PERSONAL

Contents

I'm not sure that a PIFFLE needs a section of this kind. Please skip this section if you dislike indulgent sentimentality.

1. EDUCATION

1.1. **Undergraduate.**

I started my degree at Adelaide University at a fortunate time. It was 1957, and the discovery of DNA had just hit Adelaide University (maybe a slight exaggeration - the Watson-Crick paper came out in 1953). The first-year Biology class, which I did as my last subject after tossing-up against Geology, was taken by Peter Martin, a botanist who had evidently become a recent convert to genetics, and who was responsible for attracting many students into the subject. The textbook for the course was CD Darlington's 'The Facts of Life', an idiosyncratic account based around genetics. Looking at current textbooks with their hundreds of pages of detailed cell biology, ecology, genetics etc., it seems hard to believe that such a book could have been the recommended text. But we also did the usual rat dissections, plant identification etc. I got a bare pass in the course which I'm sure was due to the genetics component balancing out the failures in the others.

I had originally intended to go on in physics, in which I did reasonably well in first year, but before enrolling I went and talked to Henry Bennett, who had just become the Professor of Genetics, . He talked me out of doing physics and into doing genetics, along with statistics and mathematics.

The genetics course at Adelaide University was one of the most rigorous anywhere. We sat doing exercises and problems in many of the practical classes, winding our mechanical calculators and looking up our chi-square tables. Probably we missed out on some things that were taught at other universities, but there were occasions later when I was a postdoc when I was struck by how much better prepared I was for the problems in population genetics than people who didn't have this sort of background.

Although I had a reasonably good background in statistics, and less so in mathematics, in other ways it was severely limited. I did no biology or chemistry after first year, and never took a biochemistry course. Not what would be recommended for someone going into genetics nowadays.

I did one other course in 1959 or 1960, a one week course in a computer language called Fortransit. This was the forerunner to Fortran, IBM's standard scientific language for many years. I was immediately attracted to programming, and seem to have spent half my life since then writing computer programs. I have never been good at building anything physical, and I think that it is the fact that computers allow one to build such complex, and sometimes working, structures that I find so attractive. Fortran seemed after a while too prescriptive, and I found Pascal a much more logical and satisfying language. Unfortunately I have never managed to move on, despite the fact that Pascal is now really a heritage language. And I never took another computing course. Maybe I should have been given some training in discipline in programming.

1.2. **Postgraduate.**

I managed to get a PhD scholarship, despite getting a second class honours degree. That's the difference between then and now. I decided to go on to do a PhD in the same department in Adelaide. In reality it was an easy choice because RA Fisher was there (see next section).

The custom for a PhD at the time was to find one's own way into the PhD. I was luckier than most because Henry Bennett suggested a

couple of possible topics. One was to take over work on the genetics of the local 'soursob' plant *Oxalis pes-caprae*, a South African import. This was being done by my friend Ian Franklin who set up many crosses as part of an honours project. Although Ian was still working on the project when I started my PhD, he was already committed to going to Berkeley for a PhD, and would have to give up the project during the year.

The other project was to look at a situation in a local grasshopper species, *Phaulacridium vittatum*. This is known as the wingless grasshopper, but occasionally winged individuals are seen. The project was to work out the genetics of this wing polymorphism. I was more attracted to the grasshopper project, and set out to start breeding work. After several months of misplaced TLC it became clear that I was not a natural grasshopper breeder. I don't recall ever managing to get a single mating to work. Maybe I never managed to tell the difference between females and males.

So, somewhat reluctantly, I started to work on soursobs. These are well known weeds around Adelaide. But the common form is a 'pentaploid', having five copies of each chromosome, and is sterile, just reproducing asexually from bulbs. The project involved a rarer form, found at only two or three sites around Adelaide, a fertile 'teraploid', having four copies of each chromosome. The reason for the interest in this species was that RA Fisher had worked out much of the theory of tetraploid inheritance, and this was a chance to apply this theory.

I won't go into detail here about the project because I have written a lot about it in the chapter on tetraploid inheritance. The project had a major difficulty in that the seeds go into dormancy for a minimum of several months, which we never learned to break. So only one generation can be grown per year. My first year, when I started late in the season, was almost a total write-off. As a result so was the second year, so that with half the project time gone I had zero results.

Fortunately things turned around from there. I learned to love *O. pes-caprae*, and the final two years were quite productive. I also managed to make some advances in the theory of tetraploid inheritance. So I ended up with a PhD after all. In fact Henry Bennett entered it into a competition for something called the Culross Prize at Adelaide University, which that year was for PhDs in biological sciences. The prize was, from memory, £20 (I think we were still on pounds at that stage). By the time this came around I was on a postdoctoral position

at Stanford, and I used the money to pay for a membership of the Playboy Club in San Francisco.

1.3. **RA Fisher in Adelaide.**

The other attraction of Adelaide University, besides being the first in Australia to have a proper Genetics Department, was that RA (Sir Ronald) Fisher came to Adelaide. He had retired from the chair at Cambridge at the statutory age of 65, and came to Adelaide on a joint appointment with the CSIRO Division of Mathematical Statistics, located in Adelaide, and the Genetics Department.

It is difficult to conceive what a godlike figure he was to us. I suspect his contributions have been downplayed in recent years, perhaps because of his conservative stance on eugenics and cigarette smoking and cancer. But he was the founder of modern statistics, was responsible for the analysis of variance (I believe that he actually introduced the word 'variance' into the language), the method of maximum likelihood, many of the principles of experimental design, and many other statistical tests. In genetics he was the founder of quantitative genetics, one of the founders of population and evolutionary genetics. A Wikipedia article http://en.wikipedia.org/wiki/Ronald_Fisher goes into some detail but leaves out a lot.

During my third and fourth (honours) year we had occasional lectures from Fisher. Sometimes I recall there were follow-up lectures from Henry Bennett to try to decipher Sir Ronald's lecture - he was not always the easiest lecturer to follow. He also lectured in statistics and I have to admit that I understood even less of these. Mostly at the time the lectures were on 'fiducial inference', a topic that I gather still puzzles statisticians.

This brings me to one aspect where being a 'disciple' of Fisher's has turned out to be a problem in later years. Fisher was always scornful of an alternative statistical approach known as Bayesian inference. Basically this approach requires you to make an arbitrary assumption in which lack of any information is initially equated to an equal probability of all events. This step is then followed up by iteration in which the derived probabilities feed back into the calculation, so that the effects of the initial arbitrary assumption are supposedly lost or diluted. Such a description presumably will sound incomprehensible to anyone reading this account, but I've always felt somehow that attempting to understand it myself would be being unfaithful to Fisher and cause him to turn in his grave. In the olden days one couldn't use this approach

anyway because of difficulties in calculating the probabilities, but with the advent of computers an approximate method known as MCMC has allowed the calculations to be done, and the method has totally swept the field of population genetics statistical inference. Admittedly there are many problems where it is difficult to derive any answer without using Bayesian statistics, and I've always thought of the method as being justified by the phrase 'any answer is better than none'.

Returning to genetics, Fisher was wonderfully helpful if he thought you were interested in a topic. I had two small projects with him. One, which turned into a paper, the first I published, was on enumerating the number of possible tetraploid tetrads (whatever that means - definitely an obscure topic and I checked up recently and there have been zero citations of the paper).

The second project was to do with the MN and Ss blood groups. These are two closely linked blood groups, and in some populations the M gene is associated with S more than expected, and in others with s. Fisher got me to draw a map of the world, and using the published statistics from Race and Sanger's textbook, plot out the regions in the world using red for the M-S association and blue for M-s. I recall that we sat trying to speculate on what it could be about the environment that led to one or the other. Fisher was, famously, a believer in the power of natural selection above all else. Although no thought could have been further from my mind at the time, I ended up being one of the initiators of the idea that such 'linkage disequilibrium' could be due to chance (see Chapter 2 of the PIFFLE). I don't think Sir Ronald would have approved.

Sadly, Fisher was diagnosed with colon cancer in 1962. I don't believe that this should have been fatal, but while in hospital he died from post-operative complications. Not the finest moment in Adelaide's medical history.

There was a large funeral at St Peters cathedral. My memory, which may be faulty on this, is that I was supposed to be one of the pall-bearers, but Henry who was organising this a day or two beforehand was unable to find me as I was in the pub all day.

If I could end on a maudlin note, I was also at the funeral of Sewall Wright, another of the trio acknowledged to be the founders of population genetics. I happened to be visiting Madison at the time, and was in fact due to have lunch with him and Jim Crow on the day he died from complications of a fall in the snow at the age of 98. Had I but

known what a place it would give me in history, I would have raced off to India in 1964 to be at the funeral of JBS Haldane, the third of the trio of founders of population genetics.

2. POSTDOC YEARS

2.1. **Stanford University.**

Walter Bodmer, now Sir Walter, offered me a two-year postdoctoral fellowship, on a joint grant he had with Sam Karlin in the Mathematics Department. I arrived to take this up in August 1965, and was given a small office in the basement, with the exobiology team!

The Genetics Department, in the medical school at Stanford, was a unique department that had been set up a few years previously by Joshau Lederberg, the founder of bacterial genetics. Josh was an incredibly high-powered intellectual with interests in diverse fields. As well as bacterial genetics, which was a substantial part of the department, he had interests in immunology (Gus Nossal had been a postdoc in the department just before I came), in analysing census data to find factors affecting fertility, and in exobiology, with a small team working on lunar landing modules (this was before the moon landing, and maybe I never really got to find out what they were doing because it was all classified).

I was not particularly happy with my basement office, and managed to move upstairs to a desk in Walter's bacterial genetics lab, where the people in the lab generously tolerated my presence even when I wasn't working on bacterial genetics. I did have a period of several months where I worked on the main lab project, which was on transformation in *Bacillus subtilis*. At the time, *B. subtilis* was the only bacteria known that would take up naked DNA. The means of doing this in *E. coli*, a critical step in genetic engineering, hadn't yet been worked out. I used a nasty mutagen called nitrosoguanidine, and managed to isolate what I believe was the first transformation-less mutant. Unfortunately this turned out not to be a single gene mutation which made it rather useless, although it took a long time before this was worked out.

Around this time I was working on the theory of genetic loads, and was in the position where the bacteria were getting in the way of writing up what we had found. Ed Reed, my collaborator, persuaded me to give up the bacteria to concentrate on the genetic load stuff. It was probably the right thing to do at the time, but it basically meant that I gave

up what was really my one opportunity to be involved in mainstream molecular biology.

I also tried, although in retrospect not nearly hard enough, to get involved in Josh Lederberg's project on the analysis of census data. A small team was working on the computer analysis of the US census data from 1960, which was available on several large magnetic tapes. Each 'pass', when the tapes were loaded up and fed into one of the available computers, was a major operation involving weeks of planning. I got involved in the analysis of 'birth intervals', my contribution being to show that there is a bias from as yet incomplete families. Owing to the long time lags between computer runs, it took some time to realise that there was a second even more unfortunate bias due to the fact that missing records were recorded as 1900, which naturally made a lot of the analysis meaningless till this was realised. My one real foray into the field was when I deputised for Josh at a conference in LA.

Although I was employed on a joint grant with Sam Karlin in the Mathematics Department, I had only a minor involvement with the people there. Sam, who sadly died recently, was an amazing character, who had made mathematical contributions in fields such as economics and probability theory, and was now determinedly moving into genetics. The mind-sets involved in higher levels of mathematics and biology are so different that it is extremely difficult to make the move from one to the other. Sam managed it, although to be truthful it really took years, but he ended up being one of the most influential people in DNA sequence analysis. This is a field that is totally reliant on computers. In the days when I was at Stanford, the idea of a computer in the maths department was anathema. My one small contribution was to do some computer calculations for Sam when he really couldn't avoid putting in a few numbers.

A major attraction for me at Stanford University was the Biochemistry Department, next door to genetics, arguably the place where genetic engineering was invented. The department head was Arthur Kornberg, who was *the* authority on DNA replication. Paul Berg and David Hogness were also there, and many other luminaries. I went along to the introductory biochemistry course for medical students, my first proper exposure to biochemistry. The lectures were a real performance - just about all the faculty went along to every lecture, which I found very impressive. As a postdoc it seemed I was also allowed to sit in on various postgraduate lectures - something for which there is no tradition in Australian universities.

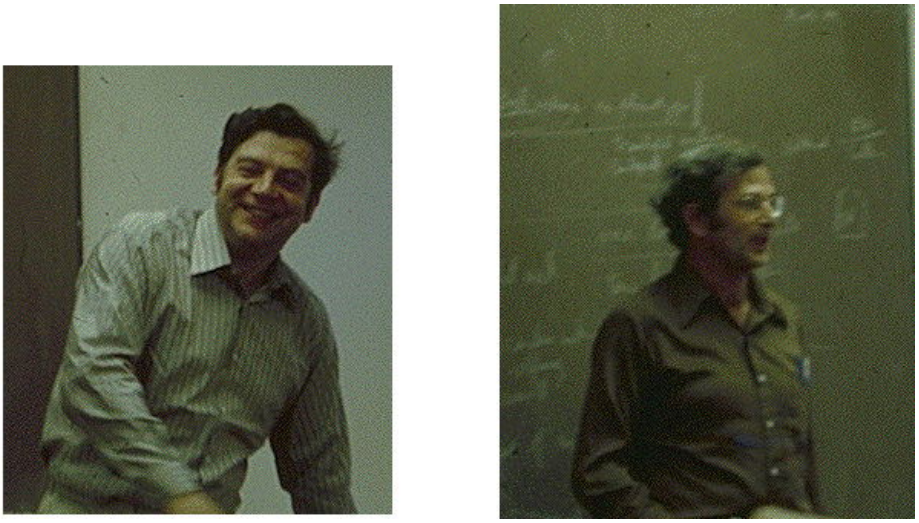

FIGURE 1. Walter Bodmer and Sam Karlin

The Genetics department was part of the medical school and Stanford hospital, although somehow this barely impinged on me. I recall late one afternoon playing some sort of superball game in the corridor outside the lab. Once I failed to catch the ball, and chased it for some distance down a long corridor. Much to my surprise I came across patients being wheeled around in beds, and retreated in dismay.

2.2. **Rockefeller University.**
Theodosius Dobzhansky offered me a one year postdoctoral position at the Rockefeller University in New York for the academic year 1967-68. The Rockefeller University is one of the world's high-powered medical research institutions, but at the time it was trying to branch out into broader fields of biology, and had offered Doby the opportunity to set up a lab in population genetics after he had been retired from Columbia University at age 65. His lab was somewhat isolated. For example the other lab on our floor was run by Christian de Duve, the discoverer of lysozomes, so that there wouldn't have been much in common.

The Rockefeller University is small enough, or at least was at the time, that everyone ate together in a large dining hall. Unfortunately I didn't have the background in topics such as physiology, neurobiology, to appreciate the work of people that I sometimes sat next to at lunch. The place also had a great bar, that must have been subsidised to some extent. I learned to drink martinis there in the evenings, and met lots of interesting drinking colleagues.

Doby's group included two senior postdocs, Francisco Ayala and Lee Ehrman, and his long-time associates Boris Spassky (not the chess player) and Olgo Pavlovsky, plus assorted odds and sods such as me. I went there to work on a project measuring viability of Drosophila chromosomes. This project eventually evolved into a joint project with Francisco Ayala, as detailed in the chapter on fitness in Drosophila.

The lab under Doby's guidance was hard working and very productive. One of his lines of work was in 'behavioural genetics', which I had a small part in. Drosophila were selected to go up or down, or alternatively towards the light or away from it, in specially constructed mazes. This sort of experiment had been successful in selecting lines of flies that behaved predictably. Doby then tried to make this experiment into some sort of social story. He started selection lines and chose the worst performers for particular behaviour, which I recall were supposed to represent the genetically inferior, and used these as migrants into unselected populations. These recipient populations started going in the opposite direction to the selected populations, but eventually reversed themselves and started going in the same direction, despite the fact that the migrants themselves were the 'worst' of their selected population. Doby was very astute but not strong in population or quantitative theory, and one of his more theoretical colleagues had told him that the result was the opposite to expectation, which he apparently believed. It seemed to me that the result was exactly what was expected, and I did some calculations to provide the expectations [1].

An incident from the publication of this paper stands out for me. Shortly after I did the calculations on this experiment and gave them to Doby, I went away on a trip to California. When I came back to the lab, the first person I saw said 'Doby wants to see you', then the second person said 'The Professor is looking for you', etc. I definitely had the impression that I was not keeping up with the expected standards. I produced a first draft of my part of the paper, I think in a day. Somewhat to my surprise this went straight off to the journal, and Doby was on to the next paper. It is a lesson in how to get ahead that I unfortunately failed to follow over the years. But looking back, it is clear that this line of Doby's work has had little impact, certainly compared to Seymour Benzer's approach of selecting single gene behavioural mutations.

FIGURE 2. Doby and the lab on a 'field trip'

3. LECTURER AT SYDNEY UNIVERSITY

I went straight from New York to a job at Sydney University. The job had been arranged with Spinny Smith-White, recently appointed as Professor of Genetics in the School of Biological Sciences. I never had to make a formal application or go through an interview.

Initially I did not think of this as a long-term job. The tradition was that one moved between universities, gradually getting promoted. But twenty-five years later I was still there, still teaching more or less the same courses. I quit the position at the end of 1994, and branched out into writing, and attempting to sell, genetics computer teaching programs.

3.1. **Colleagues at Sydney University.**

I was a member of a small group responsible for teaching genetics. The other members of the group were Chris Gillies, whose expertise was in cytogenetics, and Keith Brown, a bacterial geneticist. I taught a mixture of population genetics and elementary genetics. There was

FIGURE 3. An approx 2000 photo of John Thomson, Spinny Smith White (since deceased) and Ron Skurray. Unfortunately I seem to have no pictures of Barrie Latter.

always also a Professor, the leader of the group. Initially this was Spinny Smith White, and his successors at various times were Barrie Latter, John Thomson and Ron Skurray. By the time Ron Skurray came along, the 'genetics group' was no longer such a well-defined entity.

3.2. **Sabbatical leaves.**

Most research issues are covered in other parts of this PIFFLE. But in trying to see some sort of overview of my time at Sydney University, the only way I can see it is in terms of sabbatical leaves. Not a flattering view of my own institution, and perhaps an oversimplification. Nevertheless from a research point of view my productivity was closely linked to sabbatical leaves, rising during and immediately after, and falling gradually as the demands of teaching and administration took over. I'm sure that it is not like this for many academics, particularly those who set up viable labs. Although I was lucky to attract a few good students, I was never able to set up a substantial lab on my own. The situation only changed when I joined forces with Marianne Frommer in the early 1990s. With her enthusiasm and organisational abilities, Marianne was able to attract students and to build up a substantial

lab, into which I fitted comfortably.

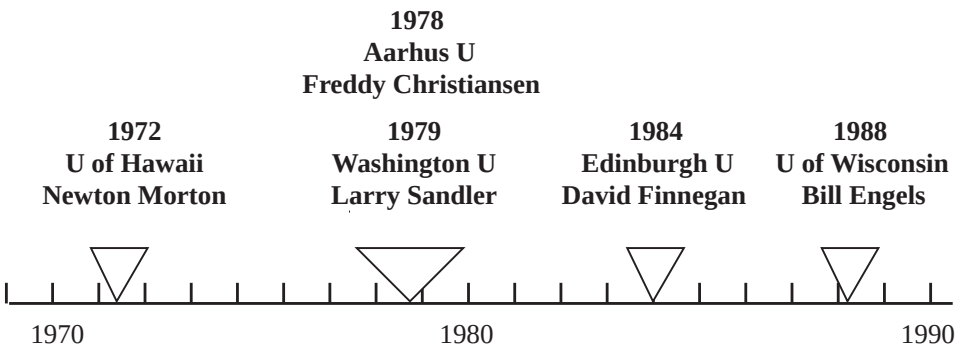

FIGURE 4. Timeline at Sydney University

3.3. **Theory and experiments.**
The topics described in this PIFFLE contain a mixture of these two rather different forms of research. Nowadays it is getting increasingly difficult to do both, although there is a bit of a tradition of this amongst my colleagues in population genetics. I have probably gone a bit further than most in spending a lot of time on mechanisms of P element mobility, which can't really be described as population genetics.

There are some disadvantages to being involved in a mixture of genetics and population genetics. One is that it is hard to get people to accept you as being serious in either field. There is a lot of truth to this. All such fields now have huge backgrounds that have to be assimilated. I have been somewhat of a dilletante, which was easier to get away with in past years than it is now.

3.4. **Some photos.**

FIGURE 5. 2008 lab photo - Bill Engels, Christine Preston, Carlos Flores and Dena Johnson-Schlitz

As outlined in the chapter of this PIFFLE on P elements, our work depended heavily on the collaboration with Bill Engels and members of his lab. It has always been a small lab, as seen from the picture, and remarkably stable and productive over the years.

FIGURE 6. Larry Sandler and students.

I had some background in Drosophila population genetics but very little in true Drosophila genetics till a sabbatical leave in Larry's lab. He had a great group of students, and the weekly group discussions of Drosophila issues were beyond anything I knew about. Larry and I also wrote a paper together, on the issue of paternal age and Down's syndrome [3]. Another benefit of Seattle was the contact with Joe Felsenstein and Monty Slatkin, both on the faculty there.

FIGURE 7. Jorgen Bundgaard and Freddy Christiansen from the Genetics Institute in Aarhus.

The Genetics Institute at Aarhus University in Denmark was for many years headed by Ove Frydenberg. Following his death in 1975, his position was not replaced, but used instead to support visiting scientists. I was fortunate to be a visitor in this way for three months at the end of 1978. I mainly went there to work with Freddy, a well known figure in theoretical and experimental population genetics. This effort was sidelined to some extent when I suddenly got enthusiastic about calculations on the evolution of mating isolation.

FIGURE 8. Dick Hudson with kids, Marianne and me

The major advance in population genetics theory in the past 20-30 years was the development of coalescence theory. Basically it is allows one to look backwards rather than forwards in defining population genetic probabilities. In practice the main benefit is that one can write computer programs to simulate a series of possible scenarios for a particular data set. The person who has done most of the work along these lines is Dick Hudson, whose *ms* program is widely used for analysis.

Dick kindly hosted me for a week and attempted to teach me the basics of such programming. In spite of his efforts I have never really managed to write any significant programs.

FIGURE 9. Alan Wilton doing the high step at a Genetics Soc. dinner. Alan always sets the dress standard, which is sadly lacking in the rest of the society.

Alan did Drosophila population genetics experiments with me for his Honours and PhD. He carried out the main experiment in which we tried unsuccessfully to select for 'super' homozygotes. In the light of modern quantitative genetic findings I think it is becoming clear that the reason for the negative results is the large number of regions of the genome involved, each of small effect. Many years ago Alan also did an experiment jointly with me and Francisco Ayala on measuring the fitness of partial chromosome homoygotes that we must get around to publishing some day.

Alan has moved on to become *the* authority on dingo and dog genetics, as well as making contributions in human molecular biology.

FIGURE 10. Dawn Verlin and me at a celebratory departmental dinner

Dawn Verlin was my research assistant for many years. Her main talent was as a 'fly pusher'. She had amazing powers of concentration and the ability to recognise genetical markers that I was incapable of seeing. In later years she also turned her talents to molecular work. She became Dawn Murray and then Dawn Reid - I was always sorry that we never published any papers together under the last name.

FIGURE 11. Xiumei Liang graduating

Xiumei has been a wonderful colleague and responsible for most of the Drosophila work in the past decade. She graduated MSc based on her work tying up numerous loose ends in the recombination study. Xiumei had the ability to set up and score large crossing experiments while simultaneously carrying out the PCR and other molecular analyses. She worked on Qfly as well as Drosophila, and is now responsible for running the undergraduate genetics laboratory classes.

FIGURE 12. Yasmine Svoboda at a 1994 meeting in the US

Yasmine started off as laboratory manager in the Fruit Fly Research Centre, and then did a PhD on P elements and recombination. She was the first author on the two papers we published in 1995 and 1996 on the hybrid element mechanism, Yasmine Svoboda on the first paper and Yasmine Gray on the second. She also published a paper "It takes two transposons to tango" [2], comparing the hybrid element results with similar findings in other organisms. Yasmine currently works for the Commonwealth Govt. in Canberra helping protect us against invasion from infectious diseases.

FIGURE 13. Me with Rebecca Colless and Leila Blackman

Leila started at Sydney University as a molecular assistant for Keith Brown, working on bacteria. Then she moved to Drosophila, and was responsible for cloning and characterising the insertion site of our P element insertion. She then moved to do a PhD on plant molecular biology, and now works at the ANU. Rebecca did her honours project on P elements. The picture was taken at a watering hole where we usually stopped on the way home from the annual Australian dipteran molecular biology meeting in Corowa.

FIGURE 14. Stuart Gilchrist at his BSc (Hons) graduation

Stuart, together with Alfie Meats, has run the fruit fly lab for a number of years. He had a background working on population cage experiments and molecular aspects of the P element project in Drosophila. He started a PhD but then decided to do law. After practicing for a year or two he returned to science to do a PhD at University College in London with Linda Partridge, before coming back to work on the fruit fly project.

FIGURE 15. JingTing Zhao; Marianne Frommer; Sheila van Holst Pellekaan; Deb Shearman

Two members of the lab graduated at this time. JingTing was our chromosome expert and responsible for the Qfly genome map. Sheila, an escapee from a human genetics molecular lab, completed her PhD on mitochondrial DNA analysis of Australian aboriginal populations. Deb, the senior molecular postdoc in the lab, is best known for her work on sex determination in fruit flies.

FIGURE 16. Antigone and other fruitfly workers at a fruit fly factory in Mexico

Marianne and I were invited to become participants in a fruitfly study section sponsored by FAO and IAEA. This involved trips over several years to meetings in Italy, Mexico, Argentina and Guatemala. The picture shows some of the participants at one meeting, including Antigone Zacharopoulou, the developer of the fruit fly chromosome genome who helped us get started with Qfly, dressing up appropriately for a visit to the factory where sterile medfly were produced.

FIGURE 17. Some Fruit Fly Lab personnel - Xiumei Liang; John Sved; Stuart Gilchrist; Kit Streamer; Marianne Frommer; Kathie Raphael; Deb Shearman; Chris Gillies; Jen Morrow; Emilie Cameron.

This 2008 picture includes most of the lab at the time, except for Alfie Meats who doesn't like having his picture taken.

FIGURE 18. Geneticists behaving badly

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