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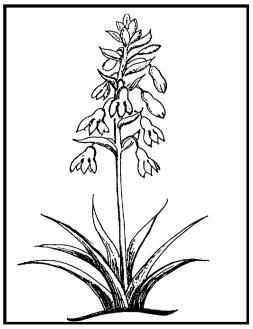

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The Galton Institute

NEWSLETTER

Issue Number 68 September 2008

EDITORIAL

A main event in the activities of the Galton Institute is the Annual Scientific Meeting of which the Galton Lecture is the highlight. Until now we have published the Galton Lecture and the other contributors to the Meeting in book form for sale and distribution. After consideration, Council has now decided to change this and aim to publish the Galton Lecture in the Newsletter and they also hope that the other contributors will wish to see their lectures published here.

We have taken this decision because a prepared lecture can very rarely be published directly as a paper and it involves the contributor in preparing two manuscripts, one to speak and the other to publish. This extra work can sometimes deter an invited speaker from accepting our invitation.

We are very fortunate to have the Galton Lecture, given by Professor Marcus Pembrey in 2006, for publication in this issue of our Newsletter. In it he expands on his ideas of transgenerational inheritance and its contribution to the nature-nurture debate.

David Galton

Dr John C Marsden

(1937-2008)

John Marsden entered my circle of awareness when he supported my election to the Linnean Society because he "liked my quirky research". A man of broad vision, strong organisational powers and a diplomat. I thought that we would have a very effective editor of our Newsletter when he joined the Galton Institute.

Essentially a chemist he, like me, spent time in the Royal Signals before going on to his degrees. After that the academic world spread before him. Oxford, Germany, Israel and then London. He became Dean of the Faculty of Engineering and Sciences from 1986 to 1988 (Polytechnic of Central London).

He was appointed Executive Secretary to the Linnean Society of London in 1989 where he protected it against government interference. In 2005 he was awarded a Fellowship (honoris causa). His voluntary services were unsurpassed, here and abroad, and he was strongly supported by his wife and children to whom we offer our condolences. He will be missed by a swathe of people and institutions and will be remembered as a great human being.

Patrick James

GALTON INSTITUE CONFERENCE 2009

The Galton Institute will be holding its Autumn conference in 2009 at the Royal Society and the subject will be: William Bateson and his influence on our scientific world.

This one-day meeting will discuss Bateson: his influence on the biological world; his biography and interesting employment of women researchers; his fascination with evolution; his championing of Mendel; his astonishing discoveries in genetics: linkage, epistasis, homeosis and meristic variation and his general effect on scientific thinking within medicine – providing the underpinning concept of an autosomal recessive trait in inborn errors of metabolism.

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THE GALTON LECTURE 2006 Abridged

Human inheritance, differences and diseases: putting genes in their place

Marcus Pembrey

Institute of Child Health, University College London

I feel very honoured to be giving the 2006 Galton Lecture and thank the Galton Institute for inviting me. It is a particular pleasure to be following in the footsteps of three of my mentors, John Fraser Roberts, Cedric Carter and Jim Tanner, all of whom were Galton lecturers and worked here at the Institute of Child Health and Great Ormond Street Children's Hospital.

As a practising clinical geneticist, I was all too aware of the need to understand how *differences* in human health and well-being arise in order to be able to help individuals, families and, indeed, populations optimise their health in the future. Basically the observed differences can be seen as the results of 'experiments of nature' the details of which one tries to reconstruct. The advances in molecular genetics over the last 30 years and more recently the human genome project have helped greatly in that process, but it is important to also recognise the wonderful contribution of families and study participants without whom none of the research I am going to talk about would have been possible. In my experience people fully understand that our responsibility to 'care for' is inextricably linked to our responsibility to 'learn from' and are keen to help. With the rare, single-gene disorders and chromosomal abnormalities, the focus of clinical genetics, the affected person or their parents usually approach us for help. On many occasions we have to enlist the help of the extended family, for example, to provide blood samples for DNA analysis in order that we may learn more about the underlying mutation that is causing the family problem. Success in defining the causal mutation then allows us to offer carrier detection or prenatal diagnosis should this be requested in the future. This 'circle of hope' has proved remarkably effective over the years, advancing both our knowledge of rare genetic disorders and human genetics in general as well as providing services for affected families. In clinical genetics, service and research go hand in hand.

A rather different approach is needed for the study of common multifactorial disorders, such as diabetes, asthma or schizophrenia. There is a trend to call this class of common disease 'complex' which is just another way of saying we really haven't a clue as to what the underlying causes are. With common complex disorders it becomes more likely that the circle of hope is entered at the 'learn from' stage. Indeed with population cohort studies one is at pains to explain that medical benefits from the research may be a long way off, but still most people are willing to participate.

Discovering the role of genes in disease

Mendelian disorders

Thanks to classical medical genetics as practised by Fraser Roberts from the 1940s we are good at finding the cause of disorders showing Mendelian patterns of inheritance. There is a very good reason for this. By definition there is a single DNA mutation that causes a condition with distinctive features. If the features were not distinct from normal variation the Mendelian pattern of inheritance would not be discernable in the extended family or collection of families. I am reminded of silly debates as a medical student about which is best, medicine or surgery. The would-be surgeons pointed to a much greater success rate with surgical treatments, but I would counter that they define what is 'surgical' by what is helped by surgery. The same could be said of medical geneticists and their focus on single gene disorders. It is a matter of 'framing' disease. In Mendelian disorders, what we call the disease is framed by its cause, so it is not surprising that we have an effective strategy for discovering the causative mutation. It is very different with common 'complex' disorders. A single example, the vanishing rare disorder of speech in the now famous KE family, illustrates the power of modern molecular genetics to discover the mutation in a Mendelian disorder.

KE Family My clinical geneticist colleague, Dr Michael Baraitser, was asked to see members of this large 3-generation family where half the members failed to develop intelligible speech until teenage years despite adequate cognitive ability and opportunity. Severe developmental verbal dyspraxia was diagnosed. In collaboration with Faraneh Vargha-Khadem, now professor of Developmental Cognitive Neuroscience at the Institute of Child Health, we set out to define the disorder more precisely and map the mutant gene responsible. As mapping techniques improved we linked up with Professor Tony Monaco and Dr Simon Fisher in Oxford and soon mapped what we called the Speech 1 locus (SPCH1) to the 7q31 region of chromosome 7. The Oxford group went on to show that the mutant gene was FOXP2, one of a family of 'forkhead box' genes encoding transcription factors with a forkhead DNA-binding domain (Lai et al 2001). Affected members have a point mutation that alters an amino-acid residue in the key forkhead domain that is invariant in the animal kingdom. Independent evidence of the involvement of the FOXP2 gene in verbal dyspraxia came from case CS who had a chromosomal translocation disrupting the FOXP2 gene.

In parallel with the genetic studies, structural and functional brain imaging comparing the affected members with the unaffected members of the KE family was able to provide further evidence that the FOXP2 gene is critically involved in the development of the neural systems that mediate speech and language Finally, having a genetic handle on the development of speech allows an evolutionary question to be put; was the FOXP2 gene central or peripheral to the emergence of speech in humans? A group from Leipzig, Germany compared the DNA sequence that encodes the FOXP2 protein from chimpanzee, gorilla, orangutan, rhesus macaque and mouse with the human. They found that, although the FOXP2 protein is highly conserved (being among the 5% most-conserved proteins), two of the three amino-acid differences between humans and mice occurred on the human lineage after separation from the common ancestor with the chimpanzee. These changes and the pattern of nucleotide polymorphisms strongly suggest that the FOXP2 gene has been a target for selection during recent human evolution (Enard et al 2002).

'Simple' gene-environment interaction

The degree to which a Mendelian disorder manifests as overt disease may depend on the environment. At one end of the spectrum of Mendelian disorders the mutation causes manifest disease whatever the environment as with the KE family members carrying the FOXP2 mutation. However there are also examples where the underlying defect is inherited in a simple Mendelian fashion, but

disease only emerges with particular environmental exposures. This might be said to represent a simple gene-environment interaction and 'favism' provides our example. However the word simple is deceptive. Note the reference to the inherited *underlying defect*. It is basically a case of simple when you know how, being wise after the event! The 'event' in this instance is more than fifty years of research on susceptibility to illness on eating broad or fava beans (*Vicia faba*), a trait that seemed to follow an X-linked pattern of inheritance. The accompanying anaemia focused attention on the blood (a readily available tissue for research) and the biochemical lesion was shown to be deficiency of glucose-6-phosphate dehydrogenase (G6PD) an enzyme that is important in reducing oxidant stress on the red cells. G6PD deficiency is very common in the oases of eastern Saudi Arabia, where I was studying benign sickle cell disease in the early 70's. About 45% of males in the Qatif oasis had G6PD deficiency. It was common because the gene had been selected for in the face of endemic malaria against which it offered some protection. The added oxidant stress of the malarial parasite destroys the G6PD - deficient red cells before the parasite can grow. That's the beneficial aspect. The downside is that the vicine and covicine in fava beans also generates oxidant stress, which results in the red cells being destroyed too quickly causing haemolytic anaemia.

Framing disease

Our example of favism is 'simple' because we are able to frame the disease as just G6PD deficiency + fava beans = anaemia. What if we had to start with unspecified 'anaemia' as just part of the differential diagnosis of the collection of presenting symptoms. Haemolytic anaemia is just one subset of anaemia and so on. Our favism framing is secured by a specific simply inherited enzyme deficiency and knowledge of the sensitivity of red cells to oxidant stress. But where is the secure footing in framing schizophrenia? The term is more historical baggage than anything else. We are still searching for the underlying defect or defects and trying to clarify the physiological and biochemical sub-phenotypes (endo-phenotypes) that would be the equivalent of undue sensitivity of red cells to oxidant stress in G6PD deficiency. Many of the common complex disorders suffer from rather arbitrary framing. That is why there are international committees that arbitrate on disease definitions! Quite simply in many cases we don't yet know enough (or are failing to look at it in the right way) for our framing of common disease to map onto human biology in a meaningful way. A serious mismatch between medical classification - doctor diagnosis - and the actual variations in people's responses to life's challenges, either helpful in restoring health or otherwise, can thwart medical research, particularly where this is based on a case-control design without incorporating functional endo-phenotypes. Such a design makes the big assumption that the chosen case definition is meaningful in terms of human biology. In essence this catch 22 stems from a payoff between outcome definition and statistical power. Framing a prior hypothesis with a tight definition of disease gives you the necessary statistical power, but your tight definition has a high chance of being inappropriate. If a discovery approach is used testing a collection of traits thought to be relevant to the health outcome of interest, you increase the chance of including appropriate measures, but you run into multiple testing problems? How to proceed? I suggest we go back to first principles.

Getting to know what we don't know

Some basic principles

It pays to start with a basic statement with which most would agree and take it from there. *Differences between people's response to life's challenges - what one can call their adult 'constitution' - are due to a combination of inheritance and developmental experience.* I couch the differences between people in terms of response, because this captures the essence of biology in one word; a stimulus triggering action that is already programmed.

A second principle has already been emphasised. Life is a compromise, a balancing act. This is true of evolved genetic differences in populations as we saw with sickle cell and G6PD deficiency in populations challenged by endemic malaria. The balancing act also applies to individuals. Development of the immune system is a tightrope walk between adequate immune response to infectious organisms and avoiding auto-immune disease, allergies or an over vigorous host response during infection.

A third principle I wish to emphasise is the slippery nature of the phrase 'genetic effect' in complex disease when the environment is not specified. 'Genetic effects' may be strongly conditional on the environmental pressures. The genetic effect, in terms of risk ratio, could peak at a *moderate* level of exposure. All genotypes are 'overwhelmed' at higher levels, whilst low exposure is barely sufficient to bring out the genetic differences. Thus not only does one have to consider the size of the effect of an environmental exposure varying with genotype, but also a genotypic effect varying with the level of an exposure. A very clear but extreme example is that if a large, representative group of people were starved for some reason, the first half to die would be genetically different from the survivors, but all would succumb in the end. It is this conditional nature of 'genetic effect' in complex diseases or traits that makes me very wary of 'heritability' estimates from twin studies when the particular environmental pressures are not specified.

A fourth principle is that development builds on what went before. The developmental process from fertilised egg to adulthood has numerous critical periods or windows of vulnerability with respect to the effect of particular environmental exposures. An adverse effect at that time cannot be undone whatever happens thereafter. Thalidomide only causes physical abnormalities when the mother takes the drug between the 35th and 50th day of pregnancy (day 1 being the first day of the last menstrual period). Sometimes the window of vulnerability to otherwise harmless exposures is a matter of immature defences. For example, red cell haemolysis due to G6PD deficiency can exacerbate jaundice in the newborn, a time when conjugation and secretion of bilirubin by its own liver has yet to reach mature capacity and, of course, bilirubin can no longer be removed via the mother's placenta. Sadly, just when unconjugated bilirubin is liable to rise, the newborn's brain is still unduly sensitive to its effects and without treatment cerebral palsy can follow.

Maladaptive 'programming'

In one sense, being caught with immature defences is just unfortunate timing, but there may be a rather more complicated difficulty during development that I will call maladaptive programming. There is circumstantial evidence that the developing baby adapts its metabolism to match the intra-uterine environment and elements of this adaptation, e.g. the particular set points for feedback control, persist for life. This view underlies the fetal origins of adult disease hypothesis that proposes that some exposures during pregnancy 'programme' the developing

fetus in such a way that the individual has an increased risk of certain adult-onset diseases (at least with Western lifestyles). One intriguing Swedish study using historical data on big swings in food supply found a link between food supply in pregnancy and death from stroke in the offspring in later life. It was not good or poor food supply that was associated with an increased risk of a cerebral vascular accident, but a *change* in mid pregnancy. The risk was there whether the food supply went from good to poor or poor to good . To me this suggests that the fetus, faced with conflicting signals, switches to a default mode of development. The default mode ensures 'good enough' growth and development to reproduce, but also carries risks of adult onset disease.

Capture of developmental experience

From the time it was accepted that all cells of the body (with very few exceptions) have all the same genes, it has been obvious that there must be a system for switching genes on and off. If our skin cells had active haemoglobin genes like blood cells, we would look like rotting tomatoes! How is gene activity (gene expression) controlled? Short-term regulation of gene activity as we go about our daily living is mediated through transcription factors. These are proteins that group together and then bind the DNA upstream of the gene, a region called the promoter, where they usher in DNA-directed RNA polymerase to transcribe the gene into messenger RNA. Messenger RNA specifies the synthesis of polypeptides that subsequently form proteins. However, development demands more than transient regulation of gene activity. As the different cells and tissues of the body emerge during embryological development, the pattern of gene expression appropriate to those cells has to be captured, in part, by selective gene silencing. Furthermore this silencing has to be faithfully transmitted during cell replication as the tissue grows and is maintained in the face of cell turnover. This developmental silencing is caused by epigenetic modification, namely selective DNA methylation and modification of histones – the main protein component of chromatin - without changes in DNA sequence. We still know very little about how epigenetic modification in response to developmental cues (from neighbouring embryonic cells, for example) or nutritional and other environmental exposures is co-ordinated. What we do know is that completion of the human genome project is just a start. It has defined the keys of the piano. We must now think in terms of the music. Research is moving on from DNA sequence or genomic structure and organisation to all aspects of gene function, developmental genetics/epigenetics and large-scale population studies that incorporate genetic variation.

Avon Longitudinal Study of Parents and Children (ALSPAC).

I hope it is clear from the foregoing that if we are going to understand complex diseases, we need a *developmental* approach to research that incorporates data on genetic variation and measured exposures and outcomes. ALSPAC, also known as Children of the Nineties, is such a study (www.alspac.bristol.ac.uk). Based at the University of Bristol it has studied children born in three local health districts in great detail over the last 15 years. Enrolled mothers were resident in these Avon health districts with an expected date of delivery between 1.4.1991 and 31.12.1992. Mothers interested in taking part and completing at least one questionnaire produced 14,541 pregnancies representing about 85% of the eligible population. The overall objectives of the study are to understand the ways in which the physical and social environment interact over time with genetic inheritance to affect health, behaviour and development in infancy, childhood and then into adulthood. I met Professor Jean Golding, ALSPAC director until last year, in 1988 during the 5-year period of planning and piloting. She asked me to lead the genetic aspects.

We have DNA with generic consent for undisclosed genetic analysis on over 10,000 children and 10,000 mothers and immortalised cell lines on over 6000 children and thousands of parents. ALSPAC has a wide range of detailed phenotypic information on health outcomes and quantitative traits or sub-phenotypes and can also bring a population perspective to genetic associations found in family and case-control studies.

This was the case with the recent discovery by Irwin McLean's group in Dundee that filaggrin gene mutations, affecting 10% of the north European population, are a significant risk factor in eczema and atopic asthma. Significantly, the starting point was a Mendelian disorder, ichthyosis vulgaris, giving dry, flaky skin and a risk of eczema. Since this Galton lecture in 2006, the impact of the two commonest filaggrin null mutations (R501X and 2282del14) have been studied in ALSPAC. The mutations were confirmed as strong genetic determinants of eczema, early wheeze and asthma in the context of eczema, and atopic sensitisation with odds ratios of 2-3. The two null mutations conferred a population attributable risk for the above outcomes of 15-16% raising the prospect that newborn screening might allow useful preventative measures in future.

Why we are interested in early growth

ALSPAC was designed with the measure of early growth as one of the key areas, because there is increasing evidence that this might allow us to gain some insight into the developmental origins of some adult diseases. As already mentioned, there is a well-established association of low birth weight and certain patterns of early growth with later cardiovascular disease and type 2 diabetes. How might this robust association across many decades be maintained? There are three broad possibilities. It could be social and lifestyle patterning, a persistence of an unhealthy life style leading first to poor fetal growth and then later to the adult disease. It could be some form of epigenetic programming of the baby by an adverse exposure but just during a critical period in its development. It might be due to classical genetics with the baby inheriting DNA sequence variants that predispose to poor fetal growth *and* adult disease risk. Finally it might be due to some other form of inheritance yet to be fully characterised. It is highly likely that the first three all play some part. Sorting out the contributions of each will be difficult but instructive.

The nature of inheritance

People tend to equate biological inheritance from parents with the information contained in the genes, the DNA sequences and their variations. However, it is important to recognise that much of the information transfer from one generation to the next is via that large fully functioning cell, the ovum. DNA does not transmit 'livingness'. This comes with the egg sailing like a self-contained spaceship from one generation to the next. It brings the cell membrane with all its signalling, the cytoplasm with all its organelles like mitochondria, as well as its nucleus carrying the maternal contribution of chromosomes and genes amongst other things. During development the mother provides further information to the baby in the form of molecules across the placenta.

These elements of biological inheri-

tance have been recognised for a very long time. In recent years we have had to add the transmission of epigenetic information, at least some key methylated DNA sequences in imprinted genes. Discovered in mammals from the late 1980s onwards, imprinted genes are characterised by being active or silent depending on their parent of origin. Exactly the same gene in terms of DNA sequence can be passed down from generation to generation, but will be active or silent in the offspring dependent on whether it last went through egg or sperm formation. Some imprinted genes are only expressed from the paternally-derived chromosome, whilst other imprinted genes are only expressed from the maternally-derived chromosome. How does the chromosome carrying such a gene know which parent it came from? It must carry a 'tag' or imprint from the egg or sperm f. In other words an epigenetic mark placed in the parental generation influences gene expression in the next generation.

Bearing in mind our interest at ALSPAC in early growth and its link to adult disease, I have chosen two examples that reveal unusual aspects of inheritance that will need to be born in mind as we try to unpick the causal factors in the rise in obesity for example. One example concerns transgenerational effects down the female line and the other down the male line. They illustrate the blurring of the simplistic concepts of nature and nurture in real life.

Maternal genetics contributes to the intra-uterine 'environment'

Blood glucose concentration is tightly regulated in humans despite considerable variation in food intake. One of the principle regulators of fasting blood glucose concentration is the enzyme glucokinase (GCK) which acts as the "pancreatic beta-cell glucose sensor". This is known from rare GCK mutations that cause a sub-type of diabetes known as maturity-onset diabetes of the young (MODY) characterised by mild, stable fasting hyperglycaemia. In pregnancy maternal fasting blood glucose concentration is one determinant of offspring birth weight with maternal hyperglycaemia stimulating the release of fetal insulin, an important fetal growth factor. Whilst it is known that rare MODY GCK mutations in either the mother or fetus have a marked impact on fetal growth, it was not known whether common variants in the GCK gene influence the fasting blood glucose level (within the 'normal' range) or birth weight. To summarise a lot of work led by Hattersley's group and including the ALSPAC samples, the common variant (G/A –30) in the promoter region of the GCK gene influences fasting glucose. Interestingly, the *maternal* but not the fetal genotype was associated with birth weight, so the mother's genotype contributes to the baby's environment.

Transgenerational effects down the male line

For the last 14 years I have been fascinated by the possibility that sperm or eggs might carry information about the ancestral environment as part of an evolved transgenerational adaptation mechanism . Indeed I have a picture of sperm in my home office with a caption asking just that question: do these carry information about the ancestral environment? This interest arose from my group's research into the inheritance of Angelman syndrome which proved to involve an imprinted gene

I love to speculate so I could not resist an invitation to wind up the Florence meeting on imprinting in 1994 with a 'no holds barred' speculation on why imprinted genes were maintained in humans. It seemed to me that if the silencing process of imprinted genes was responsive to sea changes in the environment, this could provide a mechanism for transgenerational adaptation. I soon became convinced that the only way forward in the search for evidence of epigenetic inheritance was to find transgenerational effects down the male line, because these would not be confounded by transplacental signals.

The Överkalix – ALSPAC collaboration

In May 2000 I received an email out of the blue saying 'In follow-up of long-term effects on survival using historical cohorts in Sweden I have seen intergenerational effects from good and poor availability of food during the slow growth period before the prepubertal peak. Paternal grandparental availability of food influenced the longevity of the grandchild, good availability giving a shorter life of the grandchild, poor availability giving a longer life'. It was from Professor 'Olle' Bygren, a retired public health doctor in the Social Medicine Department of Umeå University, Sweden.

You can imagine my excitement! Our collaboration was born. The grandchildren (probands) in his study (Bygren et al 2001) were born in1905 in the Överkalix parish in northernmost Sweden. In the 19th century this community was so isolated that there was no help if the probands' ancestors suffered a failed harvest. Furthermore there are very good historical records of harvests and food prices in Sweden, a practice introduced to ensure His Majesty the King got his due taxes. In the ensuing email exchanges Olle and I discussed which imprinted genes or relevant outcomes it would be sensible to target and agreed diabetes was a good candidate. In their follow-up work to look at cause of death, the Umeå group enlarged the sample to include 1890, 1905 and 1920 Överkalix cohorts. Focusing on the slow growth period in mid-childhood the study showed that the father's poor food supply and the mother's good food supply were associated with a lower risk of cardiovascular death. However, again there was also a striking association with the paternal grandfather's food supply in mid-childhood, this time with his grandchild's risk of diabetic death. Although the numbers were small there was a statistically significant four-fold risk of diabetes being on the grandchild's death certificate if the paternal grandfather had a good food supply during his slow growth period in mid-childhood.

These are difficult studies to do, having many potential confounders, but the significant outcomes had been *prior* hypotheses. Nevertheless, a key part of validating associations is replication.

Jean Golding and I decided to try and replicate some of the findings in the two generations of ALSPAC. Could we detect a transgenerational effect triggered during the paternal slow growth period? ALSPAC fathers didn't have big swings in food supply during their childhood so Jean suggested we use onset of cigarette smoking as the paternal exposure. 5357 fathers reported smoking, 166 starting before 11 years and therefore in their slow growth period. We hypothesised that any effect detected would only be with onset of smoking *before* puberty. ALSPAC has so many potential outcome measures that we had to be careful to limit these, in advance, to outcomes based on the Överkalix findings on cardiovascular disease and diabetes. We looked at birth weight and gestational length, plus height, weight, blood pressure and cholesterol at ages 7 and 9 years. We were able to correct for many confounding factors, a key one being continued paternal smoking in order to be able to test for the *onset* of smoking *per se*. We found that early onset of paternal smoking did indeed affect growth of future offspring. There was a trend of lower gestational length with earlier onset of

paternal smoking that showed a significant interaction with gender (P=0.028) with the transgenerational effect restricted to boys (trend P=0.008, two-tailed test). After appropriate adjustment there was a trend of larger body mass index (BMI) at 9 years with earlier onset of paternal smoking and this was also restricted to boys – F=3.49, P=0.015; trend P=0.025. We don't know the mid-childhood growth patterns and puberty onset of the ALSPAC fathers, but interpret the significant trend of decreasing BMI in the son with later onset of paternal smoking as reflecting the increasing proportion of fathers who had progressed from their slow growth period into the pre-pubertal growth spurt and puberty. This supports the Överkalix observation that exposure in the slow growth period, but not later in puberty, can lead to a transgenerational effect.

Did the Överkalix data show a gender effect? I emailed Olle and suggested they re-analysed by sex of the proband and waited. The answer came back yes, dramatically so! The paternal grandfather's food supply in the slow growth period was only linked to the mortality risk ratio of grandsons, whilst paternal grandmother's food supply was only associated with the granddaughters' mortality risk ratio. The concordance between the Överkalix and ALSPAC findings could no longer be a coincidence. We seemed to have uncovered a sex-specific pattern of transgenerational effects triggered by 'adverse' exposures at a specific time in the development of the paternal ancestors. What was so special about the mid childhood slow growth period and the pre-pubertal growth spurt that Olle had originally selected for special attention when planning his studies in the late 1990's? These two periods were just selected as contrasting childhood periods in terms of growth rates and therefore nutritional needs. After the initial Överkalix transgenerational effects, confined to the slow growth period, were published I speculated that the slow growth period might be relevant to the capture of environmental information by sperm, since this is when the testis is gearing up to produce the first sperm . But now we have to take account of information capture by the young paternal grandmothers. Her eggs would have formed during her fetal and infant life. To look at this, we decided to check the effects of exposure to good or poor food supply during the whole of the paternal grandparents' development from conception to 20 years. The results show four striking features.

First, as a 'control' for social patterning and other lifestyle confounders down the generations, we see absolutely no influence of the paternal grandfather's food supply on the mortality risk ratio of the *granddaughters*, or the paternal grandmother's food supply on the mortality risk ratio of the *grandsons*. The mortality risk ratios stay resolutely around 1.0. To get such a 'control' is a rarity with historical data. Secondly, the strongest transgenerational effect is seen with the paternal grandmother's food supply when she herself was a fetus through to 3 years, just when her eggs were being formed. Thirdly, the slow growth period is confirmed as an exposure sensitive period for both grandfather and grandmother. Finally, the *direction* of the transgenerational association between ancestral food supply and mortality switches during exposure in the ancestral slow growth period. Why this is so, I just can't imagine. However the overall beauty of these results comes from the pattern they produce. I argue that you would not get this pattern if we were just dealing with epigenetic changes (or similar mechanisms for capture of experience) trickling through to the next generation due to failures in erasure mechanisms between generations. I suggest the pattern we see tells us that we have revealed – perhaps 'stumbled across' might be more accurate – an evolved transgenerational response mechanism in humans.

So what's going on?

At this point we don't know whether these transgenerational responses are mediated by epigenetic inheritance, but it remains a strong candidate. We hypothesise that the Y chromosome and, possibly, the X chromosome are involved given the unusual sex-specific transmission patterns. After all the bad press the Y chromosome has had of late – degenerate, on the way out of our evolution, etc - it would be nice to think that it has a key role in transgenerational responses to environmental challenges.

Since we published our findings from the Överkalix – ALSPAC collaboration, support for our conclusions has come from studies of paternal betel nut (*Areca catechu*) chewing. Dr Barbara Boucher is interested in betel nut as a risk factor for diabetes and had already shown transgenerational effects in mice. In collaboration with colleagues in Taiwan, they have now shown that paternal betal nut chewing is associated with the early onset of the Metabolic Syndrome in non betel nut chewing offspring. The Metabolic Syndrome is a collection of features, including obesity, insulin resistance and increased risk of diabetes and cardiovascular disease which some regard as a 'maladaptation' to a modern world . It is early days in the study of male-line transgenerational responses in humans, but some coherence is emerging with respect to the outcomes observed in the Överkalix cohort (increased cardiovascular and diabetic deaths), in the ALSPAC cohort (increased BMI at 9 years) and now the metabolic syndrome in the Taiwanese studies. There is less obvious coherence in the ancestral triggers, unless one regards tobacco and betel nut addiction and swings in food supply (or something strongly associated with them) as 'uncertainty stress'. I suspect the evolved transgenerational response is fundamentally one of responding to an uncertain environment by switching the next generation(s) to a default mode that results in rapid early growth and early puberty, thereby advancing reproduction. If that is correct it makes sense that the ancestral environmental triggers have to operate before puberty, the last chance being Olle's slow growth period, otherwise the next generation is launched without the appropriate adaptations on board.

Standing the nature-nurture debate on its head.

Nature, nurture or neither? - that is the question for the conference. Like others I hope I have shown that if you mean by 'nature' - inherited genes and by 'nurture' – the physical or social environment, then it is rare that just one or the other explains the *differences* between people; it is usually a combination of both. Matt Ridley rightly points to the fact that for all of us our nature or genetic variation can only become manifest through the nurturing that permits development. Now we are faced with evidence that biological inheritance also incorporates information about our ancestors' developmental experience, so framing the debate in terms of nature or nurture has become even more meaningless. You could even say of the male-line transgenerational responses I described that dad can do some 'nurturing' before conception. How meaningless is that! So with respect to the conference question, I would go for 'neither'. I hope that I have raised some more pertinent questions for the future and in doing so put genes in their rightful place.

A two-part account of this Galton Lecture with references and figures is published in Paediatric and Perinatal Epidemiology, September and December 2008. Part 1 in volume 22**,** pages 497–504 and Part 2 in volume 22, pages 507-513.

Can a cell have a soul?

An author edited version of

BMJ Personal View

(BMJ, 17 May, 2008,
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John Burn

The recent UK parliamentary debate on amendments to the 1990 Human Fertilisation and Embryology Act has brought to the fore again the challenging debate between those who argue that all embryonic stem cell research is immoral and those who see immense medical potential in this area of research. As a clinical geneticist raised in the Christian tradition and interested in gene hunting and cancer chemoprevention I can claim to offer a dispassionate opinion. As head of the Research Institute where some of the most controversial work is underway and having been a signatory to the Donaldson report which recommended that this research should proceed, I must declare an interest.

Three aspects of stem cell research in which my Newcastle colleagues have special interest are mitochondrial transplantation, in vitro gamete development and human admixed embryos. In all cases, legitimate clinical targets may be presented as a powerful argument in favour of avoiding blanket legal barriers. Counter arguments combine anxieties about misuse of funds, threats to future family structure, dangers of cross species transfer of pathogens and unexpected malformation. None of these threats, real or imagined, requires an Act of Parliament to ensure proper address. Anyone who thinks research funds can be misappropriated on the basis of hype has clearly never seen an MRC committee at work. Existing statutory bodies, including the Human Fertilisation and Embryology Authority, have demonstrated their capacity to judge the balance of benefit and risk; an excellent example is pronuclear transfer to allow a woman carrying a mitochondrial disorder to have her and her partner's chromosomes transferred to a donor egg. This is work which promises effective intervention for families affected by mitochondrial diseases. . The HFEA have access to all necessary expertise and can reach reasoned conclusions even in the glare of catchy headlines.

But there is one criticism which such committees cannot now be left to address, one which lay at the heart of recent Easter sermons; stem cell research is an assault on the sanctity of human life. The essence of this whole issue returns to the thorny question, "When does life begin?" The Catholic Church has made its position absolutely clear. Life begins at conception and any deliberate generation of embryonic stem cells - or, to some, generation of embryos without the intention of implanting into a woman - is tantamount to murder. They support adult stem cell research which shows more promise without the "ethical problems.

For readers unfamiliar with recent Catholic history, on 29 June, 1868 Pope Pius IX issued the Bull *Æterni Patris*, convoking the first Vatican Council in 1869. . Two decisions influence the current debate; papal infallibility was made Church dogma and the *Constitution Apostolicae Sedes* rescinded the distinction between the animated and non-animated foetus in the canon law on abortion; in essence,. as a precautionary principle, life should be considered to commence at conception. Given the advances in microscopy the latter decision was defensible since the previous limit of 40 days, still used in Jewish teaching, extended to a point where an embryo is a few millimetres long with a primitive nervous system. The 40 day ruling dates back to Aristotle who concluded that Man receives his soul after 40 days and Woman hers after 80 days. Setting aside the intriguing gender difference, and voices of dissent ever since, the fact remains that this limit was accepted by the Church. Benedict XVI is the 265th pope since Peter and one of only 10 to rule in the era when the Church's official position was that ensoulment occurs at conception, which strictly speaking occurs at around 5 days when the blastocyst is "taken in" (Latin Concipere) to the wall of the uterus.

At that point the zygote, about the size of a sugar grain, contains a small group of cells called the inner cell mass which will give rise to the embryo proper, or two. Indeed these cells may rarely initiate up to five identical embryos. Only at around 14 days when the primitive streak forms can a single embryo be said to exist. If souls are delivered it is difficult to see how this can occur before the end of the second week. If an individual blastomere is deserving of personhood even if cultivated outside the body because it might become a human, then removal of a cell for preimplantation diagnosis becomes murder.

Adult stem cell research offers a limited haven for opponents; recent work suggests that introduction of four genes and selection for “nanog” expression can identify fibroblasts which have regained their embryonic potential. But if this proves really so do they not also then achieve instant ensoulment? And why all the fury about admixed embryos, the cow human hybrids of the tabloids? The stem cells being developed, using enucleated cows eggs as mini-incubators, are grown by fusion with a skin cell. They are adult stem cells. Used solely for research they present fewer ethical problems than the practice over many decades of testing human sperm by letting them fertilise Chinese hamster eggs(1), this random reference having been selected because it was from a Catholic university. Admixed embryos use tissue from the abattoir to preserve precious human eggs and advance laboratory research which offers real hope.

Just as protests about cadaver organ donation were addressed rationally and led to the widespread acceptance that the definition of death could no longer depend on biblical interpretation, so medical need dictates that the origin of human individuality must be defined with similar pragmatic precision. A cell cannot have a soul.

1. Morales P. (1) ; Llanos M. ; Yovich J. L. ; Cummins J. M. ; Vigil P. Catholic University, Santiago, Chile

Pentoxifylline increases sperm penetration into zona-free hamster oocytes without increasing the acrosome reaction Andrologia 1993; 25:359-362

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Professor **John Stillwell** of the University of Leeds and **Guy Goodwin** of the Office for National Statistics (ONS) put together two very interesting and challenging presentations for the first plenary session under the overarching title of *Developments in British Demographic Research.* John began, with an insight into the ESRC's (Economic and Social Research Council) key research challenges and the initiatives being taken to address them. These challenges include gaining further understanding of succeeding in the global economy, energy, the environment and climatic change, understanding individual behaviour and its relationship to biological and social determinants, population change, international relations and security, and religion, ethnicities and society.

He then expanded on the Population Change challenge as it was most relevant to the conference. The research in this area is geared towards understanding more about the processes of demographic restructuring, including the interconnections between declining fertility, migration and ageing in the UK and how they compare internationally. The ESRC currently funds four initiatives relevant to improving the understanding of population change. These include the New Dynamics of Ageing programme, UPTAP (Understanding Population Trends and Processes), the Centre on Migration, Policy and Society and the Centre on Micro-Social Change.

John then spoke in more detail about the UPTAP initiative for which he is co-ordinator. He explained that UPTAP was set up to build up capacity in secondary analysis and promote the use of large scale data sets. It is designed to help early to mid-career researchers gain valuable experience, and expand research into demographic trends and socio-economic processes that affect the economy, society and population.

Some of the UPTAP projects funded from the submissions in Round 1 started in October 2005. Twenty-five projects were commissioned from some 40 researchers, who were awarded funding to carry out the research in the form of post-doctoral fellowships, mid-career research fellowships, grants and studentships. The themes of research included: demographic change; residential change; fertility, motherhood and childlessness; living arrangements; child care; cohabitation; mobility; health and wellbeing; employment; education; identity, ethnicity and segregation; social and political values.

Since then the ESRC has funded another round of projects with a special theme of ethnicity and is about to announce further funding for around 10 fellowships. John encouraged early and mid-career researchers to consider the benefits of a fellowship to their work and their career.

Guy then spoke on *Demographic Research – Delivering through partnerships.* He took the audience through a whistle stop tour of demographic research in the Office for National Statistics, speaking first about the creation of the ONS Centre for Demography (ONSCD) in 2006 to set the context. ONSCD was formed from the Population and Demography division, with the objective of refocusing the work of the centre and giving it a clearer structure. ONSCD, along with their key stakeholders the UK Population Committee and the National Statistics Centre for Demography Advisory Board, highlighted two key high level challenges for the centre. These were to carry out more analysis and less production to enable the centre to be better equipped to explain more about population change and also to prioritise the research needs of key customers and collaborate with other government departments and users to decide who would be best suited to complete the work.

Guy commented that ONSCD and the ONS as a whole have had a good history of collaboration through ONS Methodology's ongoing contract with the University of Southampton, the 'Focus on' series which provides an up-to-date overview of topics such as Older People, Migration and soon Families, and involves a pooling of research by academics and other experts in government, and lastly the Census topic working groups. Guy also noted that collaboration had begun between the ONS, the Scottish Executive and the ESRC, looking at taking forward some of the good ideas in Scotland's Demographic Research Programme to use for England and Wales.

In future, Guy saw the centre forming more partnerships to build up the centre's staff expertise. These are likely to include working with ESRC-funded PhD and MSc students to further the centre's research priorities and support the students in terms of access to and knowledge about data. It is also hoped that work with the Migration Statistics Task Force will continue, investigating further the use of administrative sources for measuring migration. He saw the main research priorities as: further understanding and reconciliation of the differences between the mid-year population estimates and the census; developing our knowledge of population ageing and its implications; understanding and reporting on trends in living arrangements of older people; understanding more about who emigrates and in particular more about older migrants; furthering understanding of the changes in family structure; understanding the relationships between housing and population growth and expanding the understanding of changing trends in fertility.

Professor **Jan Hoem,** (Max Planck Institute for Demographic Research) presented the second plenary on *Early traces of the Second Demographic Transition in four countries in transition: A joint analysis of two competing risks*. The two main themes of the presentation were the changes to family structure taking place in Eastern Europe and the new method that has been developed in order to allow the joint analysis to be undertaken. He began by highlighting the fundamental decline in fertility seen in Eastern Europe and posed the question of whether this has been caused by the Second Demographic Transition (SDT), seen previously in Western Europe. SDT is characterised by declining marriage rates and increased entry into cohabitation, along with declining fertility rates, a trend towards later births and an increase in union disruption rates. Using data from the Generation and Gender Survey (2004) for four Eastern European countries (Russia, Bulgaria, Romania and Hungary) he showed that since 1980 cohabitations have increased 2.5 times whilst marriage rates have fallen by half.

He then moved on to describe the new method, based on an extension of piecewise-constant hazard regression, which analysed jointly the competing risks of a woman entering either cohabitation or a marital union. For Russia, this analysis showed that marriage was 3 times as likely as cohabitation in the period 1980 to 1984 but a complete reversal had taken place by 2000 to 2004 with cohabitation 3.5 times more likely than marriage. Overall results showed that all four countries had declining marriage rates, whilst Russia, Romania and Hungary had increasing rates of cohabitation. However, no direct relationship was found between the start of demographic changes and the varying political situations in those countries.

Jan suggested that there is a clear indication of the SDT in Russia, Romania and Hungary. He also showed that Bulgaria's experience appears to have been different, although declining rates of conversions of cohabitations into marriages and anecdotal evidence suggest that the presence of the SDT should not be ruled out. He concluded that the SDT has reached Eastern Europe, but with differing national circumstances, resulting in variations in both timing and effect.

Conference also featured a full programme of submitted papers, with two sessions on ethnicity, four on families and households, three on fertility and reproductive health, six on health inequalities, mortality and ageing, three of historical demography, three on local authority, census and planning issues, two on religious and cultural demography, and, in celebration of the venue this year, three sessions on Scottish demography, which attracted ten papers, a good number of which resulted from projects funded by the ESRC and Scottish Executive under the 'Scottish Demography Programme'. Additionally, there were three very successful sessions on transnational and subnational migration, and two UPTAP sessions.

Abstracts from the Conference, and many of the presentations themselves can be found on the 2007 Conference website at: http://www.lse.ac.uk/collections/BSPS/annualConference/2007.htm

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