutants amber mutants, the su+ strain an amber suppressor. At the same time, Alan Garen and Obaid Siddiqi (1962) found a related result: they were studying mutants in the *E. coli* gene for alkaline phosphatase. They found that a set of conditional mutants produced no enzyme in an su− strain, yet in an su+ strain, enzyme activity was restored.

Late in the infection of *E. coli* by phage T4, most of the protein molecules synthesized are the ‘head protein’, which ultimately encapsulates the phage DNA and so dominates the pattern of proteins made late in phage infection. Anand Sarabhai, Tony Stretton, Antoinette Bolle and Sydney took advantage of this to study the products of different T4 phage bearing amber mutations in their head protein genes (7). They discovered that, when such a T4 mutant phage infects a non-permissive *E. coli* host, only a fragment of the head protein is made. Using 10 different amber mutants along the head gene, they showed that the further along the genetic map the mutation occurs, the longer the polypeptide chain that is produced. Howard Dintzis (1961) had shown that, during protein synthesis, polypeptides are synthesized starting from the N-terminus; this suggested that the T4 polypeptides made are fragments, extending from
the N-terminus to a nonsense sequence, and this was soon confirmed directly on a head protein fragment (11). This proved that a gene and the polypeptide for which it codes are co-linear structures. Although this conclusion had been widely assumed—it lay at the heart of the use of acridine mutants to establish the triplet nature of the code—it underpinned a central tenet of molecular biology and opened the way better to understand the nature of nonsense mutations.

But what are nonsense mutations? Their genetic characteristic is that they are usually suppressed in \( su^+ \), but not \( su^- \), bacterial strains. Furthermore, \( su^+ \) strains, generated by mutation of an \( su^- \) strain, could be placed in one of two groups defined by their genetic behaviour on nonsense mutations: \( su_1^+ \), \( su_{11}^+ \), \( su_{111}^+ \) ... suppress amber mutations, whereas \( su_A^+ \), \( su_B^+ \) ... suppress both amber mutants and a further set of nonsense mutants, the ochre mutants. Their behaviour suggested that these two groups of suppressors have a similar mode of action. In a study of the head protein of phage T4, Stretton and Sydney showed in 1965 that in a particular mutant, a glutamine residue was altered to an amber site (11). Furthermore, when this mutant was grown in an \( su_I^+ \) host, about two-thirds of the T4 head polypeptides were completed, having a serine residue at the original site of mutation. Gursaran Notani et al. (1965) found the same result in the RNA phage f2 coat protein: a glutamine residue in wild-type gave rise to an amber mutation which, when grown in an \( su_I^+ \) host, was replaced by serine. Stretton, Sam Kaplan and Sydney extended this result to show that \( su_{11}^+ \) and \( su_{111}^+ \) insert glutamine and tyrosine respectively (10).

In 1965, through a complex series of mutant studies in the T4 rII region, Sydney, Stretton and Kaplan found that ochre and amber mutations are closely related by a single step change of an A to G transition (9). In the same year, Garen and Martin Weigert had shown that codons for both glutamine and tryptophan can give rise to an amber codon (Weigert & Garen 1965). Combining their mutational studies with a knowledge that a codon for tryptophan has the composition UGG and that glutamine is CAG, as determined by Nirenberg’s group, they concluded that the amber and ochre codons are UAG and UAA respectively. They further suggested that the process of polypeptide chain termination is congruent with chain extension and that a chain terminating tRNA exists that reads each termination codon. In an \( su^+ \) host, the amber codon is read as an amino acid, each suppressor inserting a particular amino acid. The role of UAA as a termination codon fit well with the earlier finding that polypeptide products directed by synthetic mRNAs generally code for polypeptidyl-tRNAs (including the mRNA poly UX, where X is xanthine, unreadable and therefore ‘absolute’ nonsense), yet polypeptides directed by mRNAs made of Us and As produced a large portion of polypeptides free of tRNA (Bretscher 1965).

Sydney’s group continued to underpin the role of suppressors: the reading of a nonsense codon is phase sensitive (8); different amber \( su^+ \) sites are co-linearly related to each and thus to the codon for which it codes are co-linear structures. Although this conclusion had been widely assumed—it lay at the heart of the use of acridine mutants to establish the triplet nature of the code—it underpinned a central tenet of molecular biology and opened the way better to understand the nature of nonsense mutations.

The final part of this phase was the genetic analysis of a third class of nonsense mutation (later termed opal) for which no suppressors were known. In 1967 Sydney, Barnett, Crick and Eugene Katz studied a non-suppressible nonsense mutant in the rII region of T4: it could be converted to an ochre codon (UAA) by the mutagen hydroxylamine, which is known to lead to the replacement of a C by T in the DNA, be converted to an ochre suppressor with a UUA anticodon (14).
Caenorhabditis elegans

As the 1960s matured, many molecular biologists had seen their original dreams of understanding what genes do and how they affect inheritance become a reality. With an intellectual swagger, they imagined that, with their new mental and physical tools, most of the hidden secrets in biology had become accessible. Sydney was in the vanguard of this move: his initial aim was to redeploy the strategies of molecular genetics developed from prokaryotes to study the role of genes in specifying the behaviour of higher metazoans. Unlike many of his contemporaries, who alighted on well-established model systems such as *Drosophila*, Sydney set out on a quest to identify a metazoan that could be maintained and propagated in a similar manner to the way agar plates had been so effectively used for the study of bacterial and phage genetics.

Sydney would spend summers with his young family in Woods Hole and, while they enjoyed the beach, he would scour the library studying zoology. His memory was legendary, and he believed that papers should be ‘neuroxed’ rather than Xeroxed. The phylum Nematoda soon caught Sydney’s attention. They were popular organisms for study in the late nineteenth and early twentieth century, particularly in the study of fertilization, meiosis and the nervous system. Richard Goldschmidt had shown that *Ascaris* has a simple and apparently invariant pattern of nerve fibres and neuron cell bodies (Goldschmidt 1908, 1909). The neurons were identical, and thus identifiable, in different individual worms. Theodor Boveri had shown that the germ lines segregate out in the first few divisions in the embryo, suggesting that early divisions in these organisms had a stereotyped lineage (Boveri 1892). This notion was strengthened some years later by Erich Martini, who showed that the early lineage and cell content of specific organs were invariant in a given species (Martini 1923), giving rise to the concept of eutely. Furthermore, some free-living nematodes had short reproductive cycles and so might be amenable to genetic analysis; and they were sufficiently small that they could be accommodated within the window of an electron microscope (EM), thereby facilitating anatomical reconstruction from serial sections down to the level of individual synapses. The small free-living hermaphrodite nematode *Caenorhabditis elegans* was first identified and named by the amateur biologist Emile Maupas in 1900, who also described its hermaphroditic life cycle (Maupas 1900). Ellsworth Dougherty and Victor Nigon obtained a mutant from the similar nematode *Rhabditis briggsae*, which is also a self-fertilizing hermaphrodite (Nigon & Dougherty 1950). Males are produced at low frequency and can be used as gene vectors in genetic crosses. Nigon described strategies for crossing hermaphrodites such as *C. elegans* (Nigon 1943) and determined the chromosomal basis of sex determination cytologically (Nigon 1949). Dougherty developed ways of culturing soil nematodes (Dougherty & Calhoun 1948a) and discussed the possible significance of free-living nematodes for genetic research (Dougherty & Calhoun 1948b). These pioneering studies, suggesting that *C. elegans* could be genetically tractable, clearly caught Sydney’s eye. In 1963 Dougherty sent Sydney a culture of *C. elegans*—the die was cast.

Thus it was that Sydney came to select *C. elegans* as a favourable model organism with which to study how genes specify embryonic development and nervous system function. His vision was to: (i) deduce the total connectivity of the nervous system by reconstruction of electron micrographs of serial sections; (ii) characterize the cell lineage of the developing embryo using the (then) newly available technique of differential interference contrast microscopy; (iii) isolate mutants that perturb behaviour or development; (iv) use the
techniques of (i) and (ii) to determine the cellular correlates of the perturbation and thereby deduce the function of the wild-type allele of the mutated gene.

Using the N2 strain of *C. elegans* supplied by Dougherty, Sydney found that he could culture these organisms on agar plates seeded with *E. coli* as used for phage studies, thereby providing a familiar stepping-stone to his brave new world. He isolated his first mutant in 1967. Mutants readily segregate homozygous strains because of self-crossing within the hermaphrodites. These early successes convinced him that this organism really did have the potential to revolutionize the study of the genetic specification of development and nervous system function, so he set about convincing others of this vision.

With his reputation riding high, Sydney, with a remarkably brief document, persuaded the MRC to provide space in a newly constructed extension of the Laboratory of Molecular Biology (LMB) and funds for research personnel to study on the *C. elegans*. In addition, a computer to facilitate anatomical reconstructions from electron micrographs of serial sections was ordered.

Victor (Lord) Rothschild studied bulls’ sperm in Cambridge, but decided to give up research in the early 1960s. He was an admirer of Sydney, who was garnering a reputation as the *enfant terrible* of molecular biology at the time—they shared martinis at weekends. Nichol Thomson was Rothschild’s highly gifted, but now redundant, electron microscopist whom Sydney engaged. He examined a number of different species, but found that *C. elegans* gave the best images. Soon he became a master at cutting long uninterrupted series of sections from embedded worms. From these, Sydney started reconstructing the sensory anatomy in the head and the motor neurons in the anterior ventral cord using a wax pencil on transparent overlays of EM images. These early studies suggested that reconstructing the entire nervous system of *C. elegans* from electron micrographs was feasible. He went on to undertake limited reconstructions of a couple of uncoordinated mutants, which indicated that some neuron processes in the ventral cord were misplaced in these animals.

The computer arrived in 1970. Sydney was delighted to get his hands on a real information processing machine. He proved to be a talented and obsessive programmer, successfully implementing the string programming language TRAC (*Mooers 1966*) on what was, by modern standards, a rather primitive computer. TRAC became a useful component of the operating system for the suite of programs that was being developed by John White for reconstructing electron micrographs of serial sections. In later years Sydney used TRAC for DNA sequence analysis.

Around this time, Sydney gave a series of inspirational lectures around the world to expound his vision of how *C. elegans* was an ideal organism with which the power of genetics could be used to study development and neurobiology (*figure 7*). These lectures were usually delivered with considerable panache and without the use of notes or visual aids. They were laced with Sydney’s characteristically racy and sometimes barbed wit (e.g. ‘has a mind like Fort Knox—can’t enter it or get anything out of it’) and generated considerable excitement, encouraging many talented people to join Sydney’s big adventure. By the early 1970s an enthusiastic group of MRC staff, postdocs and graduate students was studying *C. elegans* at the LMB. In addition, a small group started studying the parasitic nematode *Ascaris* with a view to undertaking electrophysiological experiments on this much larger organism. However, *Ascaris* research was not continued at the LMB, although Stretton took the project to the University of Wisconsin where he used this organism to good effect in studies of electrophysiology (*Davis & Stretton 1996*) and of neuropeptides (*Knickelbine et al. 2018*).
The main thrust of Sydney’s early work with *C. elegans* was the isolation and mapping of behavioural and morphological mutants. Along with his technician Muriel Wigby, he developed methodologies for mutagenesis and genetic crosses that are now used by all in the field. Around 300 mutants were isolated, which, after mapping, were shown to define around 100 genes, thereby enabling Sydney to establish the first genetic map of a nematode. Sydney agonized over writing this up for several months, but it was eventually published in 1974 and became Sydney’s most cited publication and the essential handbook for all who study *C. elegans* (15).

One of the earliest of the many significant discoveries to emerge from the *C. elegans* project came out of the lineage studies of John Sulston. He found that certain cells in both the embryonic and post-embryonic lineages undergo programmed cell death soon after they are born (Sulston & Horvitz 1977). Bob Horvitz, a postdoc at the LMB, picked up this project and took it to his laboratory, which he set up as a new faculty member at MIT. There, his group went on to identify and clone two key genes involved in cell death, *ced-3* and...
ced-4 (Ellis & Horvitz 1986; Yuan et al. 1993). Remarkably, these genes turned out to be conserved in humans. This work had major implications for studies of immunology and cancer where programmed cell death plays a central role, and fully vindicated Sydney’s assertion that discoveries made in *C. elegans* would be relevant in higher organisms. Sydney, Sulston and Horvitz received the Nobel Prize in Physiology or Medicine for these studies in 2002 (figure 8).

By the mid 1970s it had become clear that the *C. elegans* project was not a flash in the pan but the beginnings of what would become a sustained world-wide research effort. At the LMB, Sydney withdrew from much *C. elegans* activity and focused, together with Jon Karn and Alexander McLeod, on cloning *unc-54*, a myosin heavy chain gene, by the use of a deficiency mutant (17, 18). The inferred protein sequence provided the first primary structure of this ubiquitous muscle protein and showed that intron boundaries do not correspond to protein domain boundaries. Meanwhile, Sulston pursued the lineage studies, eventually determining the complete cell lineage of *C. elegans* (Sulston et al. 1983). White and colleagues went on to determine the connectome of the hermaphrodite nervous system (20) and Jonathan Hodgkin took over the curation of the genetic map as part of his studies on the genetics of sex determination (Hodgkin 1987). These MRC staff members worked together with an extraordinarily talented group of mainly American postdocs, several of whom (or their mentees) went on to receive Nobel Prizes for their work on *C. elegans*. However, as this was happening, Sydney’s restless mind became fixated by the possibilities offered by new developments in gene cloning, following a visit from Paul Berg, and he started to drift way from mainstream *C. elegans* work.

Berg described his pioneering work on using SV40 to clone genes (Jackson et al. 1972), but also told Sydney of his concerns for the safety of gene cloning experiments. As word of the potential of cloning techniques to move a gene from one organism to another spread
around the world, there was a considerable backlash against this type of work, culminating in
a moratorium on recombinant technology being voted for at a National Academy of Sciences
meeting in 1975. Sydney became a key figure in high-level discussions, which led to the
establishment of guidelines for such work. He constructed a ‘safe strain’ for use as a vector
for cloning human genes. With typical flamboyance, Sydney drank a glass of milk spiked with
this strain, apparently suffering no ill effects. Over time, he became an influential figure in the
field of genomics. In 1988 CSHL held its first meeting on genome mapping and sequencing,
at which Sydney proposed and founded the Human Genome Organisation, an international
organization that facilitates and coordinates research on the human genome.

SYDNEY IN THE COFFEE ROOM

In the sixties and seventies, the second-floor coffee room was the Cell Biology division’s social
centre. After lunch on most days, and on occasional evenings, Sydney would hold court to the
handful of people present, talking almost incessantly, coffee cup in hand and smoking. Topics
ranged widely: a recent paper; observations about society; a caricature of another scientist; odd
reminiscences. His wicked humour might be vicious, but mostly interesting or amusing. As he
spoke, he emphasized even small points by raising his enormous eyebrows, fixing his sharp
blue eyes on an individual and seemingly addressing that person—psychologically capturing
or mesmerizing him. Recollections by past members of the division include (1Mark Bretscher,
2Dennis Bray, 3John White, 4Tony Stretton):

1A meeting he would love to organize, in which famous individuals who are unable to
communicate, would be invited; his list included Herman Kalckar and Fritz Lipmann. (c 1968)

2The Royal Society is 90% gonad—it spends most of its energies electing new Fellows.

1His disdain for biochemists—‘I’ve never soiled my fingers with ATP’.

4On visitors—when an American finds me in the lab and advances, hand extended, smile on face,
I tell them ‘don’t touch me, I’m radioactive’.

2On one of the diffident scientists in the Structural Studies division who was reported to have
fainted—‘If you have just one neurone, you can expect erratic performance!’.

3On hearing a bad seminar—‘has halitosis of the mind’.

1The best endorsement of a scientific hypothesis is that Max Delbrück thinks it’s wrong.

1On occasion, Francis joined in. There was a time he had an obsession about panspermia. One
day Sydney told him that he could think of only one argument against it. Francis asked, what
could that be? Sydney replied that if a society was advanced enough to send a rocket to Earth,
then he was sure that it would have discovered the structure of DNA long before him. So ended
the obsession.

A wonderful series of video recordings with Lewis Wolpert capture many of Sydney’s
reminiscences and stories (26)—such as the occasion when he and Jim Watson were stopped
by a traffic policeman in Kansas (§76); how he tried to use a washing machine to grow phage
(§85); the occasion he referred Time magazine, who wished to interview Archibald Garrod, to
visit Highgate Cemetery (§87); and many more, together with his philosophy of science.
Sydney’s early days at the LMB (figure 9) were something of a honeymoon. At that time the lab was headed by Max Perutz, who acted as a benign chairman of a board of governors made up of the divisional heads, an arrangement that seemed to work well apart from some financial crises. Sydney shared an office with Crick for many years, an arrangement that suited both admirably. Sydney’s phenomenally retentive memory and boiling cauldron of ideas were complemented by Crick’s cool analytical powers and ability to see where the heart of a problem lay. However, Crick left the LMB in 1976 to take a position at the Salk Institute.

In 1974 a report from a special MRC committee headed by David Phillips recommended that funding for the LMB be cut by 25% and that any successor to Perutz should act as a conventional director. So it was that, under these gathering clouds, Sydney was persuaded in 1977 to take the appointment of anticipatory director of the LMB until Perutz retired in 1979, at which time he would become the full director, a decision that he claimed was motivated by loyalty, but that he later described as the biggest mistake of his career (figure 10).

A few days before becoming the director of the LMB in September 1979, Sydney suffered a severe compound fracture of his left leg following a motorcycle accident. Problems with this leg dogged him for the rest of his life and required him to use a walking stick. Perhaps it was this mishap that prompted Sydney to give up smoking at this time, a decision that probably extended his life span. However, his injury did not dampen his vision for the future of the LMB—indeed, he found the stick to be a useful prop when emphasizing a point. Sydney was proposing that the LMB embrace the still young and controversial DNA technology that was emerging. However, not everyone agreed, and frictions started to develop as some people unfavourably compared his perceived dictatorial directorship style to Perutz’ laissez faire chairmanship.

Sydney’s relationship with Sir James Gowans (the MRC secretary) was initially productive. In order to manage the lab finances and to facilitate MRC oversight of the LMB, Gowans relocated Bronwen Loder, a senior scientifically trained administrator from head office, to
act as administrative director of the LMB in 1980. Sydney, who knew Loder from his time at Oxford, quickly formed a close working relationship with her as they grappled with the problems of funding the LMB.

At this time Sydney started negotiating with Gowans for the establishment of a division of neurobiology at the LMB. Gowans was initially enthusiastic at this proposal but ultimately rejected it, much to Sydney’s disappointment. For reasons that were never revealed, in 1985 Gowans suddenly became disenchanted with the Brenner/Loder axis at the LMB and summarily dismissed Loder; it was made clear to Sydney that he should step down as director. These events, together with Sydney’s growing realization that he would rather be running his own research group than directing the LMB, caused him to announce that he would be retiring from the directorship in 1987. On his retirement, the MRC allowed Sydney to set up a new MRC Unit of Molecular Genetics. This was initially housed in the LMB but transferred in 1989 to its own space in the Department of Medicine on the Addenbrooke’s hospital site. The new unit was funded by the MRC and Sydney’s personal awards.

In the midst of all this turmoil Sydney somehow found time to become editor of the *Journal of Molecular Biology*, a journal founded by John Kendrew in 1958 that published some of the key papers in the emerging field of molecular biology. Sydney served on the journal from
1961 as assistant editor; became joint editor with John Kendrew in 1985 and then editor from 1987 to 1990.

**Genomics**

Sydney and Sulston started thinking about genomics around 1974 when Sulston, using reassociation kinetics, estimated that the genome of *C. elegans* is about 20 times as large as that of *E. coli* (16). Sometime later, Coulson, Sulston, Karn and Sydney collaborated in devising a strategy for DNA fingerprinting, which enabled them to obtain a preliminary physical map of the *C. elegans* genome (19). Their appetites whetted, both Sulston and Sydney were keen to take on the challenge of completing a description of the *C. elegans* genome. However, a rather trivial incident, involving a perceived lapse of attribution by Sydney of Sulston’s and Coulson’s contributions to mapping of the *C. elegans* genome published in the popular science publication *New Scientist* (Joyce 1987), caused offence to Sulston and put an end to Sydney’s involvement in the *C. elegans* genome project. The *C. elegans* genome was eventually sequenced by a collaboration headed by Sulston in the UK and Bob Waterston in the USA (Hillier *et al.* 2005). In retrospect, this was probably a fortuitous outcome, as Sulston’s single-minded determination and focus were better suited to the challenge and discipline of large genome sequencing than Sydney’s restless brilliance and flights of fancy.

At the time that international collaborations to tackle the human genome were taking shape, Sydney mooted the alternative strategy of using a vertebrate genome with a smaller DNA content. He proposed using the genome of the pufferfish fugu, which, he had learned from his perusal of the *American Naturalist* in the Wood’s Hole library (Hinegardner & Rosen 1972), had a considerably smaller DNA content than humans. His group went on to show that fugu has only one-eighth of the DNA content of humans, although the gene complement is similar (21). Given the enormous effort that sequencing a human genome was likely to take at that time, fugu seemed like a sensible alternative that could start delivering results sooner. However, Sydney initially failed to attract funds to mount a rapid assault on the fugu fish genome, but nevertheless did initiate a modest fugu project in his Molecular Genetics Unit. This project made slow but steady progress over the years but when funds eventually became available Sydney contracted the sequencing work to Craig Venter’s company, Celera, and the full sequence was published in 2002 (24). Although rapid advances in sequencing technology had rendered the small genome advantages of fugu less significant, the ability to compare genome sequences from different organisms has opened up the large and fruitful field of comparative genomics that is yielding deep insights into how evolutionary mechanisms bring about species diversity (25).

Sydney’s experiences with fugu genome sequencing convinced him that comparative genome sequencing would be a powerful tool for medical and evolutionary studies. However, he realized that in order to sequence many genomes, faster and more economical mass sequencing methods were needed than those used for the *C. elegans* and the human genome projects. He reasoned that the way to achieve this was to invent new high-throughput sequencing strategies, patent them and licence the intellectual property to a company that could develop the technology into a practical instrument. Sydney authored more than 50 patents in his lifetime and became involved in several start-up companies. These patents are a testament to Sydney’s extraordinary creativity and ingenuity. An example is his 1994 proposal
for a massively parallel sequencing machine that used polynucleotides bound to immobilized microbeads (22, 23). A machine based on this technique was developed by Lynx Therapeutics, one of several companies that Sydney co-founded. Although this pioneering technology was not ultimately commercially successful, it was a potent driver in a rapidly evolving field. Lynx eventually merged with Solexa Ltd, which developed what by 2020 became the dominant sequencing technology marketed by Illumina. Sydney’s stream of patents continued to the last years of his life, at which time he was devising ways for analysing nucleic acids from single cells (31).

**Final break with MRC**

In 1981 Sydney took up a position as a non-resident fellow of the Salk Institute, which he liked to visit in the winter months partly because Crick was based there but also because he liked the culture of free-wheeling technical innovation fuelled through venture capital that is a feature of California. He quit this position at the Salk after four years, following some internal friction, but became Distinguished Research Professor there in 2005. In 1989 Sydney took up a position of Scholar in Residence at the Scripps Research Institute in La Jolla. The position gave him lab space that enabled him to relocate some of the personnel from the Molecular Genetics Unit in Cambridge when this unit finally closed in 1992.

**The founding father**

Sydney played a key role in the establishment of several new research centres in the latter part of his career. He became the recipient of US$10 million donated by the Phillip Morris company, which was designated for no-strings attached basic research. With these funds Sydney founded the Molecular Science Institute in Berkeley, which started operation in 1998 under the directorship of Roger Brent. Another more significant venture involved working with the Howard Hughes Medical Institute (HHMI) to define the research focus and administrative structure of a new intramural research centre. In 2006 this materialized as Janelia Farm in Virginia, a large centre headed by Gerry Rubin and which provides space and research funding for groups of scientists working on neurobiology and associated technologies. Sydney became a part-time employee of HHMI and spent three months a year working at Janelia Farm.

Sydney’s greatest accomplishments in founding new research establishments were both in Asia. By the early 1990s some senior scientists and politicians in Japan were concerned that Japan was losing out in the generation of technological and scientific innovations compared to the West. Some attributed this poor performance to the hidebound hierarchical structure of the Japanese universities and research institutes. Koji Omi, a senior Japanese politician, proposed the establishment of a new academically open graduate university along western lines—the Okinawa Institute for Science and Technology (OIST). Following discussions that included a number of Western academics, the Japanese Diet approved the proposal in 2005 and designated Sydney as the first president of OIST. The Institute was established in 2011 and included a small research group of Sydney’s that studied evolutionary neurobiology (28). By 2019, with Peter Gruss as president, OIST was ranked as number one in Japan and number nine in the world in terms of the proportion of its scientific work that was published in
highly-ranked journals. At that time, it had around 70 faculty and more than 200 graduate students, half of whom came from outside Japan (figure 11).

Sydney’s most significant contribution to the establishment of global bioscience initiatives was in Singapore. This small island state was one of the Asian Tigers—countries that experienced a period of rapid financial growth. Victor Rothschild, who acted as a consultant for prime minister Lee Kuan Yew, advised that Singapore should establish an effective research infrastructure for it to remain competitive in an increasingly technological world. Sydney, who had been acting as a consultant for Rothschild’s Biotechnology Investments company, went to Singapore in 1983 and presented an overview of biotechnology in industry and, in a later visit, a concrete proposal that was enthusiastically endorsed by the Singapore government. The proposal led to the establishment of the Institute for Molecular and Cell Biology (IMCB), which opened in 1987 and by 2003 had more than 500 scientific staff. Leslie Barnett, Sydney’s scientific assistant for much of his career, helped set up a laboratory in this building where he ran a research group studying comparative genomics up to the time of his death (29).

Philip Yeo, who became chairman of the Singapore government’s Economic Development Board in 1986, was a kindred spirit of Sydney’s. Together they formulated plans for further development of Singapore’s research infrastructure. Following their advice, the Singapore government established a substantial new entity to fund and coordinate all government sponsored research in Singapore: the Agency for Science, Technology and Research (A*STAR). A large multidisciplinary research centre was constructed by A*STAR. One of the research centres in this complex (named Biopolis by Sydney) is dedicated to genomics, bioinformatics and bioengineering (figure 12). The IMCB relocated into this building in 2003.
Even late in his career, Sydney never stopped thinking about the big picture of biology. Surprisingly, he was somewhat disparaging of model systems, claiming that the only model system now needed, given the current capabilities of molecular genetics, is the human. He also was dismissive of the current prominence of systems biology, instead defending a reductionist rather than a holist approach but one in which the basic units are cells rather than molecules (27).

In recognition of Sydney’s substantial contributions in establishing Singapore as a centre where world-class biomedical research is undertaken he was granted an honorary citizenship of the country. He has several buildings and even an orchid named after him. After May’s death in 2010 Sydney’s peripatetic lifestyle became more focused on Singapore. He was successfully treated for bowel cancer and a defective heart valve there, but, eventually, his long-term respiratory problems deteriorated to the extent that he had to be supported by supplementary oxygen, which prevented air travel. In 2015 A*STAR hosted a lavish international symposium in Sydney’s honour. This allowed many of his old students, postdocs and colleagues to come to Singapore to celebrate his extraordinary career (figure 13). Sydney often said that one had to be having fun to do good science. The many that came were delighted to see that, in spite of poor health, Sydney’s sense of fun and scintillating intellect were undimmed. Sydney died in Singapore on 5 April 2019, age 92.
From 1994 to 2000 Sydney wrote a monthly column for Current Biology initially called Loose Ends. These pieces have been collected together (30) and provide a vivid insight into Sydney’s wit, creativity and sense of fun. Included are some penetrating commentaries into scientific questions of the day along with episodes of delightfully whimsical fantasy. Several articles take the form of letters from Uncle Syd to Willie, who starts as a graduate student and rapidly progresses through a career in science. These perceptive and wry insights into the way academic science was undertaken still resonate with its practitioners. He signed off his final column with a revealing description of himself:

Elderly, white, male, column writer, seven years experience, self-employed scientist, explorer, adventurer, inventor and entrepreneur seeks young, naïve, preferably female editor of newly formed scientific journal with a view to obtaining unrefereed access to as wide an audience as possible.

SYDNEY’S AWARDS AND HONOURS

| Year | Award                          |
|------|--------------------------------|
| 1964 | EMBO Membership                |
| 1965 | Fellow of the Royal Society    |
| 1969 | William Bate Hardy Prize       |
1971 Albert Lasker Medical Research Award
1974 Royal Medal of the Royal Society
1977 Foreign Associate of the National Academy of Sciences
1978 Gairdner Foundation International Award
1980 Krebs Medal
1986 Member of the Order of the Companion of Honour
1987 Louis-Jeantet Prize for Medicine
1990 Kyoto Prize
1991 Copley Medal
1992 King Faisal International Prize in Medicine
2002 Nobel Prize in Physiology or Medicine
2002 Dan David Prize
2017 Grand Cordon of the Order of the Rising Sun

ACKNOWLEDGEMENTS

Much of the material for this biographical memoir was obtained from Sydney’s verbal autobiography as relayed to Lewis Wolpert (26) and from Errol Friedberg’s biography (Friedberg 2010). The article by Victor Nigon and Marie-Anne Félix (Nigon & Félix 2017) provided a valuable historic perspective on nematodes as model organisms. We thank our many colleagues for their recollections, especially Donna Albertson, Denis Bray, Thomas Kornberg, Peter Lawrence, Marc Vaudin and Paul Wassarman; Annette Faux for archival material; and Jonathan Hodgkin, Tony Stretton and Richard Durbin for helpful comments on the manuscript. We are most grateful to Belinda, Carla and Stefan Brenner for the use of family information. Figures 1, 2, 3, 4, 6 and 7 are courtesy of the Sydney Brenner Collection, Cold Spring Harbor Laboratory Archives, NY. The digital files were obtained from the Wellcome Library. The originals are held in the CSHL archives and are shared with the Wellcome Trust as part of Codebreakers, a project on the making of modern genetics.

The frontispiece portrait image is Copyright © MRC Laboratory of Molecular Biology.

AUTHOR PROFILES

John White

In November 1969, soon after graduating with a physics degree, I joined Sydney’s newly formed group studying C. elegans at the MRC LMB and became his research student a year later. Initially, I was involved in developing a computer system to facilitate the reconstruction of serial section micrographs of the nervous system. In addition, I developed a laser scanning confocal microscope and a cell ablation apparatus to facilitate our early studies of the developing C. elegans embryo. As the computer system was being developed, I became more focused on nervous system reconstructions, culminating in our publication of the complete
connectome in 1986 (19). After this I turned my attention to studying cytokinesis and cell polarity in the early blastomeres of *C. elegans*. In 1993 I relocated to the University of Wisconsin, where I continued these cell biological studies.

**Mark Bretscher**

As a research student, I joined the MRC Unit in the Cavendish Laboratory in September 1961 as Sydney’s second research student. I was, however, guided by Francis Crick, who arranged a collaboration for me with Marianne Grunberg-Manago of Paris: she prepared synthetic ribopolynucleotides whose coding properties I determined by *in vitro* protein synthesis. This led me to find and elucidate the structure of a new intermediate in protein synthesis—the peptidyl-tRNA complex and the discovery of termination codons. After a postdoc with Paul Berg, I joined the staff of the Molecular Genetics division in the new LMB and worked on different aspects of protein synthesis—chain initiation, termination and translocation. In 1969, I studied the structure of the erythrocyte membrane—discovering that proteins span the membrane and phospholipid asymmetry. Thereafter, I worked on the mechanism of endocytosis and how cells, such as fibroblasts and amoebae, move. Until Francis migrated to California, he followed my progress carefully and offered advice, mainly about diffusion in membranes. I was head of the Cell Biology division (previously held by both Crick and Brenner) from 1985 to 1994.

**References to other authors**

Benzer, S. & Champe, S. P. 1962 A change from nonsense to sense in the genetic code. *Proc. Natl Acad. Sci. USA* 48, 1114–1121. (doi:10.1073/pnas.48.7.1114)

Boveri, T. 1892 Über die Entstehung des Gegensatzes zwischen den Geschlechtszellen und den somatischen Zellen bei *Ascaris megalocephala*. *Sitzber. Ges. Mprph. Physiol. München* 8, 114–125.

Bretscher, M. S. 1965 Studies on the Genetic Code and Protein Synthesis. January 1965, Cambridge University.

Davis, R. E. & Stretton, A. O. 1996 The motornervous system of Ascaris: electrophysiology and anatomy of the neurons and their control by neuromodulators. *Parasitology* 113 suppl., S97–S117. (doi:10.1017/S0031182000077921)

Dintzis, H. M. 1961 Assembly of the peptide chains of hemoglobin. *Proc. Natl Acad. Sci. USA* 47, 247–261. (doi:10.1073/pnas.47.3.247)

Dougherty, E. C. & Calhoun, H. G. 1948a Experiences in culturing *Rhabditis pello* (Schneider 1866) Bütschli 1873 (Nematoda: Rhabditidae), and related soil nematodes. *Proc. Helm. Soc. Wash.* 15, 55–68.

Dougherty, E. C. & Calhoun, H. G. 1948b Possible significance of free-living nematodes in genetic research. *Nature* 161, 29. (doi:10.1038/161029a0)

Ellis, H. M. & Horvitz, H. R. 1986 Genetic control of programmed cell death in the nematode *C. elegans*. *Cell* 44(6), 817–829. (doi:10.1016/0092-8674(86)90004-8)

Friedberg, E. C. 2010 Sydney Brenner: a biography. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press.

Garen, A. & Siddiqi, O. 1962 Suppression of mutations in the alkaline phosphatase cistron of *E. coli*. *Proc. Natl Acad. Sci. USA* 48(7), 1121–1127. (doi:10.1073/pnas.48.7.1121)

Goldschmidt, R. 1908 Das Nervensystem von *Ascaris lumbricoides* und megalocephala, I. Z. wiss. Zool. 90, 73–136.
Goldschmidt, R. 1909 Das Nervensystem von *Ascaris lumbricoides* und megaloecephela. *II. Z. wiss. Zool.* 92, 306–357.

Gros, F., Hiatt, H., Gilbert, W., Kurland, C. G., Risebrough, R. W. & Watson, J. D. 1961 Unstable ribonucleic acid revealed by pulse labelling of *Escherichia coli*. *Nature* 190, 581–585. (doi:10.1038/190581a0)

Hillier, L. W., Coulson, A., Murray, J. I., Bao, Z., Sulston, J. E. & Waterston, R. H. 2005 Genomics in *C. elegans*: so many genes, such a little worm. *Genome Res.* 15(12), 1651–1660. (doi:10.1101/gr.3729105)

Hinegardner, R. & Rosen, D. E. 1972 Cellular DNA content and evolution of teleostean fishes. *Am. Nat.* 106, 621–644. (doi:10.1086/282801)

Hodgkin, J. 1987 Primary sex determination in the nematode *C. elegans*. *Development* 101 suppl., 5–16.

Jackson, D. A., Symons, R. H. & Berg, P. 1972 Biochemical method for inserting new genetic information into DNA of Simian Virus 40: circular SV40 DNA molecules containing lambda phage genes and the galactose operon of *Escherichia coli*. *Proc. Natl Acad. Sci. USA* 69(10), 2904–2909. (doi:10.1073/pnas.69.10.2904)

Jacob, F. 1988 *The statue within*: an autobiography. New York: Basic Books.

Jacob, F. & Monod, J. 1961 Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.* 3(3), 318–356. (doi:10.1016/S0022-2836(61)80072-7)

Joyce, C. 1987 The race to map the human genome—1. Mapping genes: the bottom up approach. *New Scientist* March, 35–36.

Knöllbold, J. J., Konop, C. J., Viola, I. R., et al. 2018 Different bioactive neuropeptides are expressed in two sub-classes of GABAergic RME nerve ring motoneurons in *Ascaris suum*. *ACS Chem. Neurosci.* 9(8), 2025–2040. (doi:10.1021/acschemneuro.7b00450)

Lerman, L. S. 1961 Structural considerations in the interaction of DNA and acridines. *J. Mol. Biol.* 3, 18–30. (doi:10.1016/S0022-2836(61)80004-1)

Luria, S. E. & Delbrück M. 1943 Mutations of bacteria from virus sensitivity to virus resistance. *Genetics* 28(6), 491–511.

Martini, E. 1923 Die Zellkonstanz und ihre Beziehungen zu anderen zoologischen Vorwürfen. *Zeit. Anat. Entwickelt.* 70, 179–250. (doi:10.1007/BF02117179)

Mooers, C. N. 1966 TRAC, a procedure-describing language for the reactive typewriter. *Comm. ACM* 9. (doi:10.1145/365230.365270)

Nigon, V. 1943 Le déterminisme du sexe chez un nématode libre hermaphrodite (*Rhabditis elegans* Maupas). *C. R. Soc. Biol.* 137, 40–41.

Nigon, V. 1949 Modalités de la reproduction et déterminisme du sexe quelques nématodes. *Ann. des sc. Nat. Zool.* 11, 1–132.

Nigon, V. & Doughtery, E. C. 1950 A dwarf mutation in a nematode: a morphological mutant of *Rhabditis briggsae*, a free-living soil nematode. *J. Hered.* 41, 103–109. (doi:10.1093/oxfordjournals.jhered.a106095)

Nigon, V. M. & Félix, M.-A. 2017 History of research on *C. elegans* and other free-living nematodes as model organisms. The *C. elegans* Research Community, WormBook, https://doi.org//10.1895/wormbook.1.181.1.

Nirenberg, M. W. & Matthaei, J. H. 1961 The dependence of cell-free protein synthesis in *E. coli* upon naturally occurring or synthetic polyribonucleotides. *Proc. Natl Acad. Sci. USA* 47, 1588–1602. (doi:10.1073/pnas.47.10.1588)

Notani, G. W., Engelandt, D. L., Konigsberg, W. & Zinder, N. D. 1965 Suppression of a coat protein mutant of the bacteriophage F2. *J. Mol. Biol.* 12, 439–447. (doi:10.1016/0022-2836(65)80266-2)

Pardee, A. B. & Prestidge, L. S. 1961 The initial kinetics of enzyme induction. *Biochim. Biophys. Acta* 49, 77–88. (doi:10.1016/0006-3002(61)90871-X)

Pardee, A. B., Jacob, F. & Monod, J. 1959 The genetic control and cytoplasmic expression of ‘inducibility’ in the synthesis of β-galactosidase by *E. coli*. *J. Mol. Biol.* 1, 165–178. (doi:10.1016/0022-2836(59)80045-0)

Sulston, J. E. & Horvitz, H. R. 1977 Post-embryonic cell lineages of the nematode, *Caenorhabditis elegans*. *Dev. Biol.* 56(1), 110–156. (doi:10.1016/0012-1606(77)90158-0)

Sulston, J. E., Schierenberg, E., White, J. G. & Thomson, J. N. 1983 The embryonic cell lineage of the nematode *Caenorhabditis elegans*. *Dev. Biol.* 100(1), 64–119. (doi:10.1016/0012-1606(83)90201-4)

Taylor, F. S. 1934 *The young chemist*. London: Nelson.
Volkin, E. & Astrachan, L. 1956 Intracellular distribution of labeled ribonucleic acid after phage infection of
Escherichia coli. Virology 2(4), 433–437. (doi:10.1016/0042-6822(56)90001-0)

Weigert, M. G. & Garen, A. 1965 Base composition of nonsense codons in E. coli: evidence from amino-acid
substitutions at a tryptophan site in alkaline phosphatase. Nature 206(988), 992–994. (doi:10.1038/206992a0)

Wells, H. G., Huxley, J. S. & Wells, G. P. 1931 The science of life. London: Waverley Publishing.

Wiberg, J. S., Dirksen, M. L., Epstein, R. H., Luria, S. E. & Buchanan, J. M. 1962 Early enzyme synthesis and its
control in E. coli infected with some amber mutants of T4. Biochemistry 48, 293–302.

Wilson, E. B. 1925 The cell in development and heredity, 3rd edn. New York: The Macmillan Co.

Yuan J., Shaham S., Ledoux S., Ellis H. M. & Horvitz H. R. 1993 The C. elegans cell death gene
ced-3 encodes a protein similar to mammalian interleukin-1 beta-converting enzyme. Cell 75(4), 641–652.
(doi:10.1016/0092-8674(93)90485-9)

Bibliography

The following publications are those referred to directly in the text. A full bibliography is available as electronic
supplementary material at https://doi.org/10.6084/m9.figshare.c.5106137.

1. 1949 Multipolar meiosis in Elephantulus. Nature 164, 495–496. (doi:10.1038/164495b0)
2. 1957 On the impossibility of overlapping triplet codes in information transfer from nucleic acid to protein.
Proc. Natl Acad. Sci. USA 43, 687–694. (doi:10.1073/pnas.43.8.687)
3. 1959 (With R. W. Horne) A negative staining method for high resolution electron microscopy of viruses.
Biochim. Biophys. Acta 34, 103–110. (doi:10.1016/0006-3002(59)90237-9)
4. 1961 (With L. Barnett, F. H. C. Crick & A. Orgel) The theory of mutagenesis. J. Mol. Biol. 3, 121–124.
(doi:10.1016/S0022-2836(61)80015-6)
5. 1961 (With F. Jacob & M. Meselson) An unstable intermediate carrying information from genes to
ribosomes for protein synthesis. Nature 190, 576–581. (doi:10.1038/190576a0)
6. 1964 (With A. S. Sarabhai, A. O. Stretton & A. Bolle) Co-linearity of the gene with the polypeptide chain.
Nature 201, 13–17. (doi:10.1038/201013a0)
7. 1965 (With A. O. W. Stretton) Phase shifting of Amber and Ochre mutants. J. Mol. Biol. 13, 944–946.
(doi:10.1016/S0022-2836(65)80136-5)
8. 1969 (With A. O. W. Stretton & S. Kaplan) Genetic code: the ‘nonsense’ triplets for chain termination and their
suppression. Nature 206(988), 994–998. (doi:10.1038/206994a0)
9. 1978 (With S. Kaplan & A. O. Stretton) Amber suppressors: efficiency of chain propagation and suppressor
specific amino acids. J. Mol. Biol. 14(2), 528–533. (doi:10.1016/S0022-2836(65)80202-9)
10. 1981 (With A. O. Stretton) Molecular consequences of the amber mutation and its suppression. J. Mol. Biol.
12, 456–465. (doi:10.1016/S0022-2836(65)80268-6)
11. 1983 (With L. Barnett, E. R. Katz & F. H. Crick) UGA: a third nonsense triplet in the genetic code. Nature 213(5075), 449–450. (doi:10.1038/213449a0)
12. 1988 (With H. M. Goodman, J. Abelson, A. Landy & J. D. Smith) Amber suppression: a nucleotide change
in the anticodon of a tyrosine transfer RNA. Nature 217(5133), 1019–1024. (doi:10.1038/2171019a0)
13. 1971 (With S. Altman & J. D. Smith) Identification of an ochre-suppressing anticodon. J. Mol. Biol. 56(1),
195–197. (doi:10.1016/0022-2836(71)90094-5)
14. 1974 The genetics of Caenorhabditis elegans. Genetics 77(1), 71–94.
15. 1981 (With J. E. Sulston) The DNA of Caenorhabditis elegans. Genetics 77, 95–104.
16. 1981 (With A. R. MacLeod & J. Karn) Molecular analysis of the unc-54 myosin heavy chain gene of
Caenorhabditis elegans. Nature 291, 386–390. (doi:10.1038/291386a0)
17. 1983 (With J. Karn & L. Barnett) Protein structural domains in Caenorhabditis elegans unc-54 myosin
heavy chain gene are not separated by introns. Proc. Natl Acad. Sci. USA 80, 4253–4257.
(doi:10.1073/pnas.80.14.4253)
Biographical Memoirs

(19) 1986 (With A. Coulson, J. Sulston & J. Karn) Toward a physical map of the genome of the nematode *Caenorhabditis elegans*. *Proc. Natl. Acad. Sci. USA* 83(20), 7821–7825. (doi:10.1073/pnas.83.20.7821)

(20) 1986 (With J. G. White, E. Southgate & J. N. Thomson) The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Phil. Trans. R. Soc. Lond. B, Biol. Sci.* 314(1165), 1–340. (doi:10.1098/rstb.1986.0056)

(21) 1993 (With G Elgar, R. Sandford, A. Macrae, B. Venkatesh & S. Aparicio) Characterization of the pufferfish (Fugu) genome as a compact model vertebrate genome. *Nature* 366, 265–268. (doi:10.1038/366265a0)

(22) 1994 Massively parallel sequencing of sorted polynucleotides, patent application EP95937322A, Lynx Therapeutics inc. European Patent Office.

(23) 2000 (With M. Johnson, J. Bridgham, G. Golda, D. H. Lloyd, D. Johnson, S. Luo, S. McCurdy, M. Foy, M. Ewan, R. Roth, D. George, S. Eletr, G. Albrecht, E. Vermaas, S. R. Williams, K. Moon, T. Burcham, M. Pallas, R. B. DuBridge, J. Kirchner, et al.) Gene expression analysis by massively parallel signature sequencing (MPSS) on microbead arrays. *Nat. Biotechnol.* 18(6), 630–634. (doi:10.1038/76469)

(24) 2002 (With S. Aparicio, J. Chapman, E. Stupka, N. Putnam, J. M. Chia, P. Dehal, A. Christoffels, S. Rash, S. Hoon, A. Smit, M. D. Gelpke, J. Roach, T. Oh, I. Y. Ho, M. Wong, C. Detter, F. Verhoef, P. Predki, A. Tay, S. Lucas, et al.) Whole-genome shotgun assembly and analysis of the genome of *Fugu rubripes*. *Science* 297(5585), 1301–1310. (doi:10.1126/science.1072104)

(25) 2004 (With Y. H. Loh, A. Christoffels, W. Hunziker & B. Venkatesh) Extensive expansion of the claudin gene family in the teleost fish, *Fugu rubripes*. *Genome Res.* 14(7), 1248–1257. (doi:10.1101/gr.2400004)

(26) 2008 (With L. Wolpert) Coming from Eastern European stock. *Web of stories*. London: Web of Stories Ltd, Science Navigation Group. https://www.webofstories.com/play/sydney.brenner/1

(27) 2010 Sequences and consequences. *Phil. Trans. R. Soc. Lond. B, Biol. Sci.* 365(1537), 207–212. (doi:10.1098/rstb.2009.0221)

(28) 2015 (With C. B. Albertin, O. Simakov, T. Mitros, Z. Y. Wang, J. R. Pungor, E. Edsinger-Gonzales, C. W. Ragsdale & D. S. Rokhsar) The octopus genome and the evolution of cephalopod neural and morphological novelties. *Nature* 524(7564), 220–224. (doi:10.1038/nature14668)

(29) 2016 (With H. Pan, H. Yu, V. Ravi, C. Li, A. P. Lee, M. M. Lian, B.-H. Tay, J. Wang, H. Yang, G. Zhang & B. Venkatesh) The genome of the largest bony fish, ocean sunfish (*Mola mola*), provides insights into its fast growth rate. *Gigascience* 5(1), 36. (doi:10.1186/s13742-016-0144-3)

(30) 2019 *Loose ends . . . false starts*. Singapore/Hackensack, NJ/London: World Scientific.

(31) Methods for analysing nucleic acids from single cells. Patent application, 10x Genomics. US Patent Office.