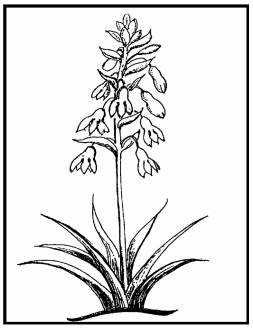
ISSN 1359-9321



Galtonia candicans

The Galton Institute

NEWSLETTER

Issue Number 67 June 2008

EDITORIAL

Presidency of The Galton Institute

At the end of six active years as President of the Galton Institute, for which, in acknowledging his constant concern, we can here warmly express sincere gratitude, Professor Steve Jones has been succeeded by Professor Sir Walter Bodmer, on whom Anthony Edwards has provided the following note.

Sir Walter Bodmer, who gave the 2008 Galton Lecture *Population genetics and the concept of individuality*, became a Fellow of the Eugenics Society in 1961 and served on the Council from 1971 to 1974. A Cambridge mathematician, in his third year he attended genetics lectures by Sir Ronald Fisher, then in his retirement year as Arthur Balfour Professor of Genetics. Sir Walter joined his department as a Ph.D. student, and happily Fisher carried on in the department pending the election of his successor, greatly influencing a whole generation of students. In the 1920s and 30s Fisher himself had been influential in the Eugenics Society, acting as its business secretary for a while.

In 1961 Sir Walter left Cambridge for Stanford University to work with Joshua Lederberg in molecular biology. While there he initiated work with his wife, Julia Bodmer, and Rose Payne, which contributed to the discovery of the HLA system. In 1970 he left his Professorship of Genetics at the Stanford Medical School to become Oxford's Professor of Genetics. He was elected FRS in 1974 and in 1979 moved to London as Director of Research at the Imperial Cancer Research Fund Laboratories, becoming the first Director-General of the Fund in 1991. Retiring in 1996, he returned to Oxford as Principal of Hertford College. Since the end of his tenure as Principal he has continued as head of the Cancer and Immunogenetics Laboratory at the Weatherall Institute of Molecular Medicine, with a special interest in cancer genetics, particularly colorectal cancer.

Knighted in 1986 for services to science, Sir Walter is a Foreign Associate of the US National Academy of Sciences and the recipient of more than thirty honorary degrees and fellowships of scientific and medical societies.

In the 1970s Sir Walter was the chairman of a British Association committee examining the implications of recent advances in genetics which resulted in a book, *Our Future Inheritance: Choice or Chance?*, co-authored by Alun Jones the committee's secretary. His well-known books with L.L.Cavalli-Sforza, *The Genetics of Human Populations* (1971) and *Genetics, Evolution and Man* (1976) are testimony to an outstanding breadth of interest in the science central to the purposes of the Galton Institute.

A. W. F. Edwards

Contents

Published by:

The Galton Institute
19 Northfields Prospect
Northfields
LONDON SW18 1PE
Telephone: 020 8874 7257

General Secretary:
Mrs Betty Nixon

Newsletter Editor:
Milo Keynes

Web site:
www.galtoninstitute.org.uk

CELEBRATING 100 YEARS OF MEDICAL GENETICS AT THE RSM

A joint meeting of The Galton Institute and The Royal Society of Medicine, May, 22-23 2008

Report on the proceedings made by David Galton

Professor Sir Patrick Bateson is a distant cousin of William Bateson (1861-1926) who invented the word 'genetics' in 1905 and who, in his book entitled '*Mendel's Principles of Heredity*' CUP 1909, had long adopted the Mendelian standpoint whole-heartedly. This led him into direct conflict with the biometricians of the day, notably Karl Pearson, who believed that heredity involved continuous variation or blending of traits. Due to the personalities involved the debate became quite bitter and was still ongoing well after 1912. The conflict was finally resolved in 1918 by R A Fisher (1890-1962) who showed how both views were compatible if one considered that a few discrete genes acting together could produce the appearance of continuous variation in inherited traits as is found, for example, in skin colour.

Professor Sir David Weatherall went on to praise the work of another early pioneer of heredity, Sir Archibald Garrod (1857-1936). Garrod was fascinated by the various colours of the urine due to the pigments produced in different conditions. One in particular, alkaptonuria causing the urine to become black on standing, was particularly interesting because in some first cousin marriages it occurred in a ratio of 1:3 in the resulting offspring. This was published in the Lancet in 1902 and William Bateson recognised these numbers as conforming to a Mendelian ratio of inheritance as initially described for the garden pea. Alkaptonuria, with the description of several other metabolic disorders, formed the basis of the Croonian Lectures given by Garrod in 1908 that firmly placed Mendelian genetics into the field of human heredity. Sir David ended his lecture by showing how a single monogenic blood disorder could still lead to a very complex phenotype depending on the influence of other factors such as: genetic modifiers; the effects of parental imprinting and other events that modify gene expression during development (e.g. epigenetic effects such as DNA methylation or histone modification); and differing adaptations to environmental conditions.

The Galton lecture was delivered by **Professor Sir Walter Bodmer.** He gave a fascinating account of how work on polymorphic systems, starting with the ABO blood groups, and then the HLA system, to the knowledge of which he made fundamental contributions, has led to an explosion in the study of how genetic variation can affect disease susceptibility. His own work on the genetics of colorectal cancer was one of the early valuable benefits of this approach; and his methods are now used routinely to detect subjects who carry such a genetic predisposition in clinics around the world. His ideas and writings on the subject have led to most fruitful developments as exemplified by the Wellcome Trust Case-Control Consortium. The rapid advances in DNA technology including the use of polymorphic markers, DNA hybridisation techniques, and fast DNA sequencing methods have entirely replaced the old serological and electrophoretic techniques and have allowed the study of the genetics of 12 common diseases discussed later in the meeting.

However Sir Walter's current interest is to use the new technology to study relationships between various human populations, their geographical origins, their migrations and to relate this to the available historical and archaeological information.

Professor Marcus Feldman continued on this theme using up to 800,000 polymorphic DNA markers to track population movements. It is difficult to do these studies in North America because ethnic status is such a politically sensitive issue – no doubt due in part to their recent history of slavery. So the project was moved to the world stage. His work has shown beyond question that hominids migrated out of Africa to colonise the middle and Far East as well as Europe. He ended his lecture by suggesting that we should drop the term 'race' which is a social construct; and adopt instead the term 'ancestry group' which is a more biological and less pejorative construct.

The rest of the lecturers for the first day dealt with genetics applied to various disorders including infectious disease (**Professor Adrian Hill),** allergies (**Dr. John Holloway)**, male infertility (**Dr. Ken McElreavey) and** the muscular dystrophies (Professor **Francesco Muntoni**).

The second day returned to some more general topics. **Professor Peter McGuffin** addressed the genetics of behaviour. Some gene abnormalities clearly influence behaviour as in Huntington and Alzheimer's diseases to give two obvious examples. However other common disorders such as schizophrenia or bipolar disorders have proved more refractory to genetic analysis. Even genome wide scans have not clarified the issues. But Professor McGuffin believes that such scans will, ultimately, improve our understanding of the neurobiology of these disorders.

Professor Mandy Fisher then dealt with the epigenetics of development, that is how patterns of gene expression are established and maintained through cell division and changed in an ordered fashion during development. She described three main ways of controlling genes over the long term: 1. Modifying the histones associated with DNA, 2. Use of small regulatory RNA molecules to silence stretches of DNA and 3. Covalent modification of DNA by methylation. Such changes can alter the packing of nucleosomes to vary the access of transcription factors and RNA polymerases. She illustrated aspects of this in her own work of attempting to re-programme lymphocytes to an induced-pluripotent state i.e. to be more like stem cells. This would have important implications for regenerative medicine.

Professor Eamonn Maher talked on cancer genetics taking von Hippel-Lindau disease as his model. This dominantly inherited cancer syndrome predisposes to retinal and cerebeller haemangioblastomas, renal cell carcinoma, and phaeochromocytoma. His laboratory analysis has shown that activation of HIF-2 transcription factors appears to be a major

drive for oncogenesis in renal cell carcinoma.

Ageing appears a necessary ordeal that we all have to endure and **Professor Tom Kirkwood** tried to explain why. Genes are clearly involved - up to about 25% of the variance in life span may be genetic - and rare diseases such as Werner's syndrome and other progerias illustrate this well. But Professor Kirkwood's view is that ageing is due to the accumulation of a multitude of small errors occurring in various bodily systems such as: DNA repair mechanisms, antioxidant defence mechanisms, inability to re-structure proteins properly, mitochondrial and somatic cell mutations, and various forms of tissue damage due to poor nutrition, trauma etc. The quest for an elixir of life appears therefore to be a very difficult issue.

Professor Peter Donnelley gave a short account of the Wellcome Trust Case-Control Consortium, a collaboration of more than 200 UK scientists studying the genetics of 12 common human diseases. He presented the results of 7 of them including coronary heart disease, hypertension and diabetes mellitus (Types 1 and 2). The analysis was based on 2000 cases and 3000 controls, 1500 of which came from two different sources. They were ethnically matched and genome wide scans were performed. 19 loci were associated with Type 2 diabetes and 30 loci with Crohn's disease. But much further work by fine-mapping, DNA re-sequencing and functional studies are needed to identify the functional gene variants that underlie these associations.

Professor Rory Collins pointed out that the important problems of gene-environment interactions are not being studied properly in either retro- or prospective studies. After giving examples he showed how small numbers of cases, inadequate analysis of all the environmental circumstances and incomplete measures of confounding factors have all led to confused and unclear results. He believes the subject needs much larger blood-based prospective epidemiological studies in a range of environmental settings with detailed follow-up of cause specific morbidity and mortality to get a clearer picture of such interactions.

The thorny topic of personalised genomics was discussed by **Dr. Joanna Mountain.** Selling people the details of their genome (for about $1000) may possibly be of use to them but is also likely to generate a great deal of anxiety in the worried-well population in a field they do not fully understand. After all the scientists who discover these gene markers do not fully understand their significance. Before these DNA markers are adopted by the medical establishment in most countries as providing cast-iron diagnostic markers for disease and susceptibility, perhaps there should be misgivings about selling the information to the general public.

The meeting closed with an impassioned argument by **Dr. Peter Corry** to do something about the consequences of the high incidence of consanguineous marriages amongst the Pakistani community of Bradford. First cousin and double cousin marriages carry greatly increased risk of ill health through genetic disease in their future off-spring. But even non-cousin *biraderi* (within clan) marriages pose risks. These are the occurrence of deafness, metabolic disorders, and microcephaly, bleeding disorders and neurodegenerative conditions in their offspring. Similar conditions apply to other UK cities with a large Asian immigrant population. What is to be done? Legislation would probably be ineffective; so advocacy and persuasion appears to be the best route. Education of the immigrant population about the hazards of cousin marriages, easy access to medical checks, group discussions amongst families that already have defective children (this is often kept secret) might all help to deter further intermarriages in such families.

The meeting ended with thanks and congratulations going to **Professor Alan Bittles** for organising such an excellent meeting for the RSM and Galton Institute.

Programme

Day 1:

Family connections: the 1908 Mendelian versus Biometrics debates
Professor Sir Patrick Bateson, FRS, Cambridge

Garrod: the Croonian Lectures and beyond
Professor Sir David Weatherall, FRS, Oxford

Galton Lecture 2008
Population genetics and the concept of genetic individuality
Professor Sir Walter Bodmer, FRS, Oxford

The race/ethnicity/ancestry debate: a genomics perspective
Professor Marc Feldman, Stanford

Genetic Predisposition to infectious diseases, past and present
Professor Adrian Hill, Oxford

Allergies to allergic disease—from 1916 to the present day
Dr John Holloway, Southampton

Declining male fertility: a threat to all or just some?
Dr Ken McElreavey, Paris

Gene therapy for muscle diseases
Professor Freancesco Muntoni, London

Day 2:

Genomic analysis of human behaviour
Professor Peter McGuffin, London

Epigenetics and development
Professor Amanda Fisher, London

Familial cancer genes: from gene to clinic
Professor Eamonn Maher, Birmingham

Ageing: part of the human phenotype or an inherited disorder?
Professor Tom Kirkwood, Newcastle

Stem cells and regenerative medicine
Professor Sian Harding, London

Genome-wide association studies
Professor Peter Donnelly, FRS, Oxford

Gene-environmental interactions in multi-factorial disorders
Professor Rory Collins, Oxford

Personalized genomics
Dr Joanna Mountain, Stanford/23andMe

Medical genetics in a multi-ethnic society
Dr Peter Corry, Bradford

Medicine May Change Our Genes

Nicholas A. Christakis

A lot of hot air is around at the moment—and quite a bit of overselling—about advances in genetics, personalised genomics, and gene therapy. Only a small part of the variance in human illness is explained by genetics; most is explained by social factors such as poverty and behaviour. Yet large sums are spent in a quixotic pursuit of the genetic basis for everything.

The hope—some say fear—is that we will be able to use advances in medical technology to reshape the genome of individual patients, curing ailments by changing somatic genes. Some even hope that we will be able to modify our species for the better by introducing changes into our germline.

Ethicists hotly debate this topic, arguing about the case for or against "perfection." Do we have the right to develop technologies that would allow us to change the human genome? Some would say this is a duty. After all, if we could develop a genetically based treatment for patients with sickle cell disease, cystic fibrosis, or diabetes, who would not support that?

But overlooked in all this debate are the ways in which—just possibly—medical advances may already be changing our genes at the population level.

It used to be thought that our genes were historically immutable and that it was not possible to imagine a conversation between culture and genetics. It was thought that we as a species evolved over a timescale far too long to be influenced by human actions. But evidence has been mounting for the past decade that we as a species are evolving genetically in real time, under the pressure of discernable social and historical forces.

The best example so far is the evolution of lactose tolerance in adults. The ability of adults to digest lactose confers evolutionary advantages only when a stable supply of milk is available, such as after milk-producing animals (sheep, cattle, goats) were domesticated. The advantages are several, ranging from a source of valuable energy to a source of necessary hydration during times of water shortage or spoilage.

Amazingly, several adaptive mutations have occurred in widely separated populations in Africa and Europe just over the past 3000 to 9000 years, all conferring the ability to digest lactose. These mutations are principally seen in populations of people who are herders and not in nearby populations who have retained a hunter-gatherer lifestyle. This trait is sufficiently advantageous that those with the trait have many more descendants than those without.

A similar story can be told about relatively recent mutations that confer advantages in terms of surviving epidemic diseases such as typhoid in Europe. As these diseases were made more likely when the density of human settlement increased and far flung trade became possible, here we have another example of how cultural change may affect our genes.

Of course, our biology and our culture have always been in conversation. For example, rising socioeconomic status with industrial development resulted in people becoming taller (a biological effect of a cultural development), and taller people required a change in architecture (a cultural effect of a biological development). Anyone marvelling at the small size of beds in medieval houses knows this at first hand. But it seems that it is also possible for genetic change to take place over relatively short time periods.

Why does this matter to medicine? Because many of the things we are already doing may be modifying our genes. Maybe we are all more myopic as a result of medieval lens grinders. Maybe our bones are weaker since we have had bone-setting technology for thousands of years. Maybe the changes in survival of patients receiving treatment for all sorts of conditions that are wholly or partly attributable to single or multiple genes (ranging from sickle cell disease to type 1 diabetes) are resulting in changes in the human genome. Maybe the introduction of penicillin and childhood immunisation has changed our genes. Some have noted that the number of children with Down's syndrome is falling in many industrialised societies as a result of selective abortion. With the onset of personal genetics, it is not hard to imagine this being taken a step further. Medical technology might change our genes indeed.

Medicine is not the only thing doing this in ways relevant to health and well-being. There may be genetic variants that favour survival in cities, consumption of alcohol, or a preference for complicated social networks. There may be altruistic genetic variants that favour living in a democratic society. Maybe even the more complex world we live in nowadays really is making us smarter.

Unfortunately, this also means it may be the case that particular ways of living and particular medical technologies create advantages for some but not all members of our species. Certain groups may acquire (admittedly, over centuries) certain advantages. The idea that the application of medical technology modifies what kind of offspring we have is as troubling as it is amazing. However, it provides a way for us to begin to think about the inevitable genetic revolution in medicine that is around the corner.

Reprinted from BMJ, vol.336, p.1101, 2008. Nicholas A. Christakis, MD is professor of medical sociology, Harvard Medical School and attending physician, Mt Auburn Hospital, Cambridge, Massachusetts

The Human Genome: past, present and future

by

Professor Steve Jones

When I give my first lecture of the year to genetics undergraduates at University College London I ask them to turn to the person to their left, and then to their right; and I tell them (reasonably accurately) that two out of three of those involved in the exercise will die for reasons connected to the genes they carry. Then I cheer them up by pointing out that had I been speaking in Shakespeare's time, two out of three of them would be dead already.

And, of course, the phrase which sets the theme of this conference comes from just that author and just that period in history. The evil monster Caliban, in *The Tempest,* is cruelly cursed with the statement that "On thy foul nature, nurture shall never stick".

The attempt to separate those two great agents of fate - nature from nurture, gene from environment - goes back to the beginnings of history. The Old Testament was the first genetics text of all, for much of the Book of Genesis is about pedigrees. The word "Begat" appears more than a hundred and fifty times in that chapter and elsewhere; and many biblical themes are concerned with inborn fate.

Francis Galton, in *Hereditary Genius*, also argued that man's nature was set at birth. It has become fashionable to decry his views but they are, in these days of molecular genetics, still very much alive. This conference will explore them and to ask what, if anything, "nature" and "nurture" mean today and whether they can still be treated as separate entities.

The human genome project, now more or less complete, has been much publicized as bringing Galton's science into the modern world. In fact, it has nothing to do with genetics. Instead it is anatomy – the dissection of a single human (or a committee of humans, with bits of DNA taken from across the world) in ultimate detail. By so doing the genome project has completed the task begun by Vesalius in the sixteenth century when he cut up a cadaver and discovered that the heart had four chambers and not, as the Greeks had insisted, three.

Anatomy, which in its modern guise includes much of molecular biology, looks backwards to those days; it is a platonic science that turns on the notion of an ideal and perfect form of human being that can stand as the essence of all others. Genetics, in contrast, began with differences and still depends on them.

Inherited differences are everywhere. Plato himself seemed to admit as much, with his men of gold, men of silver and men of iron, each born to his own allotted fate and each bound to live his life by an agenda set in his very being. Some of our physical contrasts are obvious indeed. They once seemed to divide the human race into distinct groups. Francis Galton, in true Victorian style, produced a diagram – one of the first statistical distributions ever published – which (while admitting the superior abilities of the ancient Greeks) put the English at the top of the racial tree, and the Australian Aboriginals at the bottom (with a noticeable overlap with "dogs, etc"). Even today, about three quarters of all papers in American public health journals show the race of the study population as evidence of just how important it must be.

In fact, skin-colour points at how hard it is to disentangle nature from nurture. In London, a trip on the Jubilee Line from Westminster to Newham represents a loss of six months of life expectancy for a baby born close to each of the ten tube stops. The proportion of the population from minorities goes up in parallel to the decline of a baby's prospects as we travel from the centre of the city to the East End – and, needless to say, the skin colour genes are a proxy for poverty and poor housing and have themselves little direct effect on health.

But how much of that, or any other, baby's chances is due its nurture – income, education, housing and all the rest – and how much to its inborn nature? The question seems simple: most people see the phenotype as a cake that can be sliced into a piece controlled by genes and another by environment. Every geneticist knows that is not true, and we all have our favourite ways of explaining the fact. Mine is that popular mutant, the Siamese cat, with its black ears, nose and tail (and, if it is a male, testicles) set off against a white body. Crosses show that the Siamese is a classic Mendelian recessive. The gene locus has been tracked down, and we know the DNA sequence of the normal and the mutant allele. Nothing, it seems, could be more in the cat's nature than its elegant fur.

Crucially, though, the mutation is temperature sensitive; the enzyme that makes black pigment has been damaged, but only slightly. As a result it works perfectly well in the cooler extremities of the cat's body but not on the warmer core – which explains the pattern. To make a light Siamese, keep it in a warm room, for a dark one, use a refrigerator. Inside every Siamese is a black cat struggling to get out – and the notion of slicing its attributes into a piece called nature and a piece called nurture is meaningless: to get the ingredients back one would have to

unbake the Siamese cake, which is impossible.

That odd example of the ambiguities of inheritance is a pointer to great swathes of modern genetics – much of which will be discussed during this meeting. Heart disease, diabetes, psychiatric illness and more: each is a major problem in the modern world and each has, no doubt, some genetic component. Now we are beginning to see the insights - and the ambiguities – that technology offers when trying to understand how much such conditions are in the DNA, how much in a patient's lifestyle – and how much, like the fur of the Siamese cat, turns on an interaction between the two.

Genetics has rediscovered its essence, the search for difference. About one site in every thousand in human DNA varies from person – which means three million potentially variable sites in every population. Some of the variants are rare, but many are common. The hapmap (haplotype mapping) project, as it is known, sets out to search for relatively frequent single-letter changes in the genetic alphabet, and has now found around nine million of them. Each group of variants acts as a milestone in the genome. By looking at the patterns of joint inheritance of any human attribute, normal or diseased, with those DNA changes we should, in principle, be able to track down the genes responsible.

The results are fascinating in their ambiguity. After a period when it seemed that technology would track down the genes for most of the illnesses that plague us and – perhaps – reveal our very essence there has emerged an era in which our nature is more complicated, and our interactions with nurture (the environment as it is otherwise known) more equivocal, than anyone expected.

Even simple and easily defined characteristics have become murkier than before. Everyone knows that racial difference in the ability to withstand environmental stress, the inborn ability to withstand malaria. A fifteenth-century chronicle by the first European explorers of West Africa complained that "For our sins, or for some inscrutable judgement of God, in all that we navigate along He has placed a striking angel with a flaming sword of deadly fevers". Three hundred years later, half the Englishmen who went to that part of the world died within a year. The Africans were by comparison unscathed.

Of course we now know why; sickle cell anaemia – a simple genetic condition that alters the response to infection. In fact malaria resistance is not simple at all. Instead it is a microcosm of how complicated the genetics of even what seems a simple phenotype can become.

Many of the defences turn on the red blood pigment, haemoglobin. Around 250 million people carry a single copy of a damaged globin gene; which means that one person in 15, world-wide, is a carrier. One common variant is indeed sickle-cell, a variant in the beta chain, which in single dose protects against infection although those with two copies of the damaged gene may be severely ill. The shift reduces the stability of the protein and the cell becomes an unfriendly place for parasites to live.

Sickle cell seems simple enough – but complexity soon raises its head. The hapmap segment around the damaged beta-globin gene shows that the mutation has happened independently at least four times in different parts of the world – which may explain why homozygotes in India suffer less from symptoms of sickle-cell disease than do those from west Africa. Now we know over a hundred different amino acid alterations in the beta-globin chain that produce more or less the same resistance to malaria in heterozygous form. Many more (the thalassaemias as they are called) work by deleting sections of the alpha or beta chain, often with disastrous effects in the homozygote.

Malaria resistance can also emerge from changes in quite unrelated proteins. The enzyme glucose 6 phosphate dehydrogenase is active in the red cell. Many people have an inactive form – which means that their cells are more sensitive to the waste products of the malaria parasite; which leads to death of infected cells - and of the enemies within. Other defence mechanisms involve not structural changes in a protein, but shifts in gene expression. The Duffy blood group is a cell surface molecule which comes in two forms: Fy^a in much of the world and Fy^- in west Africa. The latter gives almost complete protection against one form of malaria. The antigen is the receptor by which the parasite binds to the red cell membrane. Fy^- individuals do express the substance on many of their cells, but its production is switched off in blood cells. The parasite is beaten not by structural change in the DNA, but by gene regulation.

Other protective mechanisms were discovered because they have separate, and apparently unrelated, properties that may themselves cause problems. The inherited illness haemochromatosis is frequent among people of African ancestry. It leads to the presence of large amounts of iron in the blood which in turn can damage the liver. It is common because high levels of iron in the red cell kill malaria parasites, which keeps the gene in the population.

In a further, and perhaps general, complication to the malaria story, some genes interact to produce the phenotype:

the children of certain middle-Eastern families with sickle cell disease seem to do rather well – because they have inherited another gene that retains a form of haemoglobin normally found only in the fetus in the adult blood stream. Now, almost fifty additional genes are known to have some effect on the chances of infection by malaria, or on the progress of the disease.

Malaria resistance, which once seemed simple, involves many loci, with many alleles. Different populations, and different families within the same one, construct the phenotype in different ways, often with genes that have other, unrelated, effects on quite separate aspects of their being.

The intricacy of that phenotype has a much wider message. Malaria has been replaced as a European disease by an illness which acts as a microcosm of the nature-nurture problem; the plague of obesity now attacking the developed world. Two centuries ago, Marie Antoinette told her peasants to eat cake, and they did. Now, for the first time in history, the poor are fat and the rich are thin. The English waistline puts our continental cousins to shame, although the average belt is still drawn somewhat tighter in the Old than in the New World. Pessimists predict that my own generation – those in middle age – may be the longest-lived in history, for they gained from the healthy diet of the 1950s while their successors are losing to the pressure to eat more and exercise less. Obesity kills more Americans than does smoking and the rest of the planet is panting close behind.

Many people believe that they are fat for genetic reasons; but, rather few deny, the environment is also in part to blame. Is it possible to disentangle the two?

Obesity, more even than malaria, shows the problems now faced by genetics. Even what seems a simple problem - defining the character of interest – turns out to be annoyingly complicated. One measure of excess fat is the body mass index; a person's weight in kilograms divided by the square of their height in centimetres. That makes for a convenient graph onto which people can place themselves - and in Europe now about one man in six and one woman in four is obese on that measure. Among them, though, are many fit men and women who are so muscular that their body mass is high, even though they had no spare fat.

Another measure – a better predictor of the health effects of corpulence - is simpler; a tape-measure. Fat people come in two flavours, apples – with the excess around the stomach (a pattern found more frequently in men) compared to pears – in which the weight moves to the buttocks (more common in women). Apple obesity is far more dangerous, both because of the pressure on internal organs and also because gut fat can be more rapidly mobilised to add to blood cholesterol. A heavy man with a large behind may be at less risk than a lighter one with a generous waistband – which is an illustration of a general, albeit sometimes forgotten, problem in genetics; defining quite what we are looking at.

Nobody denies that fat runs in families but so do frying pans, which makes it hard to know whether DNA or dripping is more to blame for the modern plague of obesity. Both genes and environment are involved, and sometimes they interact in unexpected ways. Famously, fat cats tend to have fat owners. Nobody blames that on shared genes, but instead there is a joint tendency to serve up too much food.

Diet is, of course, important in weight gain, whatever the effects of genes. Some groups have suffered more than others. Native Americans – an Arizonan tribe called the Pima Indians most of all – seem to be particularly at risk. Pictures taken a century ago show them to have been slim, elegant, and healthy. For many Pima today, obesity is a plague and they have one of the highest incidences of adult-onset diabetes in the world. The genes have not changed in that time; but the environment has. The Pima have had a huge shift in dietary habits. They have always eaten corn (or maize as we know it) and once called themselves the Corn People to reflect that fact. Corn accumulates isotopes of carbon in a unique way, which means that the record of how much has been consumed is laid down in the bones. Modern Pima eat about the same amount as before – with the crucial difference that it has been through a cow, a chicken or a soft-drinks factory first. A Macdonald's meal is, in effect, corn. The chicken is fed on it and fried in it, and thirteen of a Chicken Macnugget's thirty-eight ingredients come directly from that crop.

Why do the Pima pay such a high price for the shift in the way they eat their favourite plant? They were once said to be at particular risk of an unhealthy diet because of their own DNA; they had, it was claimed, a "thrifty genotype" which was adapted to sudden bursts of feast among long periods of famine. Their special metabolism laid down fat when food was available, against the drought to come.

Now that idea has been more or less abandoned, for no such gene has ever been found. Even so, genetics certainly does have some effect on obesity. In one experiment, several pairs of identical twins were gorged, or starved, for three months. For the gourmands, the average weight gain over that period was around seven kilograms. There was a huge range

of increase, with a few gaining only a little, and others ballooning towards grotesqueness. The range was wide; but there was three and half times more variation between pairs of twins than within members of the same pair. Shared genes meant a similar response to caloric overload.

In a few cases, the genes responsible at least for morbid obesity have been tracked down. A mouse mutant – the *obese* mutation – turned up a few years ago in laboratory stocks. It eats voraciously, because it lacks a hormone called leptin that normally tells a hungry animal when to stop. A very few children are born with the same problem; they are enormously overweight and never become sexually mature. Leptin injections have a dramatic effect. Even so, every attempt to use leptin to treat the great majority of fat humans has failed. In the same way, a vaccine against another such hormone as a means of weight loss has just been abandoned. There is quite a lot of variation in the structure of the leptin gene, but there is no fit with corpulence here, either. That reflects a widespread finding that genes which lead to a severe pathological state – obesity, high blood pressure and more – are often simple, but they have nothing to do with variation in the "normal" range of that phenotype.

The search for genes predisposing to high body mass has been a disappointment. Hapmap has been much appealed to, with ambiguous results. American scientists have found a variant on chromosome 3, the French go for chromosome 10, while some of the Pima may be at risk because of a gene on chromosome 11. The effect of each supposed gene is small, and if any have a real effect in one population it does not seem to apply to the others.

Now the human obesity gene map, as it is called, contains more than four hundred genes supposed to be associated with excess fat. Most seem to apply in only one study of a single family, or a single population. Cynics – and all good scientists should include themselves among that group - claim that there are absolutely no convincing general fits of DNA variation with obesity in human populations. If genes have any real importance in today's wave of lard, we have not found them.

Obesity is a microcosm of the difficulties of sorting nature from nurture. Genes, the environment, and an interaction between the two are all important. We will hear in the Galton Lecture from Marcus Pembrey about some startling trans-generational effects that also have an effect: and although I do not want to give away the secrets of his talk it may mark a new departure in the way in which we look at the inheritance of genes, and of environments.

His work is another stake through the heart of the Shakespearean (and Weissmanian) dogma. It shows that that their shared claim that the germ line is kept safe from the thousand natural shocks the soma is heir to – is just too dogmatic.

The subtleties of that dogma are nowhere seen more clearly than in the universe of sex. World wide, women suffer more from obesity than do men, for all men have an inborn dose of that wonderful slimming drug called testosterone. Like many drugs, it has unwelcome side effects, for those who use it have a higher death rate from accidents, parasites, and violence than do their mates. An experiment carried out in 1930s America, when many young boys were treated with eugenical castration to stop them passing on their genes for mental defects, and even for shoplifting, proves its power. Cruel though their punishment may have been, those deprived of testosterone lived a decade longer than their unmutilated fellows, as evidence for just how dangerous the substance must be.

One clear attribute of the masculine phenotype is murder: men murder, and are murdered, at several times the rate of women. The effect is quite consistent, with the same pattern in London, Tokyo and Detroit. That might seem to prove the role of nature in that cause of mortality; but the murder rate itself varies by twenty times between Detroit and Tokyo (which means that an American woman is considerably more dangerous than is a Japanese man). The reason lies, of course, in nurture; in the cultural difference between the two cities, and the availability of guns. Nature and nurture interact (although in practical terms it is easier to get rid of guns than to castrate every potential criminal).

Plato admitted that his own notion of inborn fate – his men of gold, silver and iron – was a "noble lie", which although untrue should be promoted because it led to a stable society. The use of genetics as a universal alibi for obesity, crime or anything else is equally dubious. The Nobel Prize winner Sidney Brenner once told me that the gene for obesity was found long ago: it is the one that makes you open your mouth! That was rather a flippant comment on a serious subject. We shall no doubt learn a lot more about the complexities of nature, nurture and the interaction between the two during this conference. I wish all those who attend it - *bon appetit!*

This lecture was delivered by Professor Jones at The Galton Institute's 2006 Conference ***Nature, Nurture, or Neither?: Genetics in the post-genome era*** which was held in association with Progress Educational Trust at The Institute of Child Health in London.

Report of Innovation and Evolution workshop

Hannah Fluck
(University of Southampton)

The Galton Institute supported this conference with a grant of £1,000

The first international workshop on Innovation and Evolution took place at Southampton University, UK on 27-28 April 2007. Thanks to generous funding from the Galton Institute and support from the University of Southampton the workshop was a huge success.

The workshop was well attended with more than 70 people present over two days. Participants came from countries throughout Europe, including Spain, France, the Netherlands, Sweden, Germany, Poland, Switzerland, and from institutions such as Cambridge University, Portsmouth University, University of Durham, the British Museum, University College London, Royal Holloway, and the Max-Planck Institute. A range of fields of research were represented with scholars from archaeology, psychology, primatology, neuropsychology and geography and the combination of representatives from such diverse research areas promoted some fascinating cross-disciplinary dialogue and sparked a number of discussions about potential cross disciplinary research projects.

The first day began, following a short introductory talk by the workshop's main organiser Hannah Fluck, with the first three papers which set the tone for what was an extremely diverse and interesting day of papers. The session was chaired by Dr John McNabb from the Centre for the Archaeology of Human Origins at the University of Southampton. Dr William Davies (Archaeology, Southampton University) spoke about how innovation can be approached in the context of mobile populations, with particular reference to his area of expertise in the later Palaeolithic. This was followed by Dr Gordon Rugg (Computer Science, Keele University) who gave an extremely refreshing powerpoint free presentation looking at some of the ways in which technological innovations might be quantified. Finally Prof Chris Sinha (Psychology, Portsmouth University) explored the themes of time, space, semiosis and cognitive artefacts through his work with the Amondawa speaking people of Amazonia.

After this fascinating start the following session, chaired by Dr Marie Soressi, an Archaeologist from the Max Planck Institute, Leipzig, continued with a little more emphasis on archaeology. Dr Mark Roberts (Archaeology, UCL) gave an insightful presentation about his work at the important Palaeolithic site of Boxgrove in particular exploring the role played by diet and nutrition in the early hominin occupation of northern Europe. Dr Mikolai Urbanowski (Archaeology, Szczecin University, Poland) presented some exciting new data regarding innovative techniques in flint working in the late Middle Palaeolithic. Keeping with flint technology Dr Jan Apel (Executive Director of the Societas Archaeologica Upsaliensis, Sweden) spoke about the spread of new flint knapping techniques across Europe. The session was brought to a close with questions and short discussion before lunch.

The final session of papers for the day was chaired by Dr Mark White (Archaeology, Durham University). The first speaker of the afternoon was Dr Cintia Rodriguez (Psychology, Autonoma University, Madrid) who presented some interesting research into the use of gestures and objects in prelinguistic infants. This prompted some interesting discussions about the role of language in innovative behaviour. Dr Rob Hosfield (Archaeology, Reading University) spoke about anthropological research he had undertaken into technological skill transmission in a range of different extant cultures looking particularly at the social and material context of this. The final paper of the day was given by Dr. Mimi Haidle (Archaeology, University of Tübingen, Germany) and explored the issue of detecting innovative behaviour in the way in which tools are used, with a particular focus on archaeology but drawing upon a wide range of examples from other fields of research.

The afternoon discussion session, open to all, was chaired by two of the workshop's co-organisers, Laura Basell (Archaeology, Oxford University/Exeter University) and Kathy MacDonald (Archaeology, Leiden University, Netherlands). Discussions were lively pursuing the key themes of language, communication, learning and transmission that had emerged from the day's presentations.

The second day was opened by the workshop's co-organiser, Natalie Uomini (Archaeology, Southampton University), who summarised the topics from the previous day and introduced some potential directions for the day's discussions. The first session chaired by Dr Cintia Rodriguez begun with a paper by Prof Sophie de Beaune (Archaeology, University of Lyon) about the role that research in neurological and cognitive sciences can play in the understanding of technological innovations in the Palaeolithic. This was followed by Dr Andreas Kyriacou (Neuropsychology, University of Zurich) who spoke about innovation and creativity from a neuropsychological perspective. The final speaker of the session was Dr Matthew Pope (Archaeology, UCL) who looked at hominin behaviour in the Middle Pleistocene, in particular at mobility and landscape interaction.

The second morning session was chaired by Dr Farina Sternke, an archaeologist from University College Cork. The first speaker, Dr Ignacio de la Torre (Archaeology, UCL) looked at continuity and change in Neanderthal behaviour in northern Spain. Next Dr Terry Hopkinson (Archaeology, Leicester) explored the role that social networks play in creating, transmitting and maintaining innovations. Finally Prof Alan Costall (Psychology, Portsmouth University) explored in detail some of the ideas concerning affordances and materiality or as he put it 'doing things with things'.

The final session of the conference was chaired by Dr Bill McGrew (Primatology, Cambridge University) and began with a

presentation by Dr Lambros Malafouris (Archaeology, Cambridge University) exploring some of the debates surrounding the nature of materiality, human object interactions and intentionality, with a particular emphasis on human evolution. Dr Vasudevi Reddy (Psychology, Portsmouth University) then presented some of her fascinating research into infant communication and objects, looking at some of the ways in which innovative behaviours manifest themselves ontogenetically. The final presentation of the conference was given by Prof John Gowlett (Archaeology, Liverpool University) and included an audience participation experiment looking at the way in which form may be preserved in interpretations by different individuals while scale may not. In particular he considered handaxe shape and scale and the implications of this for human cognitive evolution.

The final discussion was led by Prof Paul Mellars (Archaeology, Cambridge University) and Prof Chris Sinha who began by summing up their observations of the conference. The discussions then opened up to the audience with a particular emphasis on including some of the participants from primatology who had not been able to present papers. There were some fascinating interdisciplinary discussions about the significance of language in the emergence and establishment of innovations as well as some questions about the role that innovative behaviours might have played in hominin cognitive evolution.

A closing wine reception was given at the Centre for the Archaeology of Human Origins where the discussions continuing and many new professional links were forged. It is intended that the proceedings of the conference will be published. A conference building on the success of this workshop is planned for late 2007/early 2008. The organisers are extremely grateful to the Galton Institute without whose generous grant the Innovation and Evolution Workshop would not have been able to take place.

Genetic Testing: Uses and Limitation

Many people believe that since the sequence of the human genome was published in 2001 we are now able to test for any genetic disorder. Unfortunately this is not yet the case; what we have is a book in which some of the words can be read easily, but others are still just a series of letters.

The genetic tests requested by a genetics professional, or other clinicians fall into two broad categories: chromosomal analysis, and molecular genetic testing. The mainstay of chromosomal analysis remains the standard karyotype, which is an excellent technique for picking up major abnormalities of chromosome number or arrangement, such as Down's syndrome. However, it is possible that in the next few years the karyotype will be supplanted by more detailed molecular techniques that are capable of picking up more subtle chromosome abnormalities.

Molecular genetic testing is a more complex area. Genetic testing is indicated in a variety of situations – as a diagnostic test or confirmatory test for a putative diagnosis, as a predictive test in someone at risk of a particular disease or as a cascade test for carrier status in a family in which someone has a particular disease. In order for genetic testing to be possible certain conditions must be fulfilled:

- The gene or genes must have been identified.
- The result must be interpretable.
- The test must be available either in a diagnostic lab or a research lab with the possibility of confirming a positive result in a diagnostic lab.

It is important to remember that mutations in different genes can cause the same disease, so that genetic testing may involve the analysis of a number of different genes.

Tests can be divided up into four categories:

(1) Those that give a yes or no answer. These tests could be used potentially to screen the population for a particular genetic disorder , for example, fragile X syndrome.

(2) Those that have a high pick up, with certain common mutations in certain populations.

(3) The gene is known but different mutations account for the disease in different families. Therefore the familial mutation must be identified in an affected individual before testing can be offered to other family members.

(4) The disease is caused by mutations in a number of different genes. Some genes have been identified and it is possible to test these, but clearly not those that are unknown.

Examples of the uses of genetic testing- Case studies

Case1 A patient presented with a clinical diagnosis of myotonic dystrophy. This is a neuromuscular disorder characterized by the presence of myotonia and progressive muscle weakness. The condition displays genetic anticipation – that is the presence of increasing severity and earlier age of onset in successive generations – and is caused by a dynamic CTG expansion in the DMPK gene. The expansion enlarges when transmitted from an affected mother to her child, resulting in increasingly severe disease and provides a genetic explanation for anticipation. The patient was clearly affected and genetic testing was positive showing a moderate size expansion. When he came to receive his results, he attended with his parents and sister, all of whom initially wished to be tested. However, as they all had different concerns, testing was declined and further individual appointments arranged. When they attended 2 months later, none of them wished to be tested, although they were aware that the test was definitive. Neither parent wished to carry the burden of blame and as they were completely asymptomatic there was no urgent clinical need to test them. His

sister felt that she did not wish to know, and that it would not alter her reproductive decision making. She subsequently developed polyhydramnios in her next pregnancy, and the baby was born with congenital myotonic dystrophy. However, she would not have wanted early prenatal diagnosis, or termination of pregnancy so the outcome for the child would not have been altered by genetic testing prior to the pregnancy.

Case 2 A boy of 18 months was referred with developmental delay. Prior to referral the paediatrician had arranged genetic testing for Fragile X syndrome. Fragile X syndrome is a condition associated with learning difficulties and autistic features affecting boys more frequently than girls. It is associated with the presence of a fragile site on the end of the X chromosome, now known to be due to a dynamic CGG expansion in the non-coding region of the FMR1 gene. Individuals that have fewer than 50 CGG repeats in the gene are healthy, those with >200, if male will have Fragile X syndrome and if female have a risk of being affected, and those with ~60-200 are known as permutation carriers and have a risk of passing on a larger expansion to their children who then may be affected by Fragile X syndrome. The boy was seen in the genetics clinic and the outlook for him, and the risk to future pregnancies discussed. Soon after the consultation, the mother found that she was pregnant once again. She opted for prenatal diagnosis; the fetus was found to be male, and further testing revealed that he would be affected by Fragile X. After much discussion she elected to terminate the pregnancy. Further testing was arranged in her family and it was revealed that her father was a premutation carrier.

Case 3 Another boy of 18 months was referred to the genetics clinic after a diagnosis of tuberous sclerosis was made by the paediatrician. Tuberous sclerosis (TSC) is a multisystem disorder with variable expression characterized by the presence of seizures in approximately 70%, learning difficulties in ~60%, renal complications, characteristic skin changes and perinatal cardiac involvement. The family of this child wanted further children and requested mutation analysis of the tuberous sclerosis genes in order to have prenatal diagnosis. The father had been diagnosed with a chronic renal disease in his 20s, which was thought initially to be unrelated to TSC. Two genes, known as TSC1 and TSC2, cause tuberous sclerosis, and mutations are identified in 70% of affected individuals. A mutation was identified in the affected child, and both parents were tested. Neither was found to carry the mutation but in the next pregnancy they requested prenatal diagnosis. The baby was found to be affected, and the couple opted for a termination of pregnancy. Further investigation of the father revealed that he had multiple small angiomyolipomas, the characteristic renal lesion of tuberous sclerosis. Skin was also sampled but the mutation present in his son and the affected baby was not found.

This gentleman must therefore be mosaic for the mutation, that is, he carries the mutation in some cells of the body but not others. The mutation will have arisen as a post-zygotic event in one cell. All the descendants of that cell will contain the mutation, but the other cells are healthy. The mutation must be present in renal tissue and in his germline, but as it was not detectable in blood or skin it must be absent or at a low level in those tissues. In this situation, mosaicism provides an explanation for the variability of expression in the family, but in most families there is no such explanation. The couple has gone on to have further affected pregnancies, but now have a healthy girl.

Case 4 A family history of cancer now accounts for more than a third of referrals to the clinical genetics service. It is estimated that approximately 5-10% of all breast and colorectal cancers occur as result of a dominantly inherited genetic susceptibility to cancer. Two genes, BRCA1 and BRCA2, when mutated are known to predispose to breast and ovarian cancer. In certain ethnic groups, for example the Ashkenazim, there is a high prevalence of specific mutations. However, amongst most other population groups a wide variety of different mutations have been identified, some of which are unique to a family. Therefore genetic testing is only offered to individuals affected by breast cancer, unless they are known to come from specific ethnic groups. Mutations in these genes are inherited in an autosomal dominant fashion with incomplete penetrance; that is, some individuals in a family may carry the mutation but never develop the disease.

A 30 year old woman was referred to our service because she had developed breast cancer at the age of 29. Her mother was well in her 50's, but her maternal grandmother was affected by breast cancer at 40, and grandmaternal aunts were also affected. The young age of onset and histology of her breast cancer was indicative of a BRCA1/2 mutation and she was offered genetic testing. At that time the laboratory was able to offer only a 60% screen of the genes, and the test was negative. Despite the negative test she was advised that the cancer was likely to be genetic and she elected to have both breasts removed at the time of her operation for the cancer. Two years later a complete screen of both genes was developed in the laboratory. Further analysis of her sample revealed a mutation in BRCA1. Her mother remained clinically unaffected, but must be an obligate carrier and has decided to request bilateral prophylactic mastectomy and removal of her ovaries. Genetic testing is now an option for other family members are risk.

It is not clear why some women do not develop breast or ovarian cancer when they carry a mutation in BRCA1 or 2. Non-penetrance may be due to other modifying genes, or to lifestyle factors and this is the subject of active research.

There remain many conditions for which the gene or genes are unknown. Diagnosis in these conditions still relies on clinical acumen, and indeed the identification of the genes requires careful clinical delineation of the condition

Frances Elmslie
Consultant Clinical Geneticist
St George's Hospital, London

The Powers of Natural Selection

15. Natural Selection and Eugenics

W.M.S. Russell

In the 1930s there was a widespread worry about more intelligent people having fewer children than the less intelligent; it was believed that the heritable component of intelligence would deteriorate as a result. This belief was totally irrational, and due to ignorance about evolution. Quite apart from the fact that intelligence is an obvious component of fitness, we can be absolutely sure that *natural selection will cause people with fewer children* (and correspondingly better parental care) *to have more descendants*. Again and again in evolution natural selection has *lowered* fecundity, which is just another way of saying that individuals with fewer off-spring have had more descendants.

Already in the classical 1858 paper that (along with Darwin's) introduced natural selection to the world, Wallace noted the fact of *selection for low clutch size* in birds (1958-1858); and many examples of this are given by Lack (1954) and Wynne-Edwards (1962) 'In a few highly specialised cases the remarkable condition has evolved, that only one egg is ever laid in one year, and even if it is removed or destroyed when newly-laid, there is no attempt to re-nest or replace it'. (Wynne-Edwards) There are also plenty of examples in fishes. 'It is a commonplace observation that an evolutionary advance in the degree of parental care given to the eggs and young is correlated with a lowering of fecundity'. (Wynne-Edwards, 1962) He instances pelagic fishes laying hundreds of thousands of eggs with no care of them, in contrast with the three-spined stickleback, *Gasterosteus aculeatus*, which lays a few score of eggs and has nests built and the eggs and young guarded by the male.

'The ultimate achievement of progress in organic evolution has been cultural evolution, together with human individual creativity… lower animals are in general enormously fertile… no such system could progress to cultural evolution… The first step was a huge reduction in fertility and the evolution of parental care and parental behaviour'. (Russell and Russell, 1990a) Many mammal species have already had their litter size reduced to 1 or 2, but many lower mammal species have larger litters, some much larger. The Virginian opossum, for instance, the common American shrew, the Indian mole rat and the mink can have litters of up to 10. The Western skunk and the antelope rat can have up to 12, the gray wolf up to 13, and Bachman's squirrel up to 16. But the two highest orders, the Primates and the Cetacea (whales and dolphins) regularly have one or two young per litter, and in man, with the highest degree of parental care, 'twinning usually occurs once in about 83 births; triplets are said to occur once in 83^2 and higher numbers in increasing powers'. (Asdell, 1946)

In view of all this, if the more intelligent have fewer children, we can confidently expect the heritable component of intelligence to increase and spread. So there is no conflict between the two concerns of the Galton Institute – birth control and eugenics.

Indeed nothing in my account of natural selection in any way weakens the case for rational eugenics. Individuals with very severe genetic defect or disease, anatomical, physiological or biochemical, cannot be expected to have reasonably happy lives, by comparison with those without such afflictions, or, in the worst cases, even reasonably pain-free lives; and they are bound to place a serious burden on parents, siblings and society. Once such individuals are born, of course, they deserve all possible help and care. But if we can prevent such births by genetic counselling, aided by amniocentesis (Berry, 1990), this is wholly to the good.

In doing so, we need not fear conflict with natural selection, such as occurs when artificial selection favours extreme characters (as in the Mather-Harrison experiment). On the contrary, in helping to reduce unfitness, we are *co-operating* with natural selection. We have seen that some serious diseases of homozygotes persist because of selection in favour of the heterozygote, for instance Tay-Sachs disease. I have described in an earlier issue the ingenious eugenic policy invented by Rabbi Joseph Ekstein for reducing the incidence of this disease. (Russell, 1999) Such counselling procedures are again not in any way in conflict with natural selection. In preventing the birth of badly diseased homozygotes by counselling, we are not opposing natural selection's favouring of the heterozygote: we are merely avoiding the *price* otherwise paid for this.

This is the last in the series by Bill Russell. There is a comprehensive list of references for the whole series which can be obtained from the General Secretary, The Galton Institute, 19 Northfields Prospect, London SW18 1PE or betty.nixon@talk21.com

The Galton Institute has also published a book by Claire and W M S Russell: ***Population Crises and Population Cycles.*** This volume can be obtained from the General Secretary and costs £5.