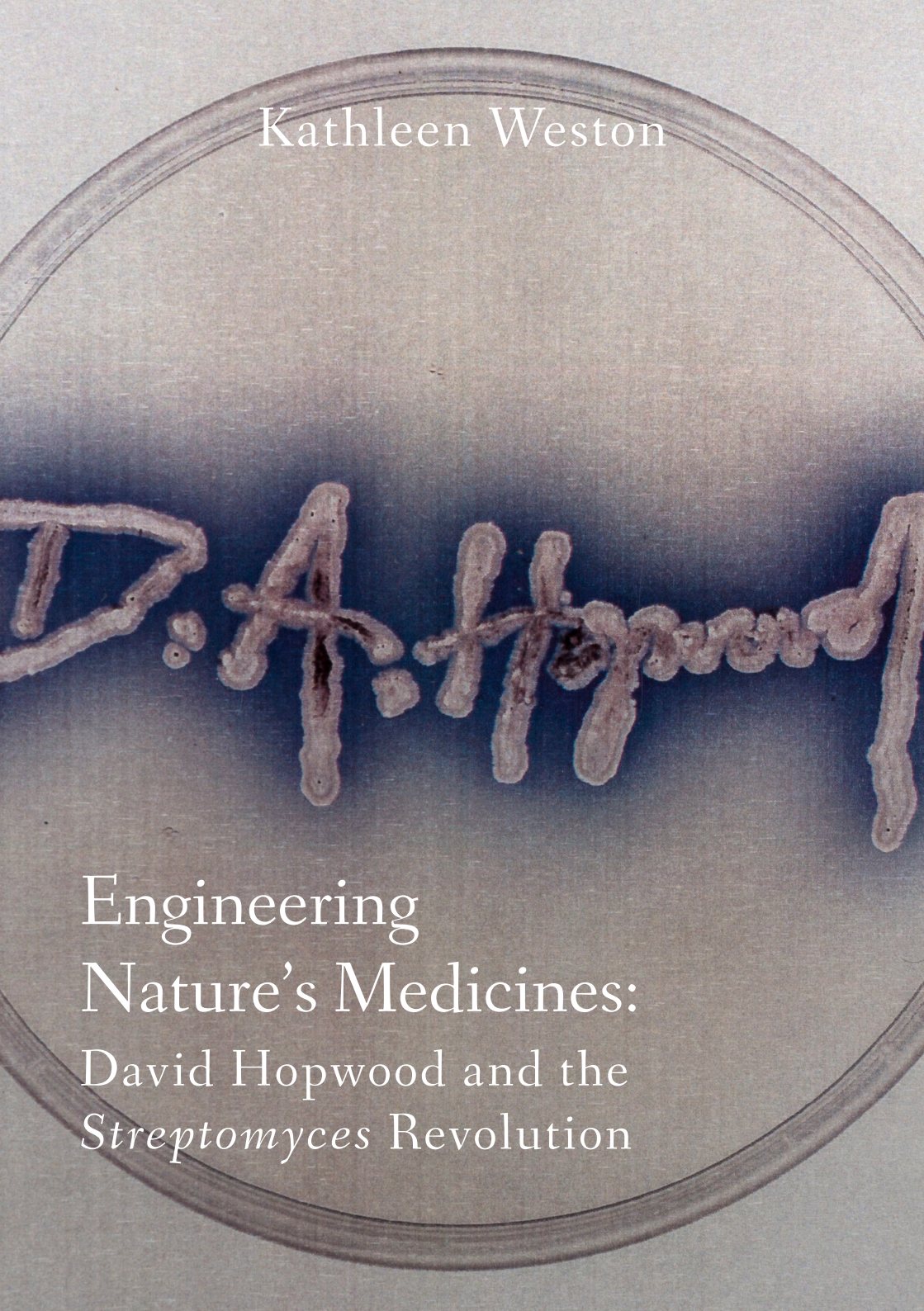
Kathleen Weston



Engineering Nature's Medicines:

David Hopwood and the *Streptomyces* Revolution

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Kathleen Weston

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Chapter 1

Introduction

Close your eyes and imagine yourself in your favourite place outdoors – perhaps lying under a tree in a sun-dappled wood, or high on a mountain, with what feels like a view of the whole world, or strolling in the heat and light of an exotic island far from home. Now, add a little moisture – a tropical downpour, a summer rain shower, an autumnal mist – and sniff. Rising from the warm, damp earth is a scent that is instantly recognisable by organisms from flies to humans, that your nose can detect at a hundred parts per trillion, and that has perfumed this planet for half a billion years: geosmin, the scent of the soil bacteria *Streptomyces*.

Living in the soil isn't easy. Unlike gut bacteria, whose warm, easy lives are an endless *smorgasbord* of digested food, soil bacteria not only have to contend with dramatic changes to their living conditions, where feast can turn to famine and drought with little or no warning, but must compete for sometimes limited resources with hordes of other micro-organisms. Hidden beneath our feet is a microscopic battleground of epic proportions.

Just as human ingenuity thrives in adversity, so soil microbes have evolved lifestyles to cope with their harsh environment, and sophisticated chemical weapons to fight their enemies. And we in turn have adapted their weaponry to fight our own foe: disease. Antibiotics, immunosuppressants, anti-cancer drugs, anti-fungals, antihelminthics – more than 16,000 specialised, so-called secondary metabolites with cell-killing activity are made by soil microbes, and their use in humans and animals has revolutionised medicine. The actinomycetes, the bacterial family to which *Streptomyces* belong, make most of the clinically relevant anti-microbial drugs in use today, and of those, most are derived from species of *Streptomyces*. *Streptomyces* not only smell nice; they have saved millions of lives.

Until sixty years ago, knowledge about *Streptomyces* was limited. In 1943, Albert Schatz in Selman Waksman's laboratory at Rutgers University had shown that *Streptomyces* might be of interest to more than a few soil microbiologists by discovering streptomycin, the first agent able to cure tuberculosis. This led to a golden age of antibiotic discovery in actinomycetes, with drug companies competing to identify new *Streptomyces* species and test their products in antimicrobial assays. However, although harnessing *Streptomyces* for drug development meant that people knew how to grow them, and purify potential antibiotics from them, there was little interest from either industry or academia in finding out what made them tick: what exactly were they – some sort of fungus, an odd type of bacterium, or a weird halfway house? How did they prosecute their complex lifecycles? How many genes did they have? How did they make the secondary metabolites that had secured their fame? The solutions to all these puzzles were unknown. How this changed, and how the *Streptomyces* research community grew from nothing into the thriving, vibrant operation that it is today, is largely down to one man: David Hopwood.

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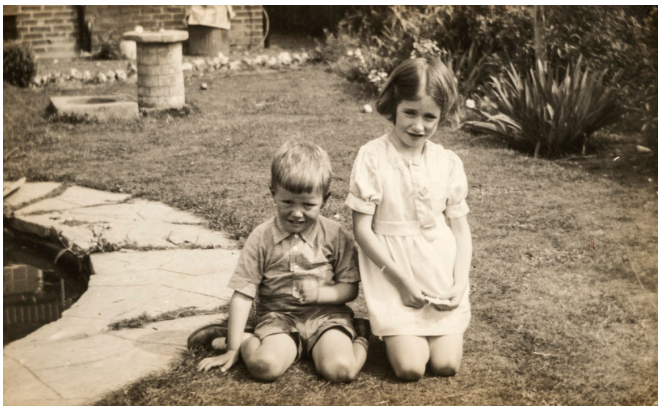
Chapter 2

Origins

David Hopwood was born on August 19th, 1933 in Kinver, Staffordshire, but he and his family moved south to Havant in Hampshire when David was a toddler, as his father, who worked for the Inland Revenue, was posted to their Portsmouth office. Nowadays, Havant is part of the urban sprawl around Portsmouth, but then, it was a market town of some 8,000 souls, where the surrounding countryside was easily accessible, and small boys could go adventuring in the woods and fields.

Education was greatly valued in the Hopwood household. In his spare time from the tax office, David's father Herbert, a working class Yorkshireman from Hull, took an external University of London economics degree, and then a law degree, finally being called to the Bar, although he never practised. Before parenthood intervened, David's mother Dora, the daughter of a painter and decorator from Leicester, had been an English and French teacher, also with an external degree from London University. Dora and Herbert were pleasant, easy to talk to, and ran an argument-free household with a liberal, left-leaning philosophy, but they were both quietly determined that their two children,

David and his older sister Joan, should be academically successful and go to university. Accordingly, the house was full of books, and Joan and David were strongly encouraged to read them.



David and Joan on the lawn of their house in Havant, July 1938. Some of their father's DIY is evident as concrete sundial, bird bath and path round a fish pond.

Dora was keen on botany and astronomy, and although the latter never interested David, he fell in love with the countryside on the long walks that he and his mother and sister took together. It was during a blackberrying expedition to the Hampshire Downs that the seven-year-old David watched Portsmouth being bombed in one of the daylight raids at the beginning of the Second World War. Perhaps because he was so young, his strongest memory of this event is not fear, but desolation that Handley's, the best toyshop in Portsmouth, took a direct hit and all the wonderful stuffed animals and ride on cars went up in smoke.

In January 1941, as the bombing of the South Coast intensified, David's parents decided to evacuate their children, and found them places at Wennington School near Kirby Lonsdale in Lancashire. Wennington was an unorthodox choice, even by today's standards. It was a self-governing community following the principles laid down by the reforming educationalist A.S. Neill that children should not be force fed knowledge, but be allowed to discover things of their own volition, free from adult coercion. Unfortunately,

at Wennington this laudable theory translated into Just William-esque anarchy, with David, the youngest boarder, being subverted by some older boys into a tiny but enthusiastic hooligan. Arriving for an Easter visit, Dora found her son wearing an eye bandage due to an injury sustained whilst throwing darts at the panelling in the dry-rot-ridden ballroom. Both children were re-evacuated back home, where the Luftwaffe were judged to represent a lesser threat to their safety.

David and Joan with their mother and her parents, Nicholas Grant and Mercy Grant (nee Cook).

Once back in Havant, Dora decided that she'd home school her two children, and so David and his sister grew up very much as a unit, rather separate from the other local children. Joan, more outgoing than the shyer David, was chief instigator of their extracurricular activities. It was Joan who in 1944 arranged for them to volunteer on the local farm, where she and David helped look after the cows; David may well be the only knight of the realm and fellow of the Royal Society who can milk a cow by hand.

David liked the rural life a lot, and spent as much time as he could helping out on the farm, especially in the summer holidays. It spoke not only

to his love of natural history, but to an intensely practical streak in him, which was also fostered by working with his father on DIY projects, something they both enjoyed greatly. However, it was also becoming clear that both the young Hopwoods, by then attending the local grammar school, were academically gifted. Joan was bumped up into a class of older children, where David joined her, despite being 17 months her junior; it is a tribute to their upbringing and characters that they managed to stay friends, albeit competitive ones, when David started to regularly beat his sister to come top of the class.

Shortly after the war, David's father was transferred from Portsmouth to Manchester, and the family moved to Lymm, just south of the Manchester Ship Canal. David and Joan went to Lymm Grammar School, which despite not having a great academic reputation, was close enough to home that Dora could feed them lunch, avoiding the awful post-war school dinners. Luckily for them, the school had recently acquired some very good staff, as it offered the valuable lure of married accommodation, something that was then in very short supply. As a result, some of the teaching, especially of science and languages, was very good. After an initial period of being bullied for being too swotty, David's schoolmates realised he was actually rather useful as he let them copy his homework; by far the youngest in the class, he became something of a mascot.

One of Lymm's new recruits, J.K. "Jake" Newman, was an enthusiastic and charismatic biology teacher, with an exotic Gloucestershire accent, bohemian floppy hair and a sideline in anecdotes about the tank corps. All of this reinforced David's existing bias towards natural history, especially as biology seemed still to be in a very exciting discovery phase, where new insights were far more accessible than in the other sciences. As he didn't like blood and dissections, a career in medicine or veterinary science was not of interest (the less squeamish Joan went on to become a vet); instead, a job that combined being outdoors with doing life sciences seemed the perfect mix.

In 1946, whilst waiting for the main feature to start at the local cinema, David stumbled across an eminently suitable career possibility. In those days, instead of the modern diet of adverts, trailers and junk food,

films were preceded by a newsreel, and the one on offer that day was a short documentary about the work of the newly established National Agricultural Advisory Service. An offshoot of the Ministry of Agriculture, Fisheries and Food, the NAAS's purpose was to help farmers take advantage of the newest agricultural research, and to advise about how best it could be practically applied to increasing food production; this was of extreme importance in the harsh post-war rationing period, when food shortages were a frequent reality. The combination of science and farming seemed perfect.

David's parents approved of his plan - both greatly respected intelligence but felt that it should be applied to something useful – and he and his mother set about finding the best way to prepare him for a job at the NAAS. Dora, even by today's standards, seems to have been a particularly enterprising mother. After some research, she wrote to the Professor of Agriculture at the University of Leeds, and took David across the Pennines to get some careers advice. Professor McGregor, told them that agriculture as an academic discipline was on its way out; the best route for David would be to take a science degree and then follow it up with a postgraduate diploma in agricultural science.

By this point, Lymm Grammar School had noticed that they were harbouring the most academically gifted pupil they'd ever had. David had taken his School Certificate (the equivalent of GCSEs) at the age of 13 instead of 16, coming top of his class, and was well on the way to the slew of distinctions he would obtain in the then equivalent of A levels. His teachers suggested that if a science degree were required, David stood a good chance of being the first Lymm student in living memory to read Natural Sciences at Cambridge.

The only route into Cambridge at that time was to take a college entrance exam, a process, given the school's inexperience, that David would have to navigate almost entirely unaided. Dora, resourceful as ever, fixed up an appointment with F. Hanly an Agriculture Department don at Cambridge, who suggested that David apply to St John's, his own college. Having tried a few practice papers, again obtained by Dora, the 17-year-old David set off by

himself for Cambridge in the winter of 1950 for his interview. The process comprised written papers, in Botany, Zoology and Chemistry in David's case, practical exams, and then, for those who were still in contention, an interview. David's interviewer, the organic chemist Peter Sykes, was unsurprisingly not familiar with Lymm Grammar School, but clearly impressed by David's drive and resourcefulness. This, combined with his performance in the entrance exams, led to St John's offering him a major named scholarship, which carried with it a small bursary.

David with his father in the Lake District, around 1950.

David seems to have been refreshingly unaffected by all this academic success. He knew that he stood out at school, but thanks to his mother was never allowed to be cocky about it. He stood firmly rooted in common sense and practicality, counterbalancing his school life with farm work and a spot of bricklaying and woodworking with his father. Dora and Herbert had taught him to do things to the best of his considerable ability, and this solid grounding was to stand him in good stead in the years to come.

After his scholastic triumph, there seemed little point in staying on at school, so David resolved to spend the remainder of his time before going up to Cambridge working for the local farmer. He was a little nervous of what his newly assigned tutor would think of this, but he'd lucked out; Ted Miller, a renowned mediaeval historian, was the son of a farm steward from Northumberland, and definitely approved of anyone with leanings towards the land. He gave David his heartfelt approval to get down to the rural life, so a happy few months ensued, with David mucking out cows and clearing pastures in the company of two Irish farm workers, who generously shared

their communal tea and sandwiches with him, and amazed him by their impressive capacity for lunchtime pints.

In autumn 1951, David started his Natural Sciences degree, taking modules in Botany, Zoology, Geology and Biochemistry, all of which would set him up perfectly for a career in agricultural science. Despite his shyness, new surroundings had never been a problem for David before, but the extreme switch from Lymm to Cambridge was daunting: 'The first term I was a bit put off because there were all these public school types. I'd never met people like them before, and I felt quite inadequate', David recalls. 'In fact, by Christmas I was quite down'. However, a dose of home comforts seems to have done the trick: 'I don't think I did anything to officially get over it,' he says, 'but by the time I went back in January I'd realised it was all hot air, and then I was fine.'

Once he'd settled down, David realised that he could more than cope; he was used to working hard, and conceptually, found the courses quite easy. Cambridge was clearly a good place to be, but the quality of the teaching was extremely variable; the nadir was one of the biochemistry lecturers, who would show up late and drunk for his morning class, read from the standard textbook for half an hour, and then lurch out again. However, there was one particular lecturer who caught David's attention. Harold Whitehouse, a *Neurospora* geneticist and moss expert in the Botany School (whose father Arnold had coincidentally been a master at Lymm Grammar School fifty years previously), was soft-spoken and the reverse of charismatic, but his lectures were enthralling, featuring the most recent discoveries in genetics, including, in David's final year, Watson and Crick's elucidation of the structure of DNA. David admits that he paid less attention to the DNA story than he might have done, but the excitement and potential of genetics, which he'd never encountered before Cambridge, fascinated him. Rather than pass on the discoveries of others as a farm inspector for the NAAS, it seemed a lot more satisfying to make some discoveries himself, so David abandoned his original career plans and approached Whitehouse about the possibility of doing a PhD. Whitehouse, who no doubt knew that he was dealing with one of the star students of the 1951 Natural Sciences intake (David eventually got the top First in Botany), readily agreed to take him on.

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Chapter 3

Cambridge PhD

Genetics in 1954 was in a very different place to where it is today. It was only ten years since Avery, Macleod and McCarty had shown that the genetic material was DNA. Watson and Crick might have just published an interesting theory about how DNA replicated, but it was still just a theory, and nobody had a clue how the information in DNA was encoded, or how cells turned that information into proteins (which themselves had only just been shown to comprise linear chains of amino acids). So genetics had no molecular component at all. Classical geneticists studied how inherited traits passed from parents to offspring by doing mating experiments, and were therefore totally dependent on sex, the more the better, preferably accompanied by a short reproductive cycle. Therefore, the fruitfly *Drosophila*, the bread mould *Neurospora crassa* (which could reproduce both sexually and asexually, and could furthermore be easily mutated), the laboratory mouse, and plants, especially maize, were the workhorses of genetics. Genetic mapping consisted of constructing linkage maps based on the frequency of segregation of particular traits, and used the statistical methods developed by RA Fisher, the red-headed, short-sighted, irascible father of biostatistics, who was the

incumbent Professor of Genetics in Cambridge.

The business about sex had meant that until recently, bacteria, which were thought to only reproduce asexually, had been excluded from genetic analysis. This changed in 1946, when Joshua Lederberg and Edward Tatum showed that *E. coli* bacteria were capable of genetic recombination: if two different mutant strains, each unable to grow on minimal medium were mixed together, wild-type colonies were observed, which could only have arisen by the mutants recombining to mend their separate deficiencies. So bacteria had sex, as they could exchange genetic material, but it turned out to be rather confusing sex. Different species had different habits, and none were remotely like the eukaryotic mechanism. Transformation involved chunks of naked DNA invading new cells, and transduction required the offices of the bacterial viruses known as bacteriophages. Conjugation, as shown by the Irish bacteriologist Bill Hayes in 1952, was the closest relation to eukaryotic sex, as it needed donor and recipient bacterial partners, but the resemblance ended there: a small tube formed between the happy couple, and some or all of the donor chromosome was transferred through the tube into the recipient cell, where it recombined with the recipient DNA to eventually generate new haploid offspring.

David, with his interest in genetics, might have been predicted to apply for a PhD with Fisher, but there was a perception that only astonishingly good mathematicians could become Fisher acolytes. This was heavily reinforced by a series of lectures that Fisher gave to the second year undergraduates. As David recalls: 'the first lecture was very simple natural history, but the following Monday he went through all kinds of algebra that nobody understood, so very quickly most people dropped out. Fisher had glasses with lenses like the bottom of beer bottles, and lectured like there was no-one beyond the front row, which by then was true!'

Besides the maths issue, Fisher's brand of genetics seemed less compelling than what was on offer in the Botany department. Whitehouse and his fellow *Neurospora* enthusiasts had pioneered the use of microorganisms in genetic analysis, and building on this, the bacterial geneticists, now able

to exploit the rapid doubling times, huge populations, and haploid genomes of their chosen subjects, were making new discoveries hand over fist. They were in the vanguard of the revolution in biochemical genetics and molecular biology that was about to transform the life sciences, and the possibility of understanding the fundamental nuts and bolts of life that lay behind the theoretical genetics was too exciting to ignore.

PhD supervisors in the 1950s were rather more hands-off than their modern counterparts, so it was not Whitehouse but Lewis Frost, a University Demonstrator in the Botany department, who suggested to David an interesting idea for his thesis project: clearing away some of the thicket of ignorance surrounding the actinomycete *Streptomyces*, the source of the antibiotic streptomycin.

David had already come across antibiotics in 1947, when he'd been cured of a grossly swollen septic finger with the new wonder drug penicillin. In the same year, he'd vaguely heard about the Waksman lab's discovery of streptomycin, and the award to Waksman of the 1952 Nobel Prize in Physiology or Medicine, for his contribution to curing the scourge of tuberculosis, was a very recent event. But on reading Whitehouse's copy of Waksman's 1950 book 'The Actinomycetes: Their Nature, Occurrence, Activities, and Importance', complete with a Walt Whitman poem entitled 'The Compost', he saw why *Streptomyces* was such a suitable subject for a PhD project. Waksman, who had devoted his entire professional life to actinomycetes, summed up the situation perfectly: 'Notwithstanding an extensive literature dealing with the actinomycetes, many aspects of their nature and physiology... are still little understood. This is due to certain factors, not least among which is the confusion regarding their morphology, life cycles and systematic position.'

In a nutshell, Waksman, and the microbiological world in general, couldn't decide whether *Streptomyces* were bacteria or eukaryotes, because they were the same size as bacteria, but behaved a lot more like fungi. Unlike gut bacteria such as *E. coli*, *Streptomyces* grew as a collective, differentiating community of cells, with a complex life cycle involving vegetative growth, to create a filamentous mycelial network, then a reproductive phase where aerial

filaments rose above the mycelium and made spores. Although *Streptomyces*, in common with the rest of the actinomycetes, had cell walls that in structure and composition were more like bacteria than fungi, their behaviour was so fungus-like that they'd been assigned their own taxonomic group, a halfway house between bacteria and fungi. Given the buzz surrounding the bizarre nature of bacterial sex, and the growing realisation of the power of microbial genetics, it would be really interesting if *Streptomyces* were indeed some kind of missing link. To his excitement, David realised that given the state of the field, he stood a very good chance of solving this problem, and even better, being the first person to develop a way of doing *Streptomyces* genetics.

Life in the Botany Department was fairly slow-paced. David would cycle into work, and spend a typical day pouring agar plates, streaking out cultures and replica plating, looking at the results of previous experiments, and thinking what to do next, which sometimes necessitated ambling over to the library in the Pathology Department to read the bacteriology journals. Equipment was very simple, and kit that the department didn't have, such as a spectrophotometer for measuring the turbidity of cultures, could be accessed by another short walk to the "Bug Hut", the prefabricated home of Chemical Microbiology. This simplicity wasn't unusual for the time – the great Joshua Lederberg was said to have a rule that if an experiment required more than six Petri dishes and four pipettes, it was over-designed[1]. In fairness, there was an equipment budget, as David remembers: 'Every year a notice came round saying there was a bit of money for small equipment, so Harold would ask what we needed. We bought a stapler and some window blinds one year!"

David was the only person working on *Streptomyces* in the department, although there were other PhD students, including Robin Holliday, of Holliday junction fame, whose work on the corn smut fungus *Ustilago maydis* laid the foundations for his seminal discoveries about homologous recombination. Supervision was minimal – David summarises Whitehouse's approach as 'here are the *Streptomyces*, they may be intermediate life forms,

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1 Gaylen Bradley, biographical memoirs of the NAS: http://www.nasonline.org/publications/biographical-memoirs/memoir-pdfs/lederberg-joshua.pdf

see you in two years' time'. However, David wasn't fazed by his isolation, as he knew what he wanted to do – replicate the *E. coli* experiments of Lederberg and Tatum to see whether sex existed in *Streptomyces*. If he could show that genetic recombination occurred, he had a way of starting to map *Streptomyces* genes.

Lewis Frost had obtained some cultures of *Streptomyces* for David from a mate of his in Glasgow, and using the recipes in Waksman's book, David grew them up, seeing for the first time the beautiful azure colonies of *Streptomyces coelicolor*, the organism with which he was destined to spend the rest of his scientific life. In the mould *Aspergillus nidulans*, pigmentation had been used as a genetic marker, so David decided to concentrate his efforts on *S. coelicolor* in preference to the other non-pigmented species he'd received, figuring with the optimism of youth that even though he had no idea how one might do linkage mapping in *Streptomyces*, such a marker could one day be useful.

Settling the issue of whether *Streptomyces* had sex was almost ridiculously easy. David isolated the first two of the many *Streptomyces* mutant strains of his career, using the replica plating technique described by Lederberg and Tatum, in which, following mutagenesis, colonies are scored for their ability to grow on complete versus minimal medium; auxotrophic colonies, those mutated to lack the means for making an essential organic compound, cannot grow on minimal medium, compared to the wild-type, fully functional prototrophs. Having got his mutants and worked out they had lost the ability to make two different essential amino acids, David mixed them together, plated the mixture out, and waited. To his delight, there was a thin sprinkling of prototrophic colonies, the hallmark of genetic recombination, on the minimal medium; *S. coelicolor* was in business as a genetically tractable organism.

David didn't get very long to rest on his laurels. In July 1955, Nature published a paper from an Italian couple, Giuseppe Sermonti and Isabella Spada-Sermonti, who had used the same mixing technique as David to come to the same conclusions – that *S. coelicolor* was capable of sex. However, it

took a little while for David to find out: 'Nature would come in, but it would go straight to Professor Briggs's office, and it wouldn't get to the library for about a week. I suppose he read it but he spent a lot of time going through the job ads, which would be summarised and posted on the notice board. But Whitehouse came in one day and said that there'd been this article in Nature. I had to go over to the Biochemistry department to read it. Not only had they done the same thing but they'd also picked *S. coelicolor* for the blue colour, which they'd actually used as a marker.'

It was very discouraging, but after some despondency, David realised that in spite of the setback, he had some rudimentary ideas about linkage that the Sermontis didn't seem to have lit upon. He carried on with characterising mutants, and after devising a rather smart way of doing linkage mapping, had the meat of his PhD thesis sorted out. The 'two lines with six genes on them', as David summarises the next several years of hard intellectual labour, got him a research fellowship at St John's, together with a mini-thesis, typed up by a 'sort of' girlfriend, Brenda - a secretary in the Maths department - which would form the basis of his final thesis and first paper.

Having sorted out the sex issue, and got the linkage mapping going, the possibility arose of resolving the other big conundrum about *Streptomyces* - whether they were bacteria, fungi, or something in between. David was having lunch at The Mill pub one day when he was introduced by a mutual friend to Audrey Glauert, an electron microscopist working with Ernst Brieger on *Mycobacteria* at the Strangeways Laboratory on Worts Causeway. Thanks to a direct line into the nearby Ciba-Geigy factory in Duxford, where her twin brother Richard worked on Araldite, Audrey had developed a customised Araldite-based embedding resin that, unlike the standard methacrylate, didn't shrink and distort bacterial cells before they were thin sectioned for study under the microscope. Audrey was getting spectacular results using the new resin, and she was more than happy to take a look at some *Streptomyces* for David. Although David got the impression that Audrey 'spending all her time with this young squirt' was not exactly pleasing her boss, Brieger, she and David showed very quickly that *Streptomyces* didn't have a nuclear envelope, putting them squarely in the bacterial camp. Their joint work on the fine

structure of *Streptomyces* comprised the final chapter in David's thesis, submitted in 1959.

Despite the fact that he'd shown they were 'just' bacteria, and that he'd been scooped on his discovery that they had sex, the new Dr Hopwood was still an enthusiastic *Streptomyces* devotee, as they were clearly rather superior bacteria with a far more interesting lifestyle than most. Furthermore, David had succeeded in singlehandedly getting a new genetic system working, and in the process had become a hardline, card-carrying geneticist. The challenge ahead was therefore too good to refuse: producing a complete linkage map of *S. coelicolor* was really something he could get his teeth into, and the mutant strains developed in the process would be the tools with which the mysteries of *Streptomyces* development could be resolved. However, as with all newly fledged PhDs, David had a more pressing question to answer: where he should go next.

David with his long-term Cambridge roommate, Richard Lloyd, in the punt which they jointly owned, around 1956.

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Chapter 4

Italy & Glasgow

Five years previously, David had taken over from Lewis Frost as a University Demonstrator, which mostly consisted of running practicals for undergraduates. His contract was due to expire shortly, but Harry Godwin, who had succeeded Briggs as the new Chair of Botany, made it clear to David that there was no possibility of his progressing further in the department. Therefore, while he was considering his options, David took up an invitation he'd received the previous year from his recombination nemesis, Giuseppe Sermonti, to spend six months with him in his lab in Italy. In April 1960, he packed his Morris Minor full of *Streptomyces* mutants and drove to Rome, taking in the Camargue and the Mediterranean coast on his way.

The contrast between 1960s Cambridge and Rome could not have been greater. Federico Fellini's film *La Dolce Vita*, depicting a sybaritic city where physical beauty masked existential desperation, was released just before David's arrival, and the scientists of the Istituto Superiore di Sanità, where Sermonti had his lab, did their best to combine academic endeavour with a healthy appreciation of Rome's many distractions.

Lecturing at the Istituto Superiore di Sanitá, Rome, 1960.

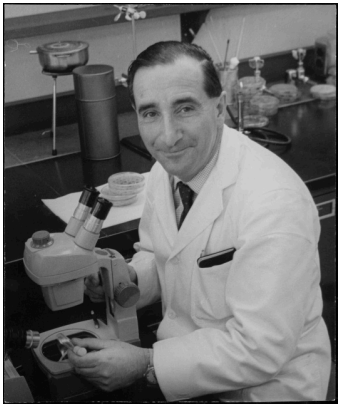
It was a lovely time. Everything stopped at 2pm for a long lunch, and post-lunch work was definitely optional. David spent many happy hours wandering around Rome and learning Italian in the company of his girlfriend Marisa Mancinelli and her brother Alberto, one of Sermonti's postdocs. At weekends, he was taken off for outings to the seaside and into the mountains, with everyone piling into the Morris Minor and Alberto's minute Fiat 500. David enjoyed himself so much that he went back again in 1961, this time concluding his trip by driving his trusty Morris Minor all the way to a meeting in Yugoslavia, no mean feat at a time when many of the roads were little more than dirt tracks.

As well as being something of a Roman holiday, David's time in the Sermonti lab was academically useful. Sadly, Sermonti eventually abandoned science and became one of Italy's foremost supporters of Creationism, but in those days, he and his coworkers were at the cutting edge of *Streptomyces* research, such as it was. For David, it was the first prolonged exposure he'd had to people whose primary scientific interest was *Streptomyces*, and who were approaching the organism from the point of view of its utility as an antibiotic-producing industrial microbe, rather than David's own more academic preoccupation with its development and lifestyle. The discussions with the Sermontis and their lab members about how *Streptomyces* might fit into the bacterial universe, and which of the lessons about bacterial sex learnt in *E. coli*

could be usefully applied to unravelling its genetics, laid down many useful trails David would follow in the future. There was a small literary benefit too; he and the Sermontis published a paper together about the potential of heteroclones, mixed colonies of parental and recombined genotypes, as mapping tools, Sermonti writing sections of the paper in Italian during night-time bouts of insomnia, and David translating his work into English in the daytime.

In the winter of 1960, shortly after his first Italian adventure, David saw an advert for a lectureship in the University of Glasgow Genetics Department. The Department was headed by Guido Pontecorvo, then one of the most influential and charismatic life scientists in the UK, and was well known as a hotbed of modern genetics. David knew it would be a stimulating place to work, so he applied, and was invited to interview.

David had briefly met Pontecorvo, universally known as Ponte, when he'd come to give a seminar in the Botany School in Cambridge, so he knew something of his reputation. From a prominent Pisan Jewish family, Ponte had fled Fascist Italy for Edinburgh in the late 1930s, where he'd done a PhD in *Drosophila* genetics. He took to his adopted country with gusto, adopting the Crawford tartan (following his great friend JBS Haldane's translation of 'Pontecorvo' into 'Crowbridge'), and becoming an enthusiastic Scottish country dancer, but after Italy joined the war on the side of Germany, he was temporarily interned on the Isle of Man. On his release, he was unable to return to his former life in Edinburgh, as it was considered too risky to have enemy aliens so near to the East Coast. Fortunately, he was rescued by the Zoology Department in Glasgow, and as part of the war effort, started working on lice and the *Penicillium* fungus, devising ways of mutating the latter to improve penicillin yields.



Ponte at the Bench

The penicillin work was halted after the government, fearing a German invasion, made a strategic decision to move penicillin research to the US, so Ponte turned instead to another fungus, *Aspergillus*, which turned out to be both tractable and genetically intriguing. In 1952, with his collaborators Alan Roper and Ted Forbes, he discovered the parasexual cycle: a rare spontaneous event in which non-sex (somatic) cells fuse together and generate offspring bearing characteristics of both parent cells, circumventing the need for mating. Ponte was far-sighted enough to propose that if somatic animal cells could be made to fuse in the same way, it would revolutionise human genetics, as linkage mapping could be done without breeding humans together, or searching family pedigrees for inherited disease traits. He was right, but it took decades before the human genetics field was technologically advanced enough to exploit his idea, and perhaps unfairly, his contributions have been largely forgotten.

In 1955, Ponte was appointed to the first Chair of Genetics at Glasgow University, but the longueurs of management were not to his liking; famously he ran the Genetics department with a part-time secretary and a waste-paper basket. Ponte also regarded lecturing as a distraction from research, and was not particularly good at it – David remembers that typically, 'he would stroll in, start talking at a tangent, and mystify the students considerably' – so the small amount of service teaching that the Genetics department was contracted to deliver was extremely onerous as far as its Chair was concerned. Therefore,

Ponte had decided to recruit a junior lecturer to take the burden from him, and it was this job that David had seen advertised.

Unknown to David, Ponte was extremely suspicious of Oxbridge-educated scientists, regarding them as mollycoddled, bumptious and overfunded, and not surprisingly, the lectureship went to an internal candidate, Bernie Cohen. However, David must have done something right, as he was offered and accepted a three-year position.

It rained constantly for David's first three weeks in his new country, but after this unpromising start, things definitely looked up. Ponte by now was heavily invested in developing human somatic cell genetics, but he encouraged David to carry on with *Streptomyces*. David was once more the sole *Streptomyces* person in the department, but he had a congenial lab-mate in the form of Bernie Cohen, and was increasingly convinced he'd made the right decision to move north.

Matters looked up even further when Bernie and his wife Moyra conspired to set David up with a blind date, in the form of their friend Joyce Bloom, who had just finished a PhD looking at lung cancer susceptibility in mice at Bernie's old stamping ground, the Institute of Animal Genetics in Edinburgh. Joyce, invited over for the weekend, remembers being told by Bernie that they'd have an addition to their outing to the cinema: 'Bernie said, "I hope you don't mind, but this terribly shy young man has just arrived from Cambridge, and we've invited him along too – is that all right?"' It was more than all right - David got over his shyness sufficiently to invite Joyce to the upcoming Highland Ball for a spot of Scottish country dancing, and matters moved quickly thereafter. After a whirlwind courtship, involving a lot of commuting between Edinburgh and Glasgow, sometimes carrying consignments of Joyce's spare mice for Bernie's experiments on albumen variants, David and Joyce got married the following year. With typical efficiency, David combined buying and presenting Joyce with an engagement ring with giving a seminar in her department in Edinburgh.

David on one of his first dates with Joyce on the Firth of Forth, Spring 1961.

Following their wedding, and after an unsatisfactory period trying to work in Edinburgh and live in Glasgow, Joyce gave up her scientific career in favour of supporting David's, which she'd decided, to David's slight bemusement, looked more promising than her own. She worked until three weeks before Nick, their first child, was born, but then, as both Hopwoods felt that children should be cared for by their parents if possible, remained at home thereafter.

Motherhood came as a bit of a shock to Joyce, as neither she nor David knew anything about babies, but looking back in 2016, after 54 years of marriage, Joyce says she never regretted her choice to put David's work before hers. And it's clear that the Hopwood partnership has been a vital ingredient in David's success: Joyce's energy and character, and the fact that she understood very well how science and scientists worked, meant that David had the support he needed not just to single-mindedly pursue his own career, but to build the *Streptomyces* community as an unusually close family. Joyce kept open house first for David's lab, and then for the wider *Streptomyces* world, welcoming everyone, cooking vast spreads of food, and tolerating hordes of scientists tramping through her home and her life. That she did all this whilst bringing up three children, and carving out an impressive career for herself in the voluntary sector, is an indicator of what a remarkable woman she is.

In addition to providing David with a life partner, Glasgow also supplied him with a scientific collaborator who'd remain with him for the rest of his career. After his temporary job had mysteriously solidified into a permanent post, Ponte suggested that David might like an assistant, and Helen Ferguson, then a very young junior technician, was delegated to him.

Helen was a local girl, who'd been hired straight from school into the University medical microbiology teaching labs at Anderson College. Whilst she got a good grounding in sterile technique as part of her training, the work was exceptionally tedious, so Helen started moonlighting in the Medical Mycology department, also based in Anderson College, to relieve the boredom. She was noticed by Ponte's lieutenant Ted Forbes, the chief technician in Genetics, who mentioned that 'there was a guy called David looking for a technician' and offered her the job. Helen accepted, despite not having met David, and fortunately, they got on.

Helen was a little dismayed when she started her new job: 'David shared a room with Bernie Cohen and they never spoke, so it was really, really quiet! I was used to working with a load of women doing media prep, and here I was in this silent room with two old men. I used to nip out for a cuppa so I could have a chat with normal people!'

However, the elderly (at that time in his early 30s) Dr Hopwood proved to be a good, if exacting boss, as Helen recalls: 'I really liked the work – I'd never heard of *Streptomyces* so David had to teach me everything, including about genetics, and he was a superb teacher. It was never a nine to five job though. David would write out a list of what to do, and I would work my way through it till I'd finished. Every day the list got longer – he had no idea how to run someone so he just piled the work on me - but I did it anyway. The ladies in the kitchens said I was ruining the job for someone else as I was working too hard!'

David, not surprisingly, has a slightly different take on all this: 'Bernie and I talked socially but usually on the way to and from lunch – we didn't talk

in the room as we were doing totally different things. And I had to keep Helen busy because she was very able!'

In 1966, the new University of Glasgow Genetics building (later called the Pontecorvo Building) opened, complete with the entertaining Health and Safety nightmare known as Paternoster lifts[2], and the increase in space meant that David could hire a masters student, Richard Harold. The group was joined shortly afterwards by two postdocs: Alan Vivian, who'd done a PhD in Reading looking at *Streptomyces* mutants, and Hans-Rüdi Wildemuth, an electron microscopist from Zürich.

By the mid-late 1960s, David, ploughing a rather solitary furrow as the only person in the UK, and one of only a few in the world working on *Streptomyces*, had made a large variety of auxotrophic mutants, and he and his fledgling lab were generating still more mutants, widening their screens to pick up loci essential for growth, and for supporting the organism's sporulating lifestyle. His original six markers had expanded to more than 100, and the first proper linkage map of *S. coelicolor* strain A3(2) was now finished.

This *tour de force* was beginning to attract attention within the burgeoning network of bacterial and phage geneticists closing the gap between the abstract concepts of classical genetics and the cellular reality of genes and proteins. It was an exciting and collegiate community, working at the interface between older, stuffier disciplines, focussed on rapid progress, and making fundamental discoveries. Due to Ponte's standing in this emerging field, Glasgow attracted a steady stream of visiting scientific hotshots. Although the majority worked on *E. coli* and *Salmonella*, there was definite interest in what David was doing; *Streptomyces* was so much more complex than *E. coli*, and

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2 Paternosters are a chain of small open compartments that move slowly and continuously round a vertical loop inside a building, in place of a standard lift. You step on or off at the desired floor, running the exciting risk of getting crushed, trapped or killed in the process. Helen recalls one of her only meetings with Ponte was when she jumped on top of him in the Paternoster whilst attempting to catch a compartment that was already part way past her floor.

working out how its genes drove its sophisticated lifestyle was a fascinating prospect.

It was through this community that David was invited to New York in February 1967 by Werner Maas, an *E. coli* person working at New York University (NYU) on biosynthesis of the essential amino acid arginine. Werner ran a biennial course on practical microbial genetics, and wanted David to teach a new *Streptomyces* segment, and also to spend some time in his lab. It seemed like a wonderful opportunity, so David and Joyce, supplemented by their two children, three-year-old Nick and 18-month-old toddler Jon, packed three suitcases and decamped to an apartment on Bleecker Street in Greenwich Village for six months.

Greenwich Village was definitely a big change from Glasgow. The scores of coffee shops and jazz clubs were inhabited by some of the coolest people on the planet, and Flower Power, the hippie movement opposed to the Vietnam War, was at its height; some of David's new colleagues were heavily involved in organising and attending anti-war marches, which appealed greatly to the Hopwoods' left-wing sympathies.

Whilst Joyce and the children explored their new city, David set to work in the lab, only slightly discouraged that he'd drawn the Roach Bench, where if you weren't careful you would find one of New York's finest *Periplaneta americana* snacking on your agar plates. Working in Werner's lab was David's first exposure to experiments involving radioactivity and other nasties, and gave him a new confidence about biochemistry that would come in useful in the future molecular biology universe he was to inhabit.

In June, the Hopwoods borrowed a tent and went on a roadtrip, distinguished by the fact that to begin with it rained almost continuously – they got as far as the badlands of South Dakota before the sun came out. Despite the unpromising start, the holiday turned into a wonderful trip over the Rockies, through the Navaho reservation and the Grand Canyon National Park, and back East along Route 66. And then it was time to go home, happily burdened with a little excess baggage – Joyce was pregnant with their last

child, Rebecca.

Helen, who'd been keeping the lab going whilst David was away, says that he had definitely loosened up when he returned; the lab took a much more informal turn, to the extent that she took the radical step of starting to address her boss as 'David' rather than 'Dr Hopwood'. It wasn't easy, though: 'Going straight from calling him Dr Hopwood to David was too hard', Helen recalls, 'so I called him Excuse Me for a whole year!'

Going to New York had broadened David's horizons in many ways, and the break had also given him time to think about his future. Glasgow had been a good experience, but it wasn't perfect; the university was very much a nine to five place, Ponte had got fed up with running the Genetics department and was preparing to leave, and David and Joyce had some doubts as to whether Glasgow in the sectarian 1960s was where they wanted to bring up their children. So when David got a postcard from an old friend alerting him to an advert for a professorship in Norwich, he was very interested indeed.

The job, as the new John Innes Professor of Genetics, was advertised as a joint appointment between the University of East Anglia (UEA) and the John Innes Institute (JII), one of the most venerable plant institutes in the UK. The JII had recently moved from its former home at Bayfordbury in Hertfordshire, and complete with a new Director, Roy Markham, was currently squatting in temporary accommodation near the recently built university campus. The glory days of the JII, when William Bateson, who coined the term 'genetics' was its Director, were decades in the past, and in its present incarnation, it was a sad, stunted shadow of its former self. However, David could see there were many positive things about the job; he'd be running a new, well-found department at the Institute, with pretty much a free hand to recruit like-minded colleagues, and he'd also be part of UEA, then a hotbed of radicalism that also boasted one of the first integrated Schools of Biological Sciences in the country. Norwich would also be a great place to bring up a family. He applied for the job, and despite being only 34, was offered it.

David is keen to dispel any illusions about the reason he was appointed to be one of the youngest professors in the country – he claims he got the job as 'very few people applied'. Applying for a professorship at such a relatively early point in his career could also be considered ambitious, but again, David doesn't see it as such; he says he's never thought of himself as ambitious, 'although perhaps some other people have'. Rather, becoming a professor 'seemed OK', and allowed him the independence to continue doing his research, together with the chance to expand his teaching commitments – he'd discovered in Glasgow that he rather enjoyed lecturing, and was good at it.

Once the decision to move was made, one of David's most important tasks was to persuade Helen to come too. By this time, Helen had morphed from a junior technician into an essential part of David's lab life, and a smooth transition from Glasgow would be far easier if she were there to help. It was a lot for her to contemplate, as she was still living at home with her parents, and moving out, let alone changing country, would be a big step. Although Norwich sounded like the back of beyond to Helen, the opportunity seemed too good to miss; she could simultaneously keep on working for David doing stuff she enjoyed, whilst building what was turning into a very satisfactory career. With Helen on board, and the rest of the lab signed up too, the Hopwood lab and family moved down to Norwich during the autumn of 1968.

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Chapter 4

Norwich

David's first day as Professor of Genetics at the John Innes Institute was something of an anticlimax. He and Helen showed up bright and early on the last Monday in August, to find the lab deserted: used to the Scottish calendar of public holidays, they'd failed to realise it was August Bank Holiday, and everyone but them had taken the day off. Undeterred, they rearranged the furniture to their satisfaction in the temporary hut they'd been assigned, and set to work shortly afterwards.

Working conditions were not quite what they should have been. There were no microbiological safety cabinets, and as the lab was basically camped in the middle of the countryside, fungal contamination from the surrounding farmland was really bad. The extremely hard Norwich water was so different from Glasgow's that they had problems making media for sporulation, and had to import Glaswegian water for a while. And there were no stores and no proper media facilities, just a little bench autoclave. Helen and David ended up designing a media kitchen modelled on the Glasgow facility set up by Ponte, and Helen supervised it, hiring and training the staff. The hut

problem was eventually resolved on a particularly hot day one summer, when David was taking one of the original John Innes family around his empire: Lt-Col Jimmy Innes, Chair of the Trustees of the John Innes Foundation, was somewhat startled to be introduced to Alan Vivian, David's postdoc, stripped to a scruffy vest and sweating profusely; clearance for a decent building for the Department of Genetics was received shortly thereafter.

The surroundings in which the lab found itself were at least partly matched by the atmosphere at the Institute. The JII had already been decimated by the time it moved from Bayfordbury, and there was a definite feeling that all the good people had left. The staff were civil servants, many of whom worked short days and always left early on Fridays. There were no PhD students, and everyone had a job for life. Whilst the JII Director Roy Markham's Department of Virus Studies was in a much better state, having been uprooted with Markham from Cambridge, David soon realised that he was facing an uphill struggle if he wanted the JII to be a place where he could do good discovery science.

Part of the problem was Markham himself. Whilst ultimately a good Director who had the interests of the JII at heart, Markham was a prickly character who had strong negative opinions about many subjects[3], including botany, universities, the United States, strange foreign accents, and, it appears, the safety of small children: Joyce remembers him advising Jon and Nick that 'if you take stones and wrap them round with sand it's like a snowball you can throw at people'. Despite the JII having moved to Norwich to be close to a university, Markham was opposed to any links with UEA; David and Roy Davies, the newly appointed Professor of Applied Genetics, had to be very persistent to forge the close bonds that exist today, in the face of their Director's total opposition.

Matters came to a head shortly after David arrived, when the Institute had a quinquennial review. The Visiting Group and their Chair,

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3 REF Matthews (1989) Roy Markham: Pioneer in Plant Pathology. Annu Rev Phytopathol 27:13-22

Kenneth Mather, savaged David, saying that his work on *Streptomyces* was inappropriate in an institute of plant science, and condemning him for a lack of vision. It seems incredible that a group of 'experts' could dismiss a soil bacterium as an irrelevance to agriculture, and more broadly, fail to see that David's expertise in microbial genetics could be used to drag the rest of the Institute into the modern world, but in the 1960s, much of the science establishment had yet to appreciate that microbial genetics and molecular biology were anything but a minority interest, and similar views held sway in many places.

Joyce remembers this time as the worst in David's whole career – 'it was a dreadful situation to be in, and it really did upset him. People had only ever accepted him as a thoroughly good thing before this'. All through school and university and in Glasgow, he'd been able to prove himself through his academic achievements, and now he was being unfairly criticised for reasons that weren't anything to do with scientific merit. David had to regroup, and to rethink a lot of things. Previously, he'd been able to make his way quietly through life, letting his actions and achievements speak for themselves, but now it was clear that if he wanted to be successful in Norwich, he'd have to behave differently - become more politically savvy, anticipate attacks, and learn how to defend himself.

David's campaign to refute the Visiting Group's criticisms was characterised by its clarity, thoroughness, and total success. He managed to get Ponte onto the Governing Council of the Institute, and also enlisted the support of Bill Hayes, who'd discovered the mechanism of conjugation in *E. coli* and was a star of the genetics field, to convince the less knowledgeable members of Council that working on the microbes that interacted with plants was as relevant and important as working on the plants themselves. In the lab, rather than continue solely with *Streptomyces*, David decided that the best way to ensure he had a future at the John Innes was to pick some examples of where microbes and plants did interesting things together, which would simultaneously play to his strengths in microbial genetics, and the Institute's expertise in plant research. In addition to continuing his *Streptomyces* work, he chose to focus on the symbiotic bacterium *Rhizobium*, vital for fixing

nitrogen in the roots of leguminous plants, *Agrobacterium tumefaciens*, about to be developed as a genetic engineering vector for strain improvement in plants, and plant mycoplasmas, strange wall-less bacteria that could only survive within plant cells. He hired excellent people to develop these topics and by the time the next Visiting Group showed up, this strategy had yielded enough scientific success stories that opposition to harbouring microbial research at the JII fell away.

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The next decade was pivotal for David, and for *Streptomyces* research. Step by step, with the meticulous care and attention that he brings to every project in his life, David built a *Streptomyces* community whose hub was the JII, but which spread far into the worlds of both academia and industry. He achieved this by turning *Streptomyces*, slowly but surely, into a full member of the molecular biology club, with the potential to find and exploit all the genetic riches it had to offer.

In 1972, Paul Berg kickstarted the genetic engineering revolution by cutting the DNA of the monkey virus SV40 and the bacteriophage λ with the restriction enzyme *Eco*RI, and ligating the two fragments together to make the first recombinant DNA molecule. Type II restriction enzymes, able to cut at specific DNA sequences, had just become available (the first, *Hind*II, had been purified by Ham Smith in 1970), and the possibilities of using them to move foreign DNA into new hosts was immediately recognised. Berg stopped short of putting his hybrid molecule back into a cell, but in 1973, Herb Boyer and Stan Cohen cloned a kanamycin resistance gene into an *E. coli* plasmid (plasmids are small pieces of DNA able to replicate independently of the bacterial chromosome) and transformed the resulting hybrid into an *E. coli* host. The following year, they spliced eukaryotic DNA from the frog *Xenopus laevis* into their plasmid vector, and showed that not only was the construct stable in *E. coli*, but it replicated and made RNA derived from the frog gene they'd introduced. The molecular biology world was electrified: they would finally be able to isolate individual genes, study them in a defined system, mutate

them, purify their products ... the list was endless and the possibilities opening up were mind-boggling. Unless it wanted to risk returning to the backwater from which it was currently emerging, the *Streptomyces* field needed to get in on the act. Fortunately, David had a head start, as his lab had the genetic evidence that S. *coelicolor* had plasmids, the essential vectors for genetic engineering.

All the work David and his lab had done on constructing a linkage map of S. *coelicolor* had relied on mutants being able to recombine their genetic material, so how this bacterial sex happened, and how its efficiency could be improved, was a topic of some interest. *E. coli* plasmids, which had been known about for some time, are required for bacterial sex – only donor strains that possess the F factor plasmid can mate with recipient strains, which lack the factor - and so hunting for plasmids in S. *coelicolor* had been an obvious thing to try.

By 1970, David's postdoc Alan Vivian had the first genetic evidence that mating in S. *coelicolor* was also plasmid-dependent, calling the presumptive S. *coelicolor* plasmid he'd found SCP1. The SCP1 activity did all the right things a sex factor should – when a strain had it, it was able to mate with a recipient strain that lacked it - but SCP1 itself proved impossible to isolate by the standard techniques of the time (all the protocols for purifying plasmid DNA relied on it being small and circular, and SCP1 turned out to be very large and linear; it wasn't isolated until 1991). However, a second sex plasmid, SCP2, had been discovered by Hilde Schrempf in Werner Goebel's lab in Germany, who made a short visit to David's lab and taught them a lot about rigorous molecular techniques. SCP2 was small and circular, and studying its properties and genetics seemed like a very good topic for David's new PhD student, Mervyn Bibb, a UEA undergraduate who started in the lab in autumn 1974.

Mervyn Bibb lecturing in Kyoto, 1982

Merv had been spotted both by David, who'd noticed him whilst giving undergraduate lectures, and also by the JII football team, for whom he'd been illegally playing since his first year at UEA. As David's genetics lectures had been superlatively good – engaging, enthusiastic and more than conveying the excitement of the work he was describing – Merv was delighted when David offered him a PhD to properly characterise SCP2, with the possibility of spearheading the quest to get cloning working in *Streptomyces*.

The Hopwood lab Merv came into was a very good place to be. Now housed in the luxurious surrounds of the new John Innes Institute building, finished in 1973, it was small, with an eclectic mix of characters, ranging from a Brummie steampunk through to a Civil War re-enaction fanatic, whose occasional spats were smoothed down by Helen, still the mainstay of the operation. David regarded Helen as his eyes and ears: 'Helen made a point of never telling tales but through her I got to know things I'd never have found out otherwise,' he says. 'Helen would smooth things out, or perhaps warn me about something.'

Merv remembers David as an inspiring PhD supervisor whose office door was always open, and who was always available for a chat about science: 'He was very intense, always sharp, but he wouldn't ever put people down and embarrass them, even if you could always tell if he thought you'd asked a bad question! He was pretty hands off, but he had a good way of cajoling you

The King of Genetic Engineering, Stan Cohen, showing his musical side. Stan came on sabbatical to David's lab from Stanford in 1976.

into his way of thinking – he'd plant ideas not by trying to tell you what you should do, but by making such reasoned, sensible arguments that you'd find yourself nodding along! And generally, he'd be right.'

With Merv in place, the *Streptomyces* cloning project got another boost from none other than Stan Cohen, king of genetic engineering, taking a six-month break from the perpetual sunshine of Stanford for the more variable climate of Norfolk. Part of David's vast network of contacts, Stan was one of a succession of high profile sabbatical visitors attracted to the JII by David's reputation. Talking to Stan on a daily basis helped convert the theoretical possibility of cloning into a determination to get on and do it; the very first restriction digest of a *Streptomyces* plasmid – cutting it with *Eco*RI and *Hind*III –happened while Stan was around.

Despite Stan's influence and Merv's keenness, there was still a big obstacle to overcome before anyone could contemplate a *Streptomyces* cloning experiment: there was no natural competence for transformation, the process of naked DNA uptake, in *Streptomyces*. Unsurprisingly therefore, Boyer and Cohen's method of getting plasmid DNA into *E. coli*, which relied on subverting the *E. coli* transformation process, was a bust in *Streptomyces*.

Fortunately, Helen and David, helped out by Merv and Stan, were busy with another project that would solve this problem: protoplast fusion.

Normally, the rigid bacterial cell wall acts like a corset, protecting the fragile membrane enclosing the contents of the cell, and excluding unwanted macromolecules such as DNA. In 1974, Masanori Okanishi and his coworkers in Japan showed how to remove the *Streptomyces* cell wall without allowing the contents to burst out of the membrane, and most importantly, how to persuade the resulting jelly-like bags, known as protoplasts, to resynthesise their cell walls and return to their normal life as a mycelium. If their methods could be combined with a protocol developed in 1976 by labs in Hungary and Paris, to fuse *Bacillus* protoplasts, it seemed likely that *S. coelicolor* protoplasts could also be made, fused, and reconstituted. If the protoplasts were from different strains, it would be a very rapid and efficient way of mixing their DNA together and getting recombinants. And perhaps, if a bit of extraneous DNA like a plasmid was dropped into the mix too, it might get carried along for the ride.

Helen and David were saved a great deal of work by the fortuitous intervention of Ponte, who happened to be visiting the JII for a Council meeting on the day of the first experiment. Ponte, by now based at the Imperial Cancer Research Fund labs in London, had been busy optimising methods for fusing animal cells, based on work on plant protoplasts that he knew about through his hobby of studying and photographing alpine plants. Ponte told David he should abandon the *Bacillus* protocol in favour of the animal cell one he'd developed, and it turned out that *Streptomyces* protoplasts fused and reconstituted far better using Ponte's method than any other tried later.

The paper describing how protoplast fusion of two different plasmid-free, and hence recombinationally inert, *Streptomyces* strains could generate extraordinarily high frequencies of genetically distinct offspring came out in Nature in 1977 [4] . It was a milestone in *Streptomyces* research, not just for

4 DA Hopwood, HM Wright, MJ Bibb and SN Cohen (1977). Genetic recombination through protoplast fusion in *Streptomyces*. Nature 268:171-174

its potential as a genetic engineering tool, but because it went to the heart of a problem that had vexed the pharmaceutical industry for many years: the dearth of methods for rapid industrial strain improvement of antibiotic-producing species of *Streptomyces*. Using the Hopwood lab methods, or a similar protoplast-based approach developed independently by Dick Baltz at the Eli Lilly Company, it would now be possible to scramble up the genes of promising strains to yield new and better recombinants, able to make products more efficiently, in just a few months, rather than years. Frustratingly, it's hard to measure the usefulness of the technique, as profitable methods of strain improvement are too commercially sensitive for companies to brag about, but it's clear that augmented versions of protoplast fusion continue to be used today to great success.

With protoplast fusion in the bag, the methodology was adapted to allow exogenous plasmid DNA to be scooped up as the protoplasts reconstituted, by tweaking some of the experimental conditions; a process Merv remembers as initially laborious but pretty straightforward in a specialist *Streptomyces* lab. The important issue of how to tell which cells had taken up the plasmid was also solved by Merv, who noticed that spores containing plasmids could be spotted by the appearance of pock marks when they were plated onto a lawn of plasmid-negative *Streptomyces*. His paper, 'Transformation of plasmid DNA into *Streptomyces* at high frequency'[5] was published in Nature almost exactly a year after the one describing protoplast fusion.

Merv had a pretty decent CV for a PhD student, and was clearly a very good thing, so it wasn't entirely surprising when Stan Cohen invited him to come and do a postdoc in Stanford. Having figured out where Stanford was ('I had to look on a map to find it; I was pleasantly surprised!'), Merv accepted, and headed out to California with his new wife Maureen. Although he'd been expecting to start a new scientific life working on 'flu virus, circumstances conspired against him; when a collaborator left him in the lurch, Merv found

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5 MJ Bibb, JM Ward, DA Hopwood (1978). Transformation of plasmid DNA into *Streptomyces* at high frequency. Nature 274:398-400

himself back in the world he'd just left, on a project with a fellow postdoc, Janet Schottel, to set up a *Streptomyces* cloning system, using versions of the plasmid vectors he had already developed as part of his PhD.

Back in David's lab in Norwich some rather similar experiments were going on, featuring David's postdoc Charles Thompson, helped by Judy Ward. Both labs decided to try to clone *Streptomyces* antibiotic resistance genes by a random 'shotgun' approach: total genomic DNA from various *Streptomyces* species were chopped up by restriction digestion, and then ligated into linearised plasmid vectors, which were then used to transform protoplasts. Recombinant strains containing vectors that had picked up a resistance gene would be able to grow on medium containing the corresponding antibiotic; methylenomycin A in Stanford, and neomycin and thiostrepton in Norwich. The experiments worked, with Merv and Janet publishing their results a few months ahead of Charles and Judy[6,7] .

All these technical advances spread around the academic labs involved in *Streptomyces* research by the usual methods of conferences, word of mouth and visiting to and fro. Working on the principle that sharing information would lead to more people getting hooked on *Streptomyces*, David had always adopted a policy of giving advice, and almost all reagents and protocols, to pretty much anyone who asked for them, and the lab frequently hosted visitors learning techniques from Helen and the other *Streptomyces* experts at the JII. Academics could have all this for free, but for industry, there had to be a different deal. *Streptomyces*, especially in their new incarnation as molecular-biology-ready organisms, had always been of great interest to industry, with its need for strain improvement and desire to find new *Streptomyces*-derived medicines, and the strategy that David developed to deal with this interest merits a quick diversion, because it was such a good idea.

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6 M Bibb, JL Schottel, SN Cohen (1980). A DNA cloning system for interspecies gene transfer in antibiotic-producing *Streptomyces*. Nature 284:526-531

7 CJ Thompson, JM Ward, DA Hopwood (1980). DNA cloning in *Streptomyces*: resistance genes from antibiotic-producing species. Nature 286:525-527

David's engagement with industry stretched back to his time in Glasgow, when he'd been approached for advice by Pfizer. After David moved to Norwich, and word spread about his expertise and generosity, more companies got in touch. Instead of locking himself into restrictive agreements with a few companies for large sums of money, David hit upon the unique idea of the *Streptomyces* Club, whose members would get help from the JII in exchange for an annual donation, as he relates: 'Over the decades I recruited about twenty different companies – typically, they would approach me and say how about helping them with strain improvement, and I would tell them about the club. I made sure any contract was very minimal – I wasn't afraid of legal stuff because of my father being called to the Bar – and the sums involved were small enough that a fairly junior manager could sign up without having to clear it with senior management. It meant that I wasn't in the pocket of one company, as I was talking to all of them. There was no exclusivity.'

The club was a roaring success: 'There was half a million quid in the fund at one point,' David says, 'we funded all the PhD students in the *Streptomyces* group and during the recession in the 1980s were funding just about all the students in the Institute. Students could also stay on for a further year after they wrote up too, and I could fund postdocs without any trouble.' From the other side of the fence, people were equally enthusiastic. Iain Hunter, ex Pfizer, and now at the University of Strathclyde, recalls the halcyon days before Material Transfer Agreements and tech transfer offices: 'We were taking preprints of papers, we were taking plasmids, we were taking constructs... The rapidity with which we were able to grab it and exploit it was just amazing.'[8]

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In 1979, in the midst of the cloning excitement, David's contribution to the global and national genetic landscape was recognised by his election as a Fellow of the Royal Society at the relatively young age of 46. He had turned

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8 Iain Hunter, quoted in 'Economic Impact of *Streptomyces* Genetics Research', BBSRC, 2010

Streptomyces into tractable experimental organisms, in the process becoming the world authority on them, built a thriving genetics department at the JII by attracting some of the best young microbial and plant geneticists around (one of these was Merv Bibb, recruited back from Stanford; David had a talent for hiring very good people and letting them get on with it), and was generally a great example of a scientific good citizen; as an illustration of the latter, David was a leading light in the Genetics Society (he started off as Junior Secretary and eventually became President in the 1980s) and did more than his fair share of lecturing and examining. As he says, 'I saw myself as an academic who was doing genetics, so all this extra stuff was an important part of what I was committed to doing – what my career was. I didn't resent it at all'.

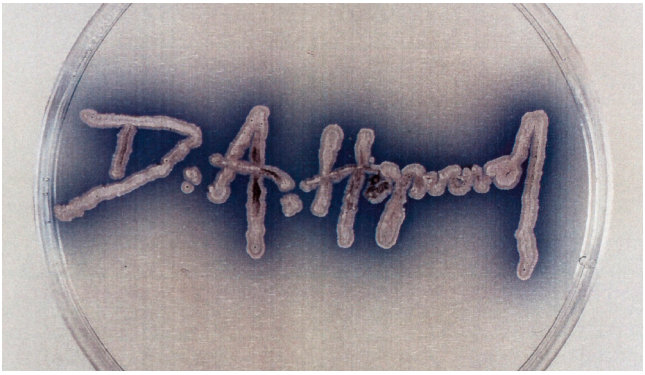
It had suited David to be the pre-eminent person in his field, not because he enjoyed control for its own sake, or required the recognition, but because he was interested in getting things to work well. It was a pattern that he followed for his whole career – his involvement in everything he did was about making it work, not enhancing his own self-image. He enjoyed being organised and wasn't intimidated by the prospect of organising things and people, so he was perfectly willing to take on challenges as long as they weren't impossible. And he brought a great positivity to everything he did, never wasting time on doing things by halves. His enthusiasm manifested in a pragmatic, practical determination to move forward as quickly and efficiently as possible. And if things didn't quite go as he wanted, he didn't brood: 'If he has a setback, his wife Joyce says, 'he frets about it for a little bit, and then he finds himself a reasonable explanation and moves on. He doesn't have major fallouts with anybody. He can be moody... things that upset his equilibrium make him moody but he shakes it off fairly quickly'.

As people in his orbit soon found out, David also had impressive people-managing skills, reaching decisions by persuasion and consensus. 'I've never been argumentative or gone in for slanging matches', he says, 'I don't believe in confrontation but in collegiality - people must feel good about decisions.' How does he persuade people to his point of view? As his long-time colleague, Mark Buttner, says: 'there is very little point in arguing with him because he's generally thought about whatever it is a lot, and come to the

right conclusions.'

The science going on in David's lab continued to dominate the field. By the end of the 1970s, not only was cloning proceeding apace, but the lab was also starting to make a splash in antibiotics research. Leaving his first love, the developmental biology of *Streptomyces*, in the highly capable hands of his friend and long-time colleague Keith Chater, David had finally got interested in antibiotics, not least because actinorhodin, the secondary metabolite responsible for *S. coelicolor's* heavenly blue colour, turned out to be an antibiotic - a weakly acting antibiotic, but an antibiotic none the less.

David's long-term colleague Keith Chater, 1987.



Streptomyces coelicolor producing the blue antibiotic actinorhodin.

The route into antibiotic research came via the elusive S. *coelicolor* plasmid SCP1 first identified by Alan Vivian in 1970. In the mid-1970s, Ralph Kirby and Fred Wright, David's PhD students, found that SCP1 encoded all the necessary genes to make the antibiotic methylenomycin, creating a bit of a stir: the idea of an antibiotic-producing cassette handily packaged on a mobile genetic element was intensely interesting, especially to industry, but sadly, the plasmid location of methylenomycin turned out to be the exception rather than the rule.

The actinorhodin (*act*) locus was more conventionally located on the S. *coelicolor* chromosome, as shown by Fred Wright in 1976, and it fell to Brian Rudd, David's next PhD student, to map the genes involved in its production. Brian isolated 76 S. *coelicolor* act mutants unable to turn the correct shade of blue, and showed that colour-wise, they fell into seven classes, each likely to be responsible for one biosynthetic step on the pathway to the finished actinorhodin molecule. He ordered the classes in the biosynthetic pathway by growing strains in close proximity and seeing which pairings resulted in restoration of the proper blue colour (a strain with a mutation close to the end of the biosynthetic pathway would be rescued by one with an earlier-acting mutation), and also demonstrated that the genes representing the seven classes were likely to be very close together on the chromosome[9]; this close association of antibiotic biosynthetic genes turned out to be a general principle.

As cloning technology developed alongside the antibiotic work, it looked increasingly feasible that the cluster of genes responsible for actinorhodin biosynthesis might be packed tightly enough together to be cloned in one chunk. It fell to Francisco (Paco) Malpartida, who arrived in the lab as a postdoc in 1982, to test this out. David describes Paco as a wizard at the bench, who 'seemed to do a lot of his thinking in the institute car park,

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9 BAM Rudd, DA Hopwood (1979). Genetics of actinorhodin biosynthesis by *Streptomyces coelicolor* A3(2). J Gen Microbiol 114:35-43

10 DA Hopwood (2007). *Streptomyces* in Nature and Medicine. (ISBN: 9780195150667) Oxford University Press, New York.

where he would pace up and down every few hours in all weathers smoking a particularly strong brand of Spanish cigarettes called Celtas, with a Celtic warrior on the packet' [10]. It has to be said that Paco may not have been in the car park out of choice: David's violent antipathy to smoking was well known amongst those of his colleagues with nicotine addictions.

Paco Malpartida in the mountains.

Whatever the reason for his apparent love of the outdoors, between cigarette breaks, Paco did a fine job. He chopped up the S. *coelicolor* genome using the *Bam*HI restriction enzyme, inserted the resulting random fragments into a plasmid vector, and used this so-called shotgun library to complement a mutant S. *coelicolor* strain missing a late step in actinorhodin manufacture. Two plasmids from the library were able to restore the proper blue colour to the mutant strain, and Paco showed that between them, the shotgunned S. *coelicolor* DNA that the two plasmids carried could rescue all seven steps of the actinorhodin biosynthetic pathway. To get the whole thing in one piece, he stitched the two DNA inserts together to make a huge 32,000 base-pair fragment, inserted it into his plasmid vector, and forced the unrelated *Streptomyces parvulus* species to start making actinorhodin. It was a technical tour de force – nobody had quite believed such a large piece of DNA could be cloned. Additionally, the fact that all of what turned out to be the 22 genes in the cluster were switched on and worked efficiently in the foreign environment of their surrogate *Streptomyces* host was a really big deal: being able to move and express genes between different *Streptomyces* species made

genetic engineering for strain improvement and drug development a most alluring prospect. Unsurprisingly, *Nature* was happy to publish yet another Hopwood lab first[11].

Paco's experiment was the last link in the chain leading from the development of transformation and cloning in *Streptomyces*, through to its emergence as a *bona fide* citizen of the new molecular biology world. It was time to try the ambitious next step – was it possible to make a novel antibiotic by genetic manipulation?

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In 1980, Merv Bibb and colleagues had suggested that 'the ability to clone genes in *Streptomyces*... may enable new antibiotics to be produced by the introduction of exogenously derived enzymes that ... lead to the synthesis of hybrid antibiotic molecules'[12]. The idea was fairly obvious, and if it worked, would have far-reaching consequences, but testing it was beyond the reach of every lab in the world except one: David's.

By 1984, David and his colleagues at the JII were not only the world experts in *Streptomyces* molecular biology, but sat at the centre of a collegial, friendly *Streptomyces* community of academic and industrial fellow-travellers from many disciplines. These included some really excellent natural product chemists, who had been using hardline chemistry to modify antibiotics to make molecules with novel properties. Taking a wholly chemical approach to this was of limited success, as secondary metabolites like antibiotics have complex structures, that can additionally display chirality, right- or left-handedness, something that's really hard to replicate in a test tube. Therefore, there was considerable interest in subverting the natural pathways used by *Streptomyces* for building secondary metabolites, and the more prescient of

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11 F Malpartida, DA Hopwood (1984). Molecular cloning of the whole biosynthetic pathway of a *Streptomyces* antibiotic and its expression in a surrogate host. Nature 309:462¬–464

12 M Bibb, JL Schottel, SN Cohen (1980). A DNA cloning system for interspecies gene transfer in antibiotic-producing *Streptomyces*. Nature 284:526-531

the natural products chemists had been talking to David and the JII about their *Streptomyces* genetics work for some years. These chemist friends told David that making just a small change in an antibiotic's structure might have profound effects on its function. The prospect of being able to engineer such a change by slightly tweaking the biosynthetic pathway seemed quite reasonable to them, and by extension, to David. And fortunately, his favourite antibiotic pathway was a perfect place to start.

Actinorhodin, the *S. coelicolor* blue antibiotic, is a member of a chemical family called the benzoisochromanequinones (BIQs for short), as are two other *Streptomyces* antibiotics: dihydrogranaticin, a beautiful purple compound made by *Streptomyces violaceoruber*, and medermycin, dull brown in hue, and a product of the more prosaically named *Streptomyces sp.* AM-7161. The structures of all three BIQs were known, and they were close enough relations to make it feasible that some of the *S. coelicolor* biosynthetic enzymes responsible for building actinorhodin might be able to recognise and modify intermediates of the others.

David wrote to his friends Heinz Floss, working at Ohio State University on dihydrogranaticin, and Satoshi Ōmura[13], who studied medermycin at the Kitasato Institute in Tokyo, and set up a collaboration in which the Hopwood lab would do the molecular genetics, and the Floss and Ōmura labs would cover the structural analysis of any new metabolites. Accordingly, in February 1984, cultures of *S. violaceoruber* and *Streptomyces sp.* AM-7161 arrived in Norwich, and Helen (now Helen Kieser, having married one of David's postdocs) set about growing them up and trying to transform them.

Neither of the new species had been used for transformation before, and it took Helen some weeks to get the experiments going. Eventually,

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13 David's great friend Satoshi Ōmura shared the Nobel Prize in Physiology or Medicine in 2015, for his co-discovery of Avermectin, made by *Streptomyces avermitilis*. Drugs based on Avermectin have 'radically lowered the incidence of River Blindness and Lymphatic Filariasis, as well as showing efficacy against an expanding number of other parasitic diseases'.

Wedding of Helen and Tobias with David and Joyce, 1983.

The world's first hybrid antibiotic. Cultures of *S. coelicolor* making blue actinorhodin, *Streptomyces sp.* AM-7161 making brown medermycin and the hybrid strain making purple mederrhodin.

things started working, albeit at far lower frequencies, and Helen began by transforming *Streptomyces sp.* AM-7161 protoplasts with plasmids carrying various permutations of the *act* gene cluster, ranging from the whole thing to smaller individual chunks. On a May morning in 1984, she and David examined the first set of plates. As David recalls: 'Some were beginning to

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14 DA Hopwood (2007) *Streptomyces* in Nature and Medicine (ISBN: 9780195150667) Oxford University Press, New York.

develop the blue colour characteristic of *Streptomyces coelicolor* making actinorhodin, and others were brown, but one was a shade of purple we had never seen before.'[14]

They were in business, and after an excited David sent the transformed strains off to Japan, Satoshi Ōmura was able to confirm that two new hybrid antibiotics, christened mederrhodins A and B, were being made, but only when part of the *act* cluster was transferred; adding the whole gene set didn't work. The result with *Streptomyces violaceoruber* was less spectacular: there was no colour change, and at first, the Floss lab couldn't find any differences at all. Finally, in November, just before David and Satoshi were about to submit their findings to *Nature*, David got an excited phone call from Heinz to say that there was a hybrid compound present, but the change was a very subtle stereochemical one; the chemical composition of the new molecule, hurriedly named dihydrogranatirhodin, was exactly the same as normal dihydrogranaticin, except for a hydrogen atom sticking out of the molecule in the wrong direction. Dihydrogranatirhodin therefore squeaked into the paper, which was submitted just before Christmas 1984.

By this time, the first announcement of the production of hybrid antibiotics had already happened, at the British Association for the Advancement of Science annual meeting, held at UEA in September. David spoke in one of a set of parallel sessions on the last day, presumably to an

David with Heinz Floss and 2015 Nobel Laureate Satoshi Ōmura, photographed in 1985 at Gracht Castle, Germany,

audience nursing sore feet and hangovers from the impact of the barn dance and conference dinner combo of the night before. He was up against sessions featuring a man from Sainsburys talking about retailing, an assessment of future developments in pig meat processing, and funnily enough, a discussion about how farming might best benefit the consumer; in a parallel universe where the young David had kept to his original plan of becoming a farm inspector, he might well have been featured in an entirely different context at the meeting.

Despite David's not providing the requisite number of copies of his paper to the BAAS Press Secretary (his letter politely states that 'unfortunately cuts in our budget preclude our providing 70 copies of the material and we trust that this will present no problems'), there was considerable interest in the work, and a particularly good write up appeared in The Economist, authored by a young Matt Ridley.

Things got more hectic in February 1985 when the *Nature* paper came out[15]. The prospect of making new, better antibiotics was a very big deal, as can still be appreciated today. Press coverage ranged from a provincial French newspaper speculating that such work might lead to raising cows bigger than elephants, to more measured coverage in the Middle East, South America, Singapore, Japan, and even Trinidad. The British papers also took up the story, although their patriotic coverage of the 'British scientists' was slightly misguided, given that David's policy of enthusiastic international collaboration meant that two-thirds of the authors on the paper were foreigners.

David was pleased by the attention, mostly because his beloved organism was finally getting the recognition it deserved. His only disappointment was that his photograph of the agar plates featuring different coloured recombinant colonies did not make it onto the cover of Nature; sadly,

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15 DA Hopwood, F Malpartida, HM Kieser, H Ikeda, J Duncan, I Fujii, BAM Rudd, HG Floss, S Ōmura (1985). Production of 'hybrid' antibiotics by genetic engineering. Nature 314:642-644

they were trumped by a picture of a mummy, illustrating Svante Pääbo's first cloning of ancient DNA.

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The hybrid antibiotic paper is a highly significant moment in the story of *Streptomyces*. Up till then, David had been leading the way through unknown scientific territory. His objective, to make *Streptomyces* a genetically tractable microbe, was considered important by a small band of enthusiasts, but most scientists had no idea of why it might matter. With the paper's publication, it was as if he'd crested a summit, revealing the wide, sunlit uplands beyond. As David puts it, 'I think we opened up the whole field to natural product chemistry and everybody's doing it now – it was the turning point when everybody started taking a genetic approach to natural product synthesis.' And he can't stress how important this change of attitude was: 'Never mind the hybrid antibiotic – this is my biggest contribution to science in general.'

David and his colleagues coped with the flood of interest in *Streptomyces* molecular biology by starting a series of EMBO training courses, where over the course of a fortnight, young scientists could come to Norwich, learn the techniques, have fun, and generally absorb the values and ethics of the *Streptomyces* community, with its emphasis on collaboration rather than competition.

These courses (and a similar one they ran in Wuhan, China), brought together a generation of *Streptomyces* researchers into an international network that continues to flourish today. Until very recently, there were few *Streptomyces* labs in the world that had not at some point interacted with the mothership of the John Innes Institute (renamed the John Innes Centre in 1994). 'Genetic Manipulation of *Streptomyces*: a Laboratory Manual', the experimental bible of the *Streptomyces* field, published in 1985 by David and his close colleagues and based on the EMBO course notes, reached everyone who couldn't come in person for advice, and its successor, 'Practical *Streptomyces* Genetics' has been equally successful.

Joyce and David at Antibiotics '89, Carmona, 10-15 May 1989, on an excursion to Jerez.

Having become a complete convert to the antibiotics field, David immersed his lab in dissecting out and manipulating the biosynthetic pathways responsible for antibiotic production; the precise, elegant cellular machinery that fashions unique, highly complex molecules from a set of simple chemical building blocks was highly appealing to a man who gains deep pleasure from a job well done. His many fruitful collaborations in the field of novel molecules, notably with Chaitan Khosla, who came as a post-doc from CalTech and went on to a stellar career at Stanford where he coined the term 'unnatural natural products' for novel molecules made by genetic engineering, continued up to and beyond his official retirement from the lab in 1998.

David had one further major contribution to make, one which neatly rounded off his half a century's involvement with *Streptomyces*. As the 1990s progressed and DNA sequencing technology blossomed, the possibility arose of sequencing the entire *S. coelicolor* genome, thereby revealing all its remaining secrets. Possibility turned into reality when David almost single-handedly persuaded the Wellcome Trust and the UK government's Biotechnology and Biological Sciences Research Council (BBSRC) to put up the money, and helped set up a collaboration with the Sanger Centre to do the sequencing.

The raw material for the DNA sequencing was a library containing the entire *S. coelicolor* genome cloned into cosmids, special cloning vectors

able to tolerate having large chunks of extra DNA spliced into them. Matthias Redenbach, a German postdoc at the JII, helped by Helen, and other colleagues from Norwich and Hiroshima, was the driving force behind the library, generating a set of 319 overlapping cosmids that between them covered the whole genome.

To establish how the cosmid library related to the genetic linkage map, it would be necessary to get samples of all the genes that had been cloned by labs around the world, and it was in this task that the strength of the *Streptomyces* community came to the fore. Helen wrote to more than a hundred people, asking them to send clones of the genes they worked on, so that she and the JII team could determine on which cosmids they were located. In some fields, asking such a big favour, which relied on trust and goodwill, would have got an almost zero return. However, in the close-knit *Streptomyces* community, people simply opened their freezers and sent Helen exactly what she needed. In David's words: 'Such was Helen's popularity, stemming from her bubbling enthusiasm, outgoing personality and interest in everyone's professional (and private) lives, almost everyone responded.'[16]

The complete 8,667,507 basepair sequence comprising the *S. coelicolor* A3(2) genome was published in 2002[17] . As well as the gratifyingly exact match between the order of genes as determined by David's linkage mapping, and their real order on the DNA sequence, there were some surprises. Most notably, there were more than 20 gene clusters likely to be able to make secondary metabolites, most of which were entirely unknown. This became the paradigm, as genome sequences of further actinomycetes, notably *S. avermitilis*, sequenced in Satoshi Ōmura's lab, appeared; to combat the uncertainties of living in the soil, actinomycetes have evolved many contingency genes to fight off a wide variety of enemies. Predictions that all possible medically useful compounds had been mined out of the actinomycetes

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16 DA Hopwood (2007) *Streptomyces* in Nature and Medicine (ISBN: 9780195150667) Oxford University Press, New York.

17 SD Bentley, KF Chater, and 41 others (2002) Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3(2). Nature 417:141-147.

were confounded at a stroke, and the enormous untapped potential of soil bacteria continues to astonish even today.

In retirement, David continues to shepherd his community from a distance, keeping in regular touch with his colleagues at the John Innes Centre, but he's been able to indulge his hobbies a little more; these days, he's a fanatical gardener, and a pretty decent cook. He remains modest to a fault, summing up his career thus: 'You could say that I've never formulated hypotheses and tested them. I see myself as collecting data and interpreting it; it's really just been asking about biology – what does it do? I haven't managed my career – it sort of just happened.'

Further evidence of David's unassuming nature is evident in his reaction to a letter he received in May 1994. Here's Joyce: 'David was due home from California after a week away. During the week, I'd been opening his mail for him, and amongst it was a letter from the Prime Minister offering him a knighthood! I thought "Good God, what am I going to do about this? He's going to turn it down given half a chance". And David: 'When I got home, Joyce gave me the mail. She'd buried the letter from the PM in the middle – she hadn't said a word about it before that; she likes people to find things out for themselves! My immediate reaction was to turn it down of course, but then I thought that taking it might reflect well on the subject and on the John Innes. And if admirably modest people like Ken Murray and Alec Jeffries had accepted, I felt it would be OK for me too.'

Why did David stick with *Streptomyces* for his whole career? Keith Chater, who worked alongside him for the best part of thirty years, thinks the reason is simple: he genuinely loves *Streptomyces*: 'It's been a lifetime companion and he knows it well – I'm sure there is an affection. He's a botanist and in some ways *Streptomyces* is the plant of the bacterial world. And it's an organism that almost has a personality and responds to you in a sense – you do get attached to it and know its moves – it does a lot more than just divide.'

Long ago, David's mother Dora once told Joyce that if David had decided to be a builder, he would have been a master builder. She was right,

but perhaps not in the way she envisioned. The modern *Streptomyces* field has been beautifully crafted, right from its beginnings sixty years ago. Built on solid foundations, it stands as a body of excellent, thoughtful research, done with great care and attention. That this has occurred is a tribute to David's vision, persistence, and character. His mother would be very proud.

Joyce and David on the Li River, Guilin, China, April 2004.

Joyce and David's Golden Wedding with their three children and their spouses plus six grandchildren, September 2012.

About the Author:

Kathleen Weston had a long career as a cancer biologist before quitting the lab in 2009 to set up as a science writer and communicator. She has previously published 'Blue Skies and Bench Space', a history of the Cancer Research UK London Research Institute.

Streptomyces

Streptomyces bacteria are globally important industrial microbes, but 60 years ago, our understanding of what made them tick was primitive in the extreme. That this has changed is due in no small part to the work of one man, Professor Sir David Hopwood. From making fundamental biological discoveries, to building a community that brought academia and industry into fruitful partnership, Sir David was the driving force of the *Streptomyces* field for his entire scientific career.

This is his story.