ISSN 2397-9917

Issue 12
Spring 2020

Galton Institute

Exploring Human Heredity

The Galton Review

www.galtoninstitute.org.uk

CONTENTS

Front Cover Image: Depositphotos.com

Published by:

The Galton Institute, 19 Northfields Prospect, London, SW18 1PE

Tel: 020 8874 7257 www.galtoninstitute.org.uk

General Secretary: Mrs Betty Nixon
executiveoffice@galtoninstitute.org.uk

Review Editor: Mr Robert Johnston

EDITORIAL

At the first ever remote Council meeting in March, it was decided to postpone this year's Annual Conference until October 2021 when hopefully some degree of normality will have returned. The theme will still be **'Genetic studies of populations: Insights into health and social outcomes'**. We greatly regret having to do this but we felt it was for the best.

At the Annual General Meeting in June, our current President, **Professor Veronica van Heyningen,** will step down having served two terms – six years. She has led the way in transforming the Galton Institute into the open and modern organisation it is today and we are very grateful to her.

In this issue, our Treasurer, **Professor Andrew Read** is the subject of 'My Life in Genetics' in which he paints a picture of a very modest and self-deprecating individual rather than the recognised expert he is in his field. He has also produced a most amusing book review which I urge you to read.

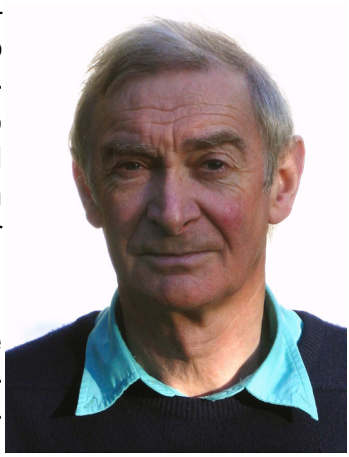
2020 is likely to be a year we shall all want to forget but perhaps we'll also recall so much of the good that has emerged from all the difficulties.

Robert Johnston

My Life in Genetics - an Interview with Professor Andrew Read, Treasurer of the Galton Institute

You began your academic career as a chemist. What inspired you to become a geneticist?

The most honest, if least creditable, answer to that is that I wasn't very good at being a chemist. I did Natural Sciences as an undergraduate at Cambridge, specialising in chemistry, then I did my PhD trying to develop a method of sequencing RNA, but as a problem in chemistry. After some less than brilliant postdocs in Heidelberg and Warwick, I felt very disillusioned about chemistry. In particular, at Warwick University the Department of Molecular Sciences was focussed on chemistry-based research into the mechanism of oxidative phosphorylation – the process by which cells respire sugar to generate energy – which to my mind completely ignored biological reality. Add to that a load of personal problems and I ended up abandoning chemistry research and worked for 10 years at Manchester University in the Extra-mural Department, organising and teaching non-vocational adult education courses across a wide range of science subjects. This was initially interesting and stimulating, but ultimately non-progressive: it was much the same, year after year. Looking for intellectual excitement, I found it in the Department of Medical Genetics.



Professor Andrew Reid

So why genetics? I'm rather proud of the fact that I've never had a single lesson in any branch of biology from anybody, ever. But there was a connection. I'd mis-spent much of my teenage years

pursuing butterflies and moths. And the main books about them, apart from identification manuals, were two in the Collins New Naturalist series by EB Ford. Ford was the professor of genetics at Oxford, and the books were really textbooks of genetics, just using Lepidoptera as examples. So by the time I went up to Cambridge I knew quite a lot of basic genetics and had been running my own breeding experiments. That all went dormant for almost 20 years, but it meant I could play a positive part in the seminars I used to attend in the Medical Genetics department, and catch the notice of the boss, Rodney Harris.

How much has genetics changed in your time?

Completely, radically and basically. I'm talking about the practice, not the principles: of course, the basic concepts of Mendelian genetics and of DNA structure and function were all in place well before 1977 when I joined the Department of Medical Genetics, and have not changed. But at that time there was absolutely nothing clinically useful that could be done with DNA. I did feel that one day it would come in handy to know something about DNA, and I guess Rodney Harris, my mentor and the head of the department, must have thought that too, which was no doubt why he was willing to take on this totally unqualified person - an act that changed my life and for which I am eternally grateful.

In 1977 patients and families could be counselled about recurrence risks, based on Mendelian principles or (for complex conditions) empiric risks; they could have their chromosomes analysed under the microscope, and amniocentesis could be used to check a fetus for chromosomal abnormalities or neural tube defects. In those first few years I worked mainly on neural tube defects, looking to improve the accuracy and sensitivity of prenatal diagnosis, and being part of the first vitamin trials that showed how giving vitamins to mothers in early pregnancy radically reduced their risk of having a baby with spina bifida or anenceph-

aly. That was also when my long and fruitful collaboration with Dian Donnai started. Additionally, Rodney had in his wisdom, and with total lack of evidence, labelled me as the person who understood computers and statistics. A complete lie, but since problems landed on my desk and there was nobody downstream that I could shunt them off to, I got down to it and ended up having quite an enjoyable time doing sums and setting up various computerised record systems – which, in 1977 meant doing your own Fortran programming on decks of punched cards.

DNA found its first sliver of clinical relevance in 1980 when Botstein and colleagues (and, often forgotten, also Solomon and Bodmer - a future president of the Galton Institute!) showed that DNA polymorphisms could be used as markers to track disease genes through families. I went to Peter Pearson's laboratory in Leiden to learn the necessary techniques (very different from those I had used in my days as a nucleic acid chemist) and set up our own embryo DNA laboratory in Manchester.

That early application of DNA analysis to clinical genetics marked the start of a continuous and continuing revolution. To select just a few high points, around 1990 the Polymerase Chain Reaction (PCR) turned analysing a patient's DNA from a whole PhD project into a diagnostic procedure; around 2000 the Human Genome Project gave us the Reference Human Sequence, against which all the individual variants could be mapped and, hopefully, understood, and around 2010 next-generation sequencing moved from research into diagnostic laboratories, seeding the data revolution in clinical genetics.

So the principles remained the same while the applications exploded all round us. But there have been additional insights that have opened up whole new areas – into mutations and the resulting mosaicism, into how gene expression is regulated, into the structure of genomes as mosaics of haplotype blocks sepa-

rated by recombination hotspots, and into the way the 2 metres of DNA in a typical human cell nucleus is organised – to name but a few.

What has been the main focus of your work?

As a University employee I was supposed to be doing research rather than delivering a clinical service. For the first few years developing the DNA Lab was indeed bona fide translational research, but my main pure research work was on identifying disease genes. Hopefully that could not only deliver insights into biology, but also help patients and their families. Having hit 65, I formally retired in 2004, but have not given up on genetics – it's far too interesting for me to walk away and spend my days as a rather cack-handed gardener.

Who have been the greatest influences on your work?

I owe a very great deal to Rodney Harris who, as I said, took me up when I had no formal qualifications whatsoever, and provided the environment where I could flourish. I also owe a lot to Dian Donnai – for over 40 years we have worked together, the clinician and the scientist, respecting each other's areas of competence and teaching each other. When I first joined the Department, I imagined genetic counselling was like handing out a betting slip ('Your risk is precisely 15.29%. Goodbye!'). Well, I had a lot to learn, but she was very patient...

Beyond Manchester I have been privileged to know some extraordinarily able people who still give me severe impostor syndrome. I won't start listing names, but an early scientific hero was Albert Szent-Györgyi. He had won a Nobel prize for discovering vitamin C. I never met him, but I greatly admired his determination to go his own way, and to tackle big problems. "When I go fishing", he

said, “I use an enormous hook.” He was wonderfully irreverent: when he had worked out that vitamin C was chemically a sugar, but didn’t know its formula, he proposed to call it ignose; the journal editor objected so he suggested godnose. And he had the courage to be massively wrong: he spent years on an entirely wrong-headed idea that quantum physics and single-electron transfers would explain much of biochemistry. I could never be like him, but I did admire him very much. That, for me, was a Real Scientist.

What do you consider to be the greatest challenges for genetics in the coming years?

I think, to remain humble. Modern genetics is wonderfully powerful. We can understand the biological basis of so many of the things that make us each unique. Even with our present imperfect state of knowledge we can predict all manner of things about a person, and the predictions will only get better as more and more millions of clinically-linked human genome sequences accumulate in the databanks. But genetics can only deal with things that are genetic, and lots of the most important things in life are not genetic. I think there is a certain danger of falling into the same trap as the early eugenicists, who apart from all their moral shortcomings, greatly overestimated the predictive value of their knowledge.

There is a tendency to trumpet a genetic discovery that explains 5% of a condition as though that is problem solved. Healthcare systems seem willing to spend millions on genetically-targeted drugs that marginally prolong the life of a cancer patient, while unwilling to spend a few thousand on hugely effective social interventions. Of course it’s very nice to be seen with awe as some sort of modern witch-doctor, but we mustn’t let it turn our heads. So let’s celebrate the wonderful achievements of genetics, now and in years to come, but remain humble about their place in the overall human story.

What do you think is the main role of the Galton Institute?

We are a small organisation with a small budget and very small numbers of active personnel. In our small way I think we do quite well. I wouldn't give up any of the things we do which, given our modest resources, means we can't do lots of additional things. I think our teachers' conferences are one activity that might be modestly expanded without exhausting our finances or energies. Maybe we can develop a presence at some annual science festival. But public engagement and public education are bottomless pits. We will continue to put in our pennyworth, but it's no good imagining we can do anything transformative.

As for the Galton name – well, ideally we wouldn't have started from there. But it's no good trying to hide the history, the only strategy is to be fully transparent, making clear where we follow and where we differ. There will always be enthusiasts who want to rewrite history, but history is there. We should celebrate Galton's very great scientific achievements and not try to ignore or hide his failings – which actually in some ways make him a more interesting and challenging human being.

Finally, please tell us one thing about yourself that is not widely known.

When I was a sixth-former I moonlighted as a professional horn player. The French Horn has the reputation of being a difficult instrument, and it is true that a certain skill is needed to make the right note come out when you blow into it – any one combination of valve positions is compatible with over a dozen different notes, and towards the top of the register they are very close together. So local orchestras were always in need of horn players. Back then in the 1950s the going rate was 3 guineas for a rehearsal and a concert. Guineas sounded much more up-market than pounds, but when the little brown envelope was handed over it clanked with coins, rather spoiling the gentlemanly effect. The wretch who abolished golden guineas has a lot to answer for.

American Society for Human Genetics Annual Conference- Houston, Texas, October 2019

I am a PhD student at the University of Edinburgh, in the MRC's Human Genetics Unit. I'm part of a computational research group that focuses on quantitative traits, and my work draws from the areas of phenotypic architecture research and population genetics. I received a Travel grant co-sponsored by the Genetics Society and the **Galton Institute** to attend, and present my PhD work at, the American Society of Human Genetics' annual meeting in Houston, Texas.

The ASHG annual conference is very large, this year running nine concurrent sessions running over four full days. I'd been to similarly large conferences previously, but this was my first major conference in genetics. The thing that struck me most was how this conference showed that human genetics, which I tend to think of as a well-defined topic, actually contains a level of complexity I can only describe as fractal. The session topics covered a wide range of areas in human genetics, including the genetics of diseases such as cardiovascular disorders, diabetes, and prostate cancer; the evolutionary mechanisms underlying phenotypic changes over time; methodological sessions on large-scale population data, polygenic risk scores, computational research; quantitative sessions on heritability and dominance; using other sources of data, such as DNA methylation, gene expression, or single-cell data and sessions on the interactions between the genetics community and the general public: discussing the role of genetics in the Disability Rights Movement. It also considered how genetics can be taught more effectively at tribal colleges and strategies to improve genetic counseling practice and education. To get a full picture, the conference website at https://www.ashg.org/2019meeting/ has a collection of materials from the conference, including slides provided by presenters and video recordings of talks for those who want them.

The conference proper also included poster sessions and an exhibitors' hall where you could watch demonstrations of various research tools or buy textbooks, and a section for those looking to advertise and apply for jobs. Additionally, there were several satellite events sponsored by various genetics companies and organisations. These covered the range of symposia with a full schedule of speakers on more niche research topics, such as the use of isolate populations, lunch seminars on the use of particular technologies, and parties where you can both network and talk with employees from a given company at length about their products and/or services.

I found the conference extremely interesting. It contained a little bit of everything, so I was able to attend talks relevant to my work, as well as ones I just thought sounded interesting. However, due to the size of the conference, as well as the physical size of the facilities necessary to hold it, it is definitely worthwhile to research sessions ahead of time and plan where you need to go. The conference does make use of an app that can be used to keep track of sessions of interest and search the schedule, which can make planning a bit easier. All in all, the conference is worth considering, despite the distance.

Bailey Harrington
University of Edinburgh

Association for Research in Vision and Ophthalmology Annual Conference, Vancouver, May 2019

I had the pleasure to attend this conference which is the biggest international conference in the field involving scientists working in all areas of vision research, as well as ophthalmologists.

The five days were full of inspiring paper sessions where top of the field scientists presented their work. One of the most relevant

of these sessions for me was the Corneal cell and Molecular Biology one, in which many researchers presented work directed at gaining knowledge about corneal development and the differentiation of the different corneal layers and cell types. **Dr Han Peng**, from Northwestern University, presented a very interesting piece of work, where they used single cell RNA seq to work out gene expression patterns that define the characteristics of early and late corneal epithelial transit amplifying cells. These are the progenitor cells that differentiate in the eye to give rise to new corneal epithelial cells, as this is one of the few adult tissues in the body that undergoes constant cell turnover. The use of single cell RNA-seq was featured on several other occasions during the conference on both paper and poster sessions, as a useful technique to study specifically the effect or characteristic of one specific cell type, in a context of cell cultures with mixed cell populations, which is perhaps a more realistic scenario compared to physiological conditions.

In addition to big paper sessions, a series of smaller symposia gave the opportunity for researchers to address more specialised topics, which made them very interesting. I would like to highlight a symposium on emerging gene-driven therapies for anterior segment diseases which offered a very interesting overview on which work is being carried out on genetic eye diseases at the moment, as well as delivery mechanisms, which is always one of the biggest challenges in the process of drug development. **Dr Robert Lavker**, also from Northwestern University, gave a very insightful talk about the importance on the microRNA network in ocular diseases, and the importance of considering them as very relevant targets for gene therapy. In the same session, **Dr Andrew Nesbit**, from Ulster University, gave a talk which was especially interesting to me, since he presented the work his group has been doing on *TGFBI*-associated dystrophies, on which my PhD project is focused. They explained how they have been using CRISPR-Cas9 technology and small interfering RNA to develop a therapeutic approach to achieve an allele-specific suppression of

the mutant TGFBI allele. Being able to discuss with him about the different approaches we are both undertaking, and the advantages and challenges they offer was one of the most enjoyable moments of the conference.

But perhaps the most beneficial part of the conference for attending scientists was the poster sessions that took over the huge basement of Vancouver Conference Centre, exhibiting up to 700 posters during the conference week. Three poster sessions per day gave plenty of opportunity for scientists to talk about their research, share knowledge, brainstorm and network. I had the chance to present my own research on *TGFBI*-associated corneal dystrophies and had the opportunity to meet for the first time and discuss with the few other groups in the world who work in these genetic corneal dystrophies. I was able to discuss my cell model and the challenges of finding a phenotype of TGFBI protein aggregation *in vitro*, as well as the therapeutic strategies that are being used to correct or supress the specific mutations, in order to ameliorate or prevent this type of dystrophy.

I personally enjoyed the chance to meet people working in the same area as me, and sharing thoughts in a very supportive environment where I received some very encouraging words about my work that really motivated me and helped me focus when I arrived back in the lab. Overall I found this was a very inspiring experience, at the perfect time of my PhD research to help me get some perspective of where I am with the project and helped me reflect about the direction I want to take it, from now until the end. I am most grateful to the Genetics Society and the **Galton Institute** for their support.

Beatriz Sanchez
Institute of Ophthalmology, UCL

21st European Molecular Biology Laboratory PhD Symposium - EMBL Heidelberg, November 2019

'Facing the Future – Challenges and Perspectives of Life Sciences'

This year's symposium looked into the future of life sciences. The theme of the conference has been very important to us, as the new century we stepped into confronts us with a burden of long-ignored problems on a global scale. Yet, the rapid technological progress equips us with previously unimaginable ways to handle them. As early stage researchers, it is up to us to decide how are we going to approach the challenges that the future will bring and how are we going to use the opportunities presented to us.

The symposium organizing committee was composed of 30 first year PhD students from EMBL sites in Germany, UK, France, Italy and Spain. We have been delighted to host almost 200 participants from 27 countries spread over all continents. Early-stage researchers have been given an opportunity to talk to established group leaders both in academia and industry, as well as philosophers and policy makers from a broad range of disciplines that implement highly promising approaches to tackle the current scientific questions as well as the global problems we face.

The agenda of the conference consisted of focused sessions addressing one of the points of interest of life sciences in the future, where talks from keynote speakers, invited speakers and selected participants complemented each other. In total, we had the pleasure to listen to 20 talks from invited speakers as well as 12 short talks and 12 flash talks from selected participants. The conference was opened by the Director General of EMBL **Edith Heard** who spoke about the upcoming plans for EMBL that would bring together different scales at which life sciences re-

search is performed; from atoms and molecules to populations and communities. The first session entitled “Life Science Innovations” saw talks from **Silvia Marchesan**, **Albert Cardona** and **M. Madan Babu** who shared their state-of-the-art research conducted by advanced technologies and approaches emerged in the 21st century.

In the session “Science beyond academia” **Tony Wood** from GlaxoSmithKlein talked about modern drug discovery and design. In the Thursday afternoon session “Physics in Biology” **Alba Diz-Munoz** and **Titus Franzmann** presented how interdisciplinary research can help tackle some biological questions and allows us to quantitatively describe biological systems as well as modify them. Friday morning’s session focused on “Machine Learning and Big Data”. We hosted **Upinder Bhalla, Christophe Dessimoz** and **Tempest van Schaik** who talked about the challenges posed by the amount of data currently generated and cutting edge methods to deal with such data and use it for creating more comprehensive biological models. In the following “Science and Society” talk **Charles Pence** used Darwin’s approach to evolution to discuss how breadth in biology is both a challenge and an opportunity.

The second session on Friday entitled “Systems and Synthetic Biology” welcomed **Petra Schwille, Jenny Molloy** and **James Briscoe** who talked about combining our knowledge at different scales and understanding of life via building it. The Saturday morning session focused on “Medicine, Health and Diseases” with lectures from **Jannie Borst** and **Michael Zimmermann** showing novel approaches to tackling the still persistent problems of health and revolutionizing medical treatments using translational research. In a “Science Policy” lecture **Francoise Baylis** called attention to the ethical issues involved in heritable human genome editing and outlined the policymaking responsibility we all bear as scientists. The last session of the symposium was concerned with “Environmental Issues”. In the face of climate

change, listening to possible solutions offered by **Tobias Erb, Mark Post** and **Alejandro Andres Murillo Cordova** was captivating. Together, all our speakers touched upon a variety of topics that concern us within the 21st century and offered a varied and down-to-Earth picture of the opportunities and challenges that we are presented with.

Beside the lectures, participants were also given an opportunity to attend hands-on workshops which dealt with a range of topics and transferable skills, as for example, storytelling, poster design or public engagement. Panel discussion with scientists, ethicists and editors regarding the future of publishing was an opportunity for us to reflect upon knowledge-dissemination and how we could improve the way we share our findings. Poster sessions allowed participants to present their research to each other directly. The poster prizes were awarded to **Karolina Spustova** from Center for Molecular Medicine Norway (Norway) and **Paula Weidemueller** from EMBL-EBI (UK). Additionally, selected participants were invited to give short talks during each of the mentioned sessions. Many of them were awarded travel grants to come and present their research. All agenda details, as well as information about speakers can be found on our website **http://phdsymposium.embl.org/**.

The conference would have been impossible without the generous support of the **Galton Institute,** whose financial award has been used to cover such essential expenses, as the event venue facilities, printing and promotion. Not only was it an invaluable help from an organisational point of view, but also we are happy that our vision of the necessary improvements for the future is shared by such a prominent institution.

Agata Misiaszek
European Molecular Biology Laboratory

BOOK REVIEW

Carl Zimmer: She Has Her Mother's Laugh

Picador 2018 pp 650

Carl Zimmer teaches science writing at Yale, and as a science journalist has a series of popular science books to his name, particularly on aspects of evolution. Here he has written a sweeping overview of genetics: how we got to our current understandings, what pitfalls there were on the way, and what problems we now face. Zimmer is a good journalist, filling his chapters with intriguing facts and driving his narrative along with stories, usually of people who made important discoveries. There is little straight exposition. He assumes no prior knowledge of biology.

It's quite an old-fashioned and determinedly unglamorous book: page after page – 650 of them in all – of rather poor quality paper, all covered with words. I suppose he doesn't want it to look like a textbook, so there are no diagrams or other display items to break up the text, even when a diagram would be worth a thousand words, as when explaining meiosis, for example. Part of the determination not to write a textbook extends to giving almost all chapters uninformative titles – 'Attagirl', 'Nine foot high complete' and so on. This has the unfortunate effect of making this big book almost impossible to navigate except by starting at page 1 and reading through to page 650 (although there is an index, together with some notes and an extensive bibliography). For people used to getting information from snappily packaged internet resources, it may look pedestrian. I think it's fair to say it's rather a cheap production.

So there are a number of barriers to getting the full benefit from this book. This is a pity because the content is interesting, wide-ranging and up to date. I won't try to summarise the 19 chapters

– suffice it to say that everything you might have wanted to know about genetics, especially about how the science developed, is probably there - somewhere. Engagingly, Zimmer has an immense store of anecdotes to personalise his narrative, and this is one of the best aspects of the book. For example, I was fascinated by his reporting the truth behind the story of the Kallikaks – the horror family much quoted by inter-war eugenicists to argue that some people just shouldn't be allowed to reproduce. It was all fake news: the real family mostly consisted of ordinary decent folks ground down by extreme poverty.

Humans are his main focus but he introduces a wide range of animals, plants and microbes. At the same time, to my mind he fetishizes 'Mendel's Law' which, for me, is just an incidental consequence of being diploid. And he worries much more than I would about chimaeras and about who your parents are if you're the product of various reproductive technologies. That's particularly strange because he wants to see heredity as including not just your genes or epigenetics, but your whole mental culture and everything else that a parent or a society might pass on to a child – which reduces questions about the precise number or origin of the gametes that made you to rather a marginal detail. I suppose when thinking about who one is, that is a sensible approach and indeed one that most people instinctively take – but it's not very helpful for analytical scientific thinking. But these are isolated gripes (a reviewer must show he's read the book!) – Zimmer is overwhelmingly sensible, well-informed and judicious, and seems to have spoken to absolutely everybody who is making waves in current genetic research.

A big part of Zimmer's message is that we must be on our guard against misuses of genetics. Very true. But the bit I found most minatory in that respect is not in the main text at all, but in the prologue. He often uses his own family to good effect throughout the book, to make points. Here in the prologue they are expecting their first child. I quote: "The worst scares of my life

have usually come from unfamiliar places… but the greatest scare of all… swept over me when I was sitting with my wife Grace in the comfort of an obstetrician's office…. Our obstetrician had insisted we meet with a genetic counsellor. We didn't see the point…. Still, our doctor insisted.." And so , if Zimmer is to be believed, a couple in their first pregnancy and with no problematic history or warning signs were strong-armed into seeing a counsellor, who scared the pants off them by mining through their pedigrees to try to find problems, and detailing every possible risk. If he really is telling the truth, two professionals badly needed to be struck off. Surely, even in the heavily commercialised American system, such unethical behaviour would count as malpractice?

I imagine Zimmer would be a wonderful pub companion – he could keep one intrigued and enthralled for hours with his endless supply of stories and curious knowledge. But if you're looking for a present for your aunt to help her understand what you do, make sure first that she's a persistent and determined sort of girl.

Andrew P Read
Manchester Centre for Genomic Medicine
University of Manchester

Galton Institute Annual Conference

Due to the current Covid-19 pandemic we have rescheduled our 2020 annual conference and plan to present this year's programme in the autumn of 2021.

The conference title will be:

Genetic studies of populations:
Insights into health and social outcomes