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Exploring Human Heredity

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EDITORIAL

I apologise for the considerable time that has elapsed since the last issue was published but I hope that you've managed to cope throughout this trying year. Following discussions over many months, the Trustees of the Galton Institute have chosen a new name for our organisation – **Adelphi Genetics Forum**.

On page 19 you will notice that once again there will be no Conference this year so the next Conference will be in the autumn of 2022 and will be devoted to the history and legacies of Galton and Mendel.

Our Treasurer, **Professor Andrew Read**, has contributed two typically entertaining articles. One is a book review and the other is a very topical argument for use with any vaccine deniers you may encounter.

Finally, there is a fascinating article concerning Francis Galton by our Vice-President and expert in this field, **Professor Gregory Radick**.

Robert Johnston

My Life in Genetics

**An Interview with Professor Nicholas Wood
Trustee of the Galton Institute**



Professor Nicholas Wood

What first appealed to you about studying genetics?

I bought a book in the summer after O-levels - titled something like 'the physical basis of personality'. It was old even as I bought it but I think it intrigued me that something encoded in our genes could influence complex behaviours. I actually forgot I had bought it till many years later, and certainly post medical school. But I ended up being intrigued by neuroscience and genetics. So the book turned out to be prophetic.

What have been your main areas of expertise?

I have tried to combine my interest in how the nervous system works, and in disease states fails to work, and my interest in genetics. So I have spent much of the last 30 years studying the genetic bases of neurological disease. This has involved pretty classical linkage and gene identification strategies as well as trying to dissect complex traits using GWAS.

Who have had the greatest influence on your work?

It is always difficult to single out individuals, because of course we are all influenced by large numbers of people who have come before us. The debate of a century or more ago about what we would now call single gene and complex traits, still resonates with me now. We now have tools to address these issues in a systematic manner and that is pretty exciting. Personally, my PhD Supervisor Prof Alastair Compston FRS, has had a great influence on my scientific training, introducing me to complex trait genetics through work on multiple sclerosis. In fact, during my thesis I used the method of sib-pair analyses pioneered by Lionel Penrose.

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

I believe we need to continue and improve our engagement with the general public to inform them of what genetics can, and cannot, offer. I am very excited about the prospects for ge-

omic medicine for both rare (single gene) and also complex traits such as Alzheimer's and Parkinson's and hope we get to introduce some disease modifying treatments in the next few years.

What do you think the Galton Institute can contribute to the field of genetics?

I think that a forum that helps improve knowledge transfer is incredibly important to our field and the Galton Institute has a role in this.

Tell us something about yourself that's not generally known

I went to a not very academic comprehensive school and although it didn't turn out too many academics, Paul Hollywood (Great British Bake Off) and Simon Rimmer (TV chef) were there at the same time. So it did turn out cooks.

Previous contributors to the *My Life in Genetics* series are:

Professor Dallas Swallow	Issue 14
Professor David Galton	Issue 13
Professor Andrew Read	Issue 12
Professor Veronica van Heyningen	Issue 11
Professor Dian Donnai	Issue 10
Professor Philippa Talmud	Issue 9

Some thoughts about vaccine risks

The Pfizer and Moderna Covid vaccines are synthetic messenger RNA molecules encoding the virus spike protein. Claims are circulating on social media that the vaccines are dangerous because the RNA might permanently alter a person's genome. A colleague forwarded me one such, let us call her correspondent Donald, and asked my opinion because Donald's message looked rather scientific, including references to publications about possible atypical actions of DNA polymerase. This is my reply:

Rational people know that nothing is ever "safe" in any absolute sense. Instead of demanding that a vaccine should be totally free of every possible risk, they look at probabilities. The vaccine works by getting spike protein mRNA into the cytoplasm of cells. So let us consider a molecule of the vaccine RNA that has got into a cell.

- First, to be dangerous, it must get into the nucleus. That's not a normal thing for cytoplasmic RNA to do. Proteins have nuclear localisation signals that engage a specific nuclear import mechanism, but RNA molecules do not. Retroviral gene therapy vectors are restricted to dividing cells precisely because they can only access the nucleus during mitosis when the nuclear membrane has dissolved. So we should not dogmatically assert that our vaccine molecule cannot enter the nucleus, but the odds against must be several powers of ten.
- Having nevertheless entered the nucleus, our RNA molecule must be reverse transcribed into DNA, which must

then integrate into the host genome. Ordinary cells lack the reverse transcriptase needed to do this, but it is suggested that DNA polymerase might occasionally do it. This cannot be a frequent event. If it were, the nucleus being full of nascent mRNA, cells could not maintain the integrity of their genome. So, maybe not impossible, but a good few more powers of 10 on the odds against.

- Having integrated into the genome, the spike protein sequence must somehow affect transcription of other genes. The precedent for concern comes from early trials of gene therapy for immunodeficiency using retroviral vectors. Occasionally the vector integrated upstream of the LMO2 oncogene. The powerful retroviral promoter activated the oncogene, causing the patient to develop leukaemia. But the relevance is questionable because, unlike those vectors, the vaccine molecule has no promoter. I suppose it might integrate into a sequence that is already being expressed from its own promoter – but the odds against any such event being pathogenic must be several more powers of ten.
- So against all the odds, we have a single naughty cell somewhere near the injection site in the muscle of our upper arm. Please, dear Donald, explain why this matters – in return for some more powers of 10.
- Anyway, there we are. Rather an unlikely risk of the vaccine, but as a good scientist I'm not prepared to say utterly impossible. So Donald declines vaccination. So with a probability between 10% and 80% he gets infected. And what's the first thing the virus does when it gets inside him? It injects its mRNA into his cells. Go to (1).

Andrew Read

**CHASE Africa progress report
to the Artemis Trust of the Galton Institute
1st July – 31st December 2020**

As described in our previous report, the COVID-19 pandemic necessitated significant changes to our family planning service delivery methods during the first half of 2020. Those successful adaptations then formed the template for our continued work during the second half of the year, to improve access to family planning information and services in marginalised rural communities of Baringo County, Kenya. The biggest changes from the original plan were the substitution of large mobile day clinics with smaller scale ‘back-pack nurse’ outreaches, and the scaling up of door-to-door visits by Community Health Volunteers (CHVs) for awareness raising and referrals. Although these changes resulted in a smaller number of people being reached with family planning information (because of the lack of large crowds gathering for meetings), the home visits and private discussions have been very effective in changing people’s perceptions of modern family planning, leading to a high number of first time users.

Outputs

During the second half of 2020, Community Health Volunteers continued to make door-to-door visits in marginalised rural communities in the Eldama Ravine area of Baringo County, where tradition and cultural norms strongly oppose the use of family planning. In the targeted communities, knowledge and understanding about modern contraceptives is extremely poor, and many negative myths and misconceptions abound, further dis-

suading people from taking an interest in using modern methods of family planning. The purpose of the door-to-door visits is to engage residents in conversation about the benefits of modern family planning and to correct any misinformation and erroneous beliefs held by the householders. Between July and December 2020, 12 CHVs made door-to-door visits and were able to make referrals to 6 linked health facilities when women chose to try family planning. Those 12 CHVs were supported by a further 26 CHVs who were trained to assist with the door-to-door visits and discussions.

In some communities visited, the nearest health facility is very far away or the roads are very poor, and this presents a problem for accessing family planning services due to the time and cost involved in travelling. These are the areas in which, ordinarily, our partner organisation - Dandelion Africa - would have arranged a mobile day clinic to provide the lacking services. Since the large day clinics are currently suspended due to the coronavirus pandemic, Dandelion Africa has instead set up 'safe spaces' at 3 such locations (Andama, Gatarakwa, and Soy mining). These 'safe spaces' are rooms from which the back-pack nurses can run their mini clinics, offering reproductive health services. Two back-pack nurses visit each safe space once a month, so clients living near to the safe spaces are referred to one of the back-pack nurse outreaches, rather than a distant health facility, making the family planning services more accessible.

During the reporting period, 2,754 females and 1,102 males were reached with family planning information, totalling 3,856 people altogether (a slight increase from the 3,499 people reached during the first half of the year). 1,706 women received contraceptives, of which 1,018 were first time users.

This is in line with our estimate that 1,620 women would receive a family planning method during the second half of the year. In an effort to ensure our services are available to all, 11 women living with disability were visited at home by the 'back-pack nurse', rather than requiring them to attend the 'safe space' to receive family planning services (persons with disability includes physically disabled, hearing impaired, visually impaired, mental health problems, learning difficulties, albinism). The total couple year protection (CYP) provided during the reporting period was 2,655.



A community Health Volunteer provides information to a client about the available types of contraceptives at a back-pack nurse 'safe space'

Challenges

In September/October, late November and throughout December, MoH healthcare providers in Eldama Ravine went on strike over the level of pay. This meant that for a significant portion of the reporting period the CHVs were unable to refer clients to the health facilities for family planning services, and this limited the number of contraceptives provided overall.

Heavy rains and poor infrastructure also hindered the fourth quarter's performance, with rivers flooding and roads impassable, preventing clients from accessing health facilities, and CHVs had difficulties with movement. This was mitigated partially by the three 'back-pack' nurse safe spaces. In addition, however, the rains from October to December gave community members a chance to engage in agricultural activities, which were given priority over reproductive health services during that period, and this further affected the total number of women who received family planning.

It was unfortunate that the second half of 2020 saw additional challenges on top of the coronavirus pandemic, which further curtailed the number of people we were able to reach. However, it is encouraging that during this reporting period we were able to improve on the number of people reached with family planning information compared to the first half of 2020. Also, despite the difficulties, the number of women who chose to receive family planning during this reporting period remained in line with our projection.

We are very grateful for the support we receive from the Trustees of the Artemis Trust of the Galton Institute.

BOOK REVIEW

Paul Nurse: What is Life?

David Fickling Books, 2020

This attractively produced little book is an obvious homage to the little book of the same title that the Nobel prize-winning physicist Erwin Schrödinger (he of the cat) wrote in 1944. That book has been credited with motivating physicists to move into biology. I have to say either Schrödinger didn't have the art of homely analogy, or maybe I don't have the art of thinking like a physicist. For years I was baffled by his conclusion that living organisms are systems that feed on negative entropy from their surroundings. Why couldn't he have said that living organisms and their cells need mechanisms to create and maintain order, and they need external energy to power those mechanisms? A kitchen fridge provides a good analogy. As long as the compressor works and has a power supply it can pump heat from its cold interior to the warm kitchen, and avoid thermodynamic equilibrium. You could say it runs on negative entropy from your kitchen – but would you?

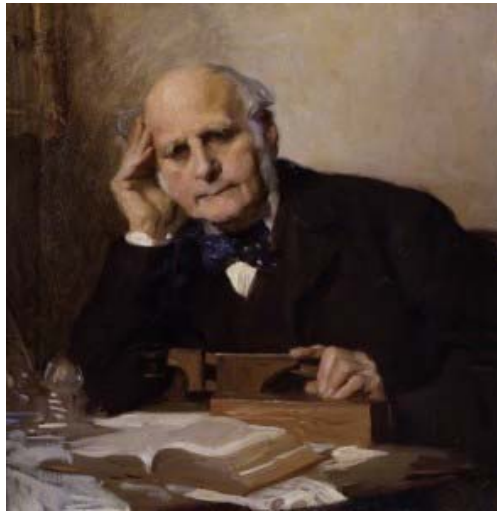
So how does Nobel prize-winner Paul Nurse do? Reading his book is like having an informal chat with a knowledgeable uncle. There are no figures or other display items, no index or references – deliberately, I'm sure. In general it feels aimed at the Greta Thunberg demographic – which is no bad thing. His subtitle is *Understand Biology in Five Steps*. So there are five central chapters: Cells, Genes, Evolution by Natural Selection, Life as Chemistry and Life as Information, sandwiched between a short general introduction and a chapter on Changing the World. His conclusion is that all living things have three cardinal

properties: their ability to evolve by natural selection, their existence as bounded physical structures, and their nature as chemical, physical and informational machines. It's interesting how different this list is from Schrödinger's much more abstract view. None of Nurse's principles would have been unfamiliar to biologists in Schrödinger's day, though of course they are now supported by much larger bodies of evidence. I have to conclude that Nurse understands Life better than Schrödinger, and not just because we know so much more now.

It's all rather cosy, some might say a bit pedestrian. Nurse doesn't do razzmatazz. The overall picture is of a CP Snow world of benign individuals collaborating to build the tree of knowledge. But let's not be cynical – we humble toilers know that's somewhere between 90% and 99% accurate. And times have changed, thank goodness. We're once more allowed to respect expertise and admire the scientists who have produced the Covid vaccines. He includes an aspect that Schrödinger did not understand: the inherent contingency and messiness of biology. Sadly for those physicists, evolution does not progress by the gradual unfolding of grand designs, but by an endless succession of small bodesges and quick fixes. The more you get down to molecular detail, the less evidence there is of elegant universals. Even the double helix gets messy when closely examined. And Nurse gives ample expression to the sheer wonder that anybody who understands a bit of biology must feel when contemplating Life, the Universe and Everything. So, a good one for your interested teenager, though you may have to put in a bit of work explaining the chemistry.

Andrew Read
Treasurer of the Galton Institute

Francis Galton and the Complexities of History and Heredity



Sir Francis Galton

What comes to mind when we think of Francis Galton? The inescapable first thought has to be: eugenics. It's not merely that Galton gave us the word (from Greek elements: *eu*, good + *gen*, birth), or that he campaigned hard for the uptake of the idea, inspiring the founding in 1907 of the Eugenics Education Society, ancestor to the Galton Institute. The dream of steadily improving physical, mental and moral quality in the human "stock" through selective breeding really did spur Galton to his decades of innovative work in heredity and statistics. And that dream, of course, went on to become an appalling nightmare

for millions of men, women and children around the world.

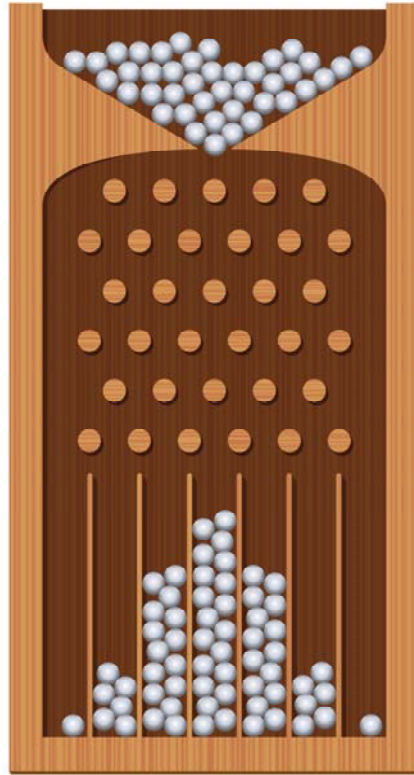
So it's right and fitting that Galton has come to be so closely identified with eugenics. But behind that identification lie some complexities. For one thing, although Galton invented the name that stuck for human stockbreeding, he was hardly the first person to propose the idea. It goes back at least to Plato, and gained adherents throughout the nineteenth century, by multiple routes. Among that era's asylum doctors, for example, "eugenics was old hat" before Galton had published anything on heredity, according to the historian of science Theodore Porter in his prize-winning *Genetics in the Madhouse: The Unknown History of Human Heredity* (Princeton, 2018). The asylum doctors' statistical studies convinced many of them that insanity was inherited, and that the best way to halt its spread was to prevent insanity-prone individuals from breeding. Had Galton never existed, eugenics would probably have emerged as a public force in the early twentieth century, under another name and with different figureheads.

Other complexities are to do with Galton's own views on heredity. Understandably enough, it's widely supposed that anyone who backed eugenics must have believed that heredity is destiny. Why else endorse selective breeding as a cure for society's ills? Many eugenicists were – and, alas, are – "hereditarians" along exactly these lines. A notable hereditarian in Galton's immediate circle was the UCL mathematician Karl Pearson. Pearson could not have been more indifferent to the modifying power of the environment. The same was true of another major Galtonian of the day, the Cambridge biologist William Bateson, champion of the new science of Mendelism. Opposed in the debate that broke out in the early

twentieth century over Mendelism, Bateson and Pearson were alike in agreeing, as Bateson's ally Reginald Punnett declared in a popular book on Mendelism in 1905, that "[p]ermanent progress is a question of breeding rather than pedagogics; a matter of gametes, not of training." For if, Punnett went on, there was one thing that the new scientific students of heredity were learning, it was that "the creature is not made but born."

Yet Galton took the interacting effects of heredity and environment – and more generally, the shaping influence of contexts, internal and external – seriously, as I stress in a book to be published next year with the University of Chicago Press, *Disputed Inheritance: The Battle over Mendel and the Future of Biology*. It's well known, of course, that Galton in the mid-1870s introduced the now-familiar juxtaposing of "nature" and "nurture" into everyday English. What's not widely appreciated is that Galton at this time was concerned that, as he saw it, he was being caricatured as a hereditarian. ("Hereditarian" was then a new word, first used disparagingly in connection with Galton.) A lazy response would have been to draw attention to passages in his previous writings on heredity where he had given contexts their due – as in his explanation of why, so often, hereditarily gifted parents do *not* produce equally gifted offspring, even when the latter inherit the gametic ingredients. Instead he threw himself into a series of new clarifying projects. Out of this burst of creativity came not just the phrase "nature and nurture" but a new, context-foregrounding theory of the physiology of heredity; the inauguration of twin studies; and the invention of a mathematical demonstration device that now goes by several names, including the "Galton board" and the "quincunx."

Watch one of these devices in action – the internet is full of examples, real-life and computer-generated – and you’ll see pellets bounce their way down from a central opening at the top through an array of pegs to form a bell-shaped pile at the bottom. (The pegs are arranged in a repeated five-point pattern, hence “quincunx”: an old, Latin-derived word.) The quincunx has long been the standard way to show how chance and causation combine to produce a normal-curve distribution. Galton first used the device publicly in an 1873 lecture not on statistics, however, but on heredity, indeed on “nature and nurture.”



Understood as a nature-and-nurture device, the quincunx shows development as a process whose result is in no way fixed from the start. With each pellet representing a hereditary character, bound initially for averageness, and each peg representing an impinging cause, internal (to the gametes, to the mother’s uterus) or external (light, heat, nutrition, upbringing), any individual character/pellet can take any number of possible developmental trajectories, depending on the particular causes encountered and the chance outcomes of the encounters.

Later, in the debate over Mendelism, the Oxford biologist W. F. R. Weldon drew on Galton's quincunx-vintage work to counter what Weldon saw as the systematic ignoring of context and variability built into Mendelian concepts and methods.

So yes, by all means, let us think first of eugenics when we think of Galton. But our second thought, I suggest, should be of the quincunx, recalled in the spirit in which Galton introduced it: as an emblem of the notion that inherited characters are multifactorial in their causation and variable in their expression. Interpreted in this way, the quincunx can thus serve as a reminder at once of the complexities of heredity and the complexities of history – Galton's history very much included.

Gregory Radick
University of Leeds

Galton Institute Annual Conferences

Due to the current Covid-19 pandemic we have postponed our *Genetic studies of populations* conference to 2023.

2022 is the 200th anniversary of the birth of both Galton and Mendel and we are planning a conference around this theme in the autumn of 2022.

