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Galton Institute

Exploring Human Heredity

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Front Cover Image:
Professor Sir Barry Cunliffe receiving the Galton Plate from Professor Veronica van Heyningen at our 2019 Conference at the Royal Society

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EDITORIAL

In 2020, our President, **Professor Veronica van Heyningen CBE, FRS**, steps down after six years of dedicated and inspirational leadership. She has overseen major changes to the Galton Institute including the new website, the Teachers' Conference, the Artemis Trust and this publication. We thank her for her committed service. To mark the occasion, she is the subject of this issue's 'My Life in Genetics' which makes for absorbing reading and can be found on page 14. In it she reveals some fascinating details of her childhood and undergraduate days at Cambridge. Our new President, who will take over at the AGM in June, will be unveiled soon.

In October, the Annual Conference was held at the Royal Society and the theme was 'New Light on Old Britons'. The programme was put together by **Professor David Coleman** and resulted in a thought-provoking insight into the history of the British people. A superb variety of speakers took part and the various podcasts can be viewed on our website – just follow the links from the Home page. There is also a detailed report of each talk, starting on page 4 of this issue.

Preparations for the 2020 Conference are well under way and the theme will be **'Genetic studies of populations: Insights into health and social outcomes'**. The chief organiser is Professor Caroline Relton and it looks set to be a superb event with a range of top notch speakers. There is already some information regarding this conference on our website where more details will emerge in the coming months.

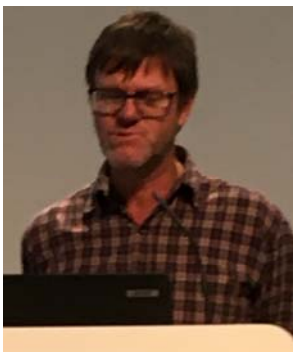
Robert Johnston

The Galton Institute Annual Conference
New Light on Old Britons
30 October 2019 at the Royal Society

This year's conference was held as usual in the Wellcome Trust Lecture Hall of the Royal Society. The full programme is available on our website and was the brainchild of **Professor David Coleman,** ably assisted by **Professors Caroline Relton** and **Dallas Swallow.** The President, **Professor Veronica van Heyningen, CBE, FRS** opened proceedings with a brief account of the aims and activities of the Galton Institute, details of which can be found at **www.galtoninstitute.org**.

The opening session was chaired by **Professor David Coleman** and the first speaker was **Professor Nick Ashton** (British Museum), whose talk was entitled **"The climate, palaeogeography and early human settlement of Britain over the last million years"**.

Professor Ashton began by describing a time when South East England was still attached to mainland Europe, and the Thames flowed further north, with its estuary at Happisburgh Beach in Norfolk. Archaeological evidence unearthed at the site has revealed that ancient humans first arrived in Britain more than 800,000 years ago, when temperatures remained below freezing all winter and only reached highs of 18^0C during summer.


Professor Nick Ashton

These early pioneers shared the grasslands surrounding the river with giant herbivores including elk, mammoths and beavers, explained Professor Ashton, who is part of the Ancient Human Occupation of Britain (AHOB) project that carried out the research. Their excavations revealed flint tools that could have been used for skinning animals, as well as ancient pollen and insects that have provided vital clues to the vegetation and climate.

In May 2013, fossilised human footprints were discovered at the site in a newly uncovered layer of 'laminated sands'. A technique called palaeomagnetism established their age as being 800,000 - 1 million years, making them the oldest human footprints in Europe. Professor Ashton showed the rapt conference audience a cast of one of the footprints, which are thought to have belonged to a mixed group of adults and children, perhaps a family. The size of the footprints makes them likely members of the ancient human species *Homo antecessor*, remains of which have been found at the Atapuerca cave site in northern Spain.

Fast-forwarding to our more recent prehistory, Professor Ashton described the glaciation event of around 450,000 years ago that separated Kent from Europe. Scientists have discovered human remains and artefacts from around this period at an important site near Boxgrove in Sussex, including scrapers that may have been used to make hides. Discoveries in nearby sites have revealed remains of ancient rhinos and lions, as well as burnt flints that may be evidence of human fires.

Professor Ashton's whistle-stop tour ended with an account of more recent arrivals in Britain, who were able to migrate to the country during key interglacial periods - when the climate was warmer but also crucially when the country was still connected to

mainland Europe. Overall, there is evidence for at least 10 colonisations of Britain by ancient humans, with the first modern Britons appearing around 11,000 years ago.

The second talk was presented by **Dr Silvia Bello** and **Professor Chris Stringer, FRS** (both of the Natural History Museum) who spoke about **"The first Britons: bones and behaviour"**.

Professor Stringer spoke first and began by stating that evidence suggests that there were at least 10 separate colonisation events of Britain by early Man. The oldest archaeological site is Happisburgh which probably represents *Homo antecessor*. Huge numbers of fossils of these have been found in Spain and there is significant evidence of cannibalism. By 600,000 years ago, *Homo heidelbergiensis* appears with significant evidence at Boxgrove. The Anglian glaciation followed so that there is no evidence of further colonisation until Neanderthals appear. It would seem that they probably crossed from mainland Europe via Doggerland as did many large mammalian species.

Professor Chris Stringer

The last evidence of Neanderthals in Britain is from 48,000 years ago and it would seem that their demise was due to a lack of genetic variation so that they lost out in competition with *Homo sapiens* and failed to adapt to an ever-changing climate. There is however considerable evidence of cross-breeding between the two species as modern Man would appear to have approximately 2% Neanderthal DNA.

Dr Silvia Bello then considered the evidence for art and other symbolic expression from early Man. For example, Gough's cave

in Somerset provides plenty of specimens of artefacts such as carved ivory, perforated batons and the use of colourants, while it would appear that dead bodies were cannibalised to produce items such as skull cups and engraved radius bones. Other sites provide evidence of ceremonial burial while cave art by Neanderthals has also been found.

Dr Silvia Bello

La Cotte in Jersey reveals the first evidence of social interaction such as co-ordinated hunting groups and the use of bone tools. Quite how such behaviour came about is unclear but it would seem that symbolic behaviour evolved from essential practical behaviour.

The second session, chaired by **Professor Dallas Swallow,** began with **Dr Selina Brace** and **Professor Ian Barnes** (both of the Natural History Museum) discussing **"Ancient DNA and the changing structure of the prehistoric British population: from the Mesolithic to the Bronze Age"**.

They introduced the use of ancient DNA into testing hypotheses concerning the long- held questions of the relative role of the diffusion of ideas and genes. Recently, advances in DNA sequencing technologies have provided a means to generate genome-wide datasets from archaeological remains dating back over thousands of years. Dr Brace explained how these technologies had developed and the complexities and difficulties of generating reliable data. She then introduced the background to their own studies.

Dr Selina Brace

Professor Barnes then reviewed two recent papers of their own, one concerned with the 'Beaker phenomenon' in North West Europe and part of a very large collaboration involving the Reich Group (Boston), focussing on the advent of the Beaker people about 4,300 years ago (approx. 2300 BC) and a second very recent study, focussed specifically on the British Isles, where they were the lead group. For this latter study they used 6 Mesolithic and 67 Neolithic individuals found in Britain, dating from 8500–2500 BC. Using Principal Components analysis and admixture assessment by so-called F4 ratio testing, they showed that the British Mesolithic individuals were more similar to Western Hunter Gatherers than to modern humans, and the Neolithic samples were more similar to modern Iberians than central Europeans. Genetic affinities with Iberian Neolithic individuals indicated that British Neolithic people were mostly descended from Aegean farmers who followed the Mediterranean route of dispersal. With the advent of the Beaker people, another marked change occurred, with another apparent replacement and introduction of a component corresponding to Steppe ancestry.

Professor Ian Barnes

The final speaker of the morning was **Professor Sir Walter Bodmer, FRS** (Weatherall Institute, University of Oxford) who spoke about **"The genetic structure of the populations of the British Isles"**.

The aim of this research was to help trace the mainland European origins of the peoples of different parts of the British Isles. Sir Walter first described how DNA samples were obtained from

volunteers whose parents and grandparents had all lived in the same local area. They were principally from rural communities since people living in urban areas did not generally fulfil this criterion. The DNA was tested for SNPs (Single Nucleotide Polymorphisms) and analysed using a technique that maps their patterns of similarities of distribution along the chromosomes and the individuals were then grouped into separate hierarchical genetic clusters.

This revealed a striking concordance between genetic clusters and geography. Further analysis of the shared ancestry between these UK clusters and similarly analysed samples from surrounding European countries revealed regional patterns of genetic differentiation that carry clear signals of influx events in the history of the UK population. There were 17 significantly different clusters found across the British Isles, revealing just how stable local (rural) populations seem to remain for hundreds of years. The most striking example was in Orkney where the results gave a clear indication of their Norwegian Viking ancestry.

The study also revealed the influx of Anglo Saxons and Danes to different regions as well as the widespread introduction of populations from Northern France. It also highlighted the subtle differences between neighbouring areas such as North and South Wales. Sir Walter went on to consider the evidence for genetic admixture and how such studies have been extended to Irish populations and their relationships to the UK regional patterns. Finally, the problem of how to relate these findings to ancient DNA studies was addressed.

Professor Sir Walter Bodmer

The first afternoon session was chaired by **the President, Professor Veronica van Heyningen, CBE, FRS,** who introduced **Professor Turi King** (University of Leicester) whose topic was **"Genetics and history: how DNA can be used as a window onto the past"**.

Professor King described work carried out for her PhD thesis, when she investigated whether sections of DNA on the Y-chromosome are more likely to be shared by men who share a surname – since both are inherited from fathers. In Britain, the concept of an hereditary surname was introduced by the Normans in the 11th century, and by 1881 there were some 440,000 surnames. Although potentially confounded by false paternity and adoption, Professor King's research into 150 pairs of British men did indeed show that the rarer the surname, the more likely men are to share Y-chromosome DNA.

Professor Turi King

Professor King's interest in genetics and history lead her into studying ancient DNA, another area of research fraught with challenges - notably the contamination of ancient samples with modern DNA. She explained that following early reports of 'dinosaur DNA sequences' that have not been replicated, researchers now adhere to strict guidelines, with DNA from a 700,000 year-old horse being the oldest sequenced so far. For scientists studying ancient human samples, it seems the petrous bone (which contains the inner and middle ear) is currently regarded as the best source of good quality DNA.

Professor King went on to describe her most well-known discovery, the identification of human bones found buried under a car park in Leicester in 2012 as being those of King Richard III.

Aged 32 when he was killed in battle, the skeleton bore evidence of numerous battle injuries, as well as the severe curvature of the spine known to affect the unfortunate monarch. To confirm his identity, the scientists compared his mitochondrial DNA (mtDNA) with that of two living relatives, one of whom was a direct descendant of the king's sister. Since mtDNA is inherited solely through the maternal line, the scientists avoided the false paternity issue inherent with using Y chromosome DNA analysis, and were able to declare with great certainty (odds of 67 million to 1) that the skeleton was indeed Richard III.

Professor King finished by sounding a note of caution about the new 'gold rush' to sequence ancient DNA, saying that minimum sampling must be carried out and precious samples properly archived. She also stressed the importance of multidisciplinary teams working together on such projects, so that all the evidence could be pieced together.

The President then introduced **Professor Sir Barry Cunliffe, CBE, FBA** (University of Oxford) who gave his Galton Lecture on **"The 'Celts' in Britain: a romantic fiction?"**.

Sir Barry began by considering the Celts alongside other ancient peoples. Societies need to understand their origins and how they have evolved. But in the absence of hard facts, early antiquarians had to use their imaginations. For example the Ancient Greeks were a distinct culture with a defined architecture, a rich literature, a recorded history and life style, (they seemed to have spent most of their time fighting each other). The Ancient Greeks called the peoples living north of them in Eastern Europe the *koltoi* (Celts) or barbarians. The Romans called them *Gauls* and were there to be conquered and civilized Roman-style. Antiquarians writing about the Celts between about 1650-1850 had to in-

vent plausible stories about them. Stonehenge apparently was a Celtic temple run by priests called Druids. The Druids were revered as teachers and judges, they worshipped Nature Gods, and Oak Trees, they indulged in blood sacrifices, etc. Surprisingly, Celto-mania has lasted to present times and modern 'Druids' assemble at Stonehenge to continue worship of the Sun at the summer solstice.

However, modern views on the Celts have to take into account hard facts using techniques such as comparative archaeology and Indo-European linguistics to follow the trail of place names, artefact analysis (tools, pottery, and weaponry) and more recently, DNA studies. The Celts might have originated from the Anatolian invasions of Europe around 2500 BCE. The Celts reached their cultural high point in Central Europe between 700 and 100 BC, as exemplified in the La Tene and Hallstadt artefacts in Switzerland and Austria respectively. These two cultures, and presumably many of the other Celtic centres, were assimilated by the expansion of the Roman Empire by about the 1st Century BC.

Professor Sir Barry Cunliffe

At the conclusion of the lecture, the President presented Sir Barry with the Galton Plate to commemorate his lecture.

The final talk of this very successful day was chaired by **Professor Caroline Relton** and was given by **Dr Lara Cassidy** (Trinity College Dublin) on the topic of **"The genomic History of Ireland"**.

Dr Cassidy gave a fascinating account which ranged from the earliest peopling of Ireland to the present day. As well as available

modern samples, she made use of more than 150 ancient samples. These included two rare hunter-gatherer genomes from the Mesolithic period (older than 4000 BC), with the rest ranging in date from the Neolithic (from 3800 BC) and Bronze Age (from 2,200 BC), through to the Late Iron Age and Medieval period (350 AD onwards).

Dr Lara Cassidy

The dataset could be divided into three distinct populations on the basis of ancestry, corresponding to periods of major migration at the start of the Neolithic and Bronze Age. A combination of low coverage shotgun sequence (~1X) and genotype imputation allowed for segments of shared ancestry and haplotype homozygosity to be identified and, together with Y chromosome data, enabled conclusions to be drawn about continuity, patterns of relatedness and the origins of Ireland's modern population. For example, Irish hunter-gatherers show evidence of an extreme population bottleneck, while strong continuity is seen in Ireland from the Bronze Age onwards. However, there is also evidence of more recent migration from elsewhere in Europe, consistent with historical information.

Dallas Swallow
Jess Buxton
David Galton
Robert Johnston

Podcasts

Most of our speakers recorded a podcast, with short video highlights, on the day and you can hear/see them on our website at:

http://www.galtoninstitute.org.uk/podcasts/

My Life in Genetics – an Interview with Professor Veronica van Heyningen, CBE, FRS, President of the Galton Institute

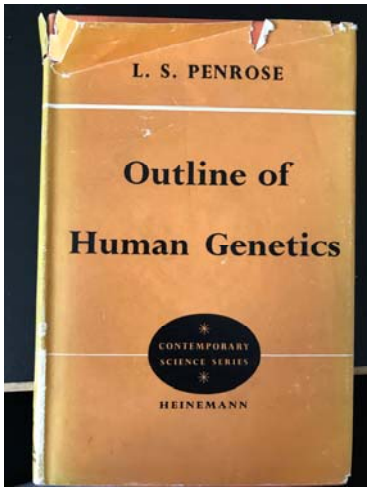
Tell us about your family background and early education

My family came to the UK in January 1958, soon after the 1956 Hungarian uprising. My parents, both holocaust survivors who had lost all the rest of their families, had longed to leave Hungary since their return from the camps in 1945, but the arrival of Russian communism prevented it. After the uprising, there was a bit of a gap that allowed people to leave. When we finally arrived, I was 11 years old and my sister not quite 9. We went straightaway to primary school in Worthing, Sussex where my mother's retired uncle lived. We had entered the UK with a proper immigrant passport and entry permit. Uncle Peter, in Britain since 1919, had agreed to "vouch" for us. We lived with him in his bungalow for a few months until my father, an experienced textile engineer and well-published expert in knitting technology, got a job in Loughborough, Leicestershire, with a knitwear company that made merchandise for Marks and Spencers.

Veronica

In 1958 the 11+ still ruled, but the exam had taken place just a few days after we arrived in Worthing, so I took a special exam at the Leicestershire Education office in August. Though I passed

with flying colours, there were no places left at the top Loughborough schools, so they sent me to a somewhat experimental, large, heavily streamed, comprehensive in a nearby village. It was a diverse and interesting school: a centre for music education (which I enjoyed, but was not gifted at), and excellent science teaching which eventually reconciled my father to the school being mixed. The whole top stream took eleven O-levels in four years. One of the O-level prize books I chose that year was "Outline of Human Genetics" by Lionel Penrose. In 1962 I entered the sixth form to study Biology, Chemistry and Physics. With these three A-levels under my belt, while working to take A-level Maths, I also took the entrance exams for both Oxford and Cambridge. With offers from both places arriving by telegram after the January 1965 interviews, I chose to go to Girton College Cambridge to read Natural Sciences.



What were your early steps towards genetics?

Cambridge was exhilarating, lots of hard work but also great fun. There were only single-sex colleges then, just three for women, so the ratio was nine men to every woman undergraduate. The colleges were *in loco parentis* in those days and we had to be back in college by 10.45 pm, a long bike ride from the centre of Cambridge. It was in those days that my night-owl character emerged, writing three essays a week after returning by the early Cinderella hour from debates, cinema, theatre and party trips most evenings. In the second year, after a bout of infectious mononucleosis (Epstein Barr virus infection) I did not do well enough to get into

Biochemistry for the third year, but recalling with great pleasure our school Drosophila breeding experiments and my reading, at school and in Cambridge, about genetics, viruses, evolution and life cycles, I happily signed up for Genetics Part 2, despite the disappointment of the Part 1 results. There was a compulsory “long vacation term” for Genetics during the summer of 1967 and it was during this time that I started meeting socially with Simon van Heyningen, who had given Biochemistry supervisions to me and another Girtonian during the second year. We both happened to be going to Israel (separately) just after their “six-day war” and our friendship was cemented there and we got engaged in October just before I began Genetics in earnest with nine young men in our class of ten. Much of the course that year was very exciting. I recall Sidney Brenner visiting the department to tell us he was going to study a small 1000 cell worm (*C. elegans*) to decipher neural development. At the end of the year I got an upper second and the Genetics Department would have accepted me for a PhD, but Simon finished his thesis, we got married and went to Northwestern University near Chicago for his postdoc.

After two interesting years, with a Northwestern Master’s degree in biochemistry, we left for Oxford where Simon was appointed a University Demonstrator in Biochemistry. I managed to get a DPhil place with Walter Bodmer, just arriving in 1970 from Stanford University to take up the new Chair of Genetics, created in a sub-department of Biochemistry. Walter was a very young Professor who had recently turned to the new technology of human gene mapping using somatic cell hybrids. This was of huge interest to me as I had been reading about biochemical genetics and regulation of gene expression at Northwestern. At that time before the dawn of DNA technology, we could only study genes through their protein products. In fact, throughout my doctoral studies, we had excellent collaborations with young scientists such as Sue Povey and Dallas Swallow at the MRC Human Bio-

chemical Genetics Unit which was then led by Harry Harris who was Galton Professor of Human Genetics at UCL. Their expertise in electrophoretic separation of polymorphic enzyme variants was critical for the studies to distinguish human and rodent enzymes for human gene mapping.

Tell us about the fast progressing world of new genetic technologies

Like everything in biology our work evolved with the environment: meaning both the state of knowledge and technical know-how and where we found ourselves. Once more, the last time it was necessary, I followed Simon to Edinburgh, where he took up a University Lecturer post. Luckily, I had been awarded a portable (and prestigious) Beit Memorial Fellowship and could choose my postdoc place. I went to the MRC Mammalian Genome Unit, where Ed Southern was just inventing the eponymous DNA-blotting technique.

It is generally impossible to do meaningful research in genetics in isolation from progress near and far. There have just been unprecedented advances in our understanding of genetics within my professional career span. Somatic cell hybrids (fused products between two cell types – in this case two species, human and rodent) were enormously useful, but now pretty passé. Gene mapping technologies evolved with the advent of Southern blotting and later PCR amplification and then sequencing. Combined with the use of natural or artificial chromosomal rearrangements, fine mapping also helped with early identification of disease causing gene variants. Mapping chromosome 11 with my great collaborators Nick Hastie and Wendy Bickmore became a major project as I evolved into a group leader at the MRC Human Genetics Unit. It was intertwined with the search for the genes mutated in the childhood kidney tumour gene WT1 and the gene altered in aniridia

(absence of the iris). Varying size deletions on chromosome 11p were implicated with the occurrence of the two diseases together. Using these, immortalised in somatic cell hybrids, led to the identification and validation of the two genes. PAX6, the aniridia-associated gene, emerged in 1991 and turned out to be a major regulator of eye and brain development. Since then I have worked mainly on eye development and disease. My small lab, with Dirk Jan Kleinjan as the critically important long-term postdoc, then spent many years exploring the detailed function, downstream targets and regulation of expression of PAX6. We worked with great diagnostic ophthalmologists and wonderful scientists, particularly with clinician-scientist David FitzPatrick at MRC HGU, to study the full spectrum of PAX6 related disease and to identify other genes implicated in severe eye malformations: such as microphthalmia (small eyes) and anophthalmia (no eyes). We were intrigued and excited to find that most of the identified genes worked together in complex finely tuned networks. In many individuals carrying mutations in SOX2 and OTX2, two other major eye and brain development genes, there were severe associated brain anomalies.

What are the current and future approaches to understanding gene function?

Animal models were always important for testing hypotheses and observing in detail the effects of mutations, moving from disease to biology and back. A major emerging interest has been the study of gene regulation. PAX6, SOX2 and OTX2 are interacting DNA-binding transcription factors, involved in regulating development through controlling the expression of target genes. They are finely controlled by each other, by themselves (feedback self-control) and other genes. The large non protein-coding regulatory domains flanking the PAX6 gene particularly, “empty” regions pre-

viously considered junk DNA were our major target for exploration. Most recently, in “retirement”, we have identified non-coding region mutations on two different chromosomes in developmental disease of the macula. Molecular and functional dissection of non-coding regulatory variants is one of the future challenges for genetics, particularly since almost all common disease “markers” identified by huge population studies lie clearly in the non-coding regions of the genome. Increasingly affordable whole genome sequencing will pinpoint these variants. We have used dual colour fluorescent transgenic techniques in zebrafish to explore the function of different variants at regulatory sites. Refinements of this approach, perhaps using human stem cells as the read-out, may be the way forward to understanding mechanisms of gene regulation, in health and disease. Gene editing to ameliorate disease cannot be contemplated until we understand how things go wrong in genetic disease. I think germ-line gene editing is a long way in the future and may never be feasible. But somatic gene editing may be a more achievable and safer possibility, for example in some late onset diseases. Meanwhile, RNA technologies to modulate faulty DNA function, are in clinical trials with some very severe neuro-degenerative diseases such as Spinal Muscular Atrophy and in Huntington Disease.

You have taken on a number of important leadership roles. Explain why you put yourself forward

If you look at my CV, you see that I have been on a lot of committees and been President of the European Society of Human Genetics, the Genetics Society and now the Galton Institute. When asked to fill such roles I like to challenge myself to undertake the task to the best of my ability. One of the most enjoyable aspects is the opportunity to be involved in organising good meetings with clear cutting-edge themes, to educate participants, and

ultimately myself too, during the process of developing ideas and creating new links between scientific areas and diverse speakers. I like to write a one-page summary so the invited speakers can see how I hope they will fit together and gratifyingly often they rise to this challenge superbly.

Tell us a surprising thing about yourself

People probably consider me confident and fearless in public, but I am often very nervous before and sometimes during public appearances, so much so that I feel I will forget what I wanted to say and even what words to use, although I have quite a good memory when relaxed. Often I could probably sound more natural and convey ideas more smoothly if I could discard these fears.

Professor Veronica van Heyningen, CBE, FRS