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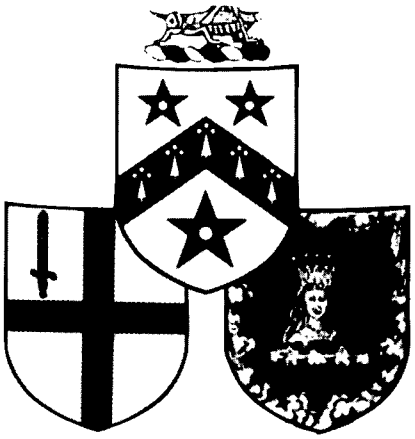

THE BIOLOGICAL CONSTRUCTION OF RISK: FROM MENDEL'S 'HIDDEN DETERMINANTS' TO DNA SEQUENCES

First of Two Lectures by

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Gresham Lecture -Spring 2000
Lecture Four Part 1: Genes and Risk
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ARRIVING AT THE RISK SOCIETY

This fourth lecture in the current series begins by focusing on risk and what social theorists increasingly call the 'risk society. As a highly scientific and technological culture we take for granted that our concept of risk is deeply informed by probability theory. However few things are culturally tidy, so we may avoid walking under ladders consult horoscopes and engage in a variety of superstitious activities, nonetheless we live in a society where risk assessment is routine and institutionalised. (Not least by the insurance industry.) The safety of transport is a good example : motor bikes versus family cars; a 20 year or a fifty five years old drivers? crowded or empty roads? fog and black ice or a clear dry day. And where are push bikes, planes trains and feet?
Today in our increasingly geneticised culture DNA testing is transforming our notions of risk. I raise some of the problems not least for individuals and families who are newly confronted by DNA risk assessments either for themselves or for their potential offspring. Having sketched out the problems as it impacts on peoples lives understand Steven will then take over in order to explain today's genetic construction of risk. This means that there is a rather sharp division between the social and the biological in this lecture - our hope is that in the second of this pair of lectures on risk, the social and the biological come together rather more comfortably

Like many sociologists I found the Risk Society (Beck 1992) a compelling and optimistic analysis, and yet as someone preoccupied for a number of years with 'science' and 'society' 1, I am also still enough of a Gramscian to go on arguing for both optimism of the will and also pessimism of the intellect. Thus I want to support Beck's core and optimistic argument that the only way to manage the risks integral to rapid technological change is through a radically new openness - which requires new institutions which would both reflect and create more trust between the manifest social stakeholders and also the citizen who presently exists only as a 'virtual stakeholder'(Cronberg 1996). However I read this global task of building trust between 'science' and 'society' as having to be worked through locally not least because of very different histories of the civil society / state relationship. What can be done for example, within the democratic traditions of Denmark and a relatively small biotechnology research base in managing new technologies, as against what can be done in Britain with its pathological love of secrecy, and as the second largest producer of

molecular biological research, has to be confronted with an appropriate level of intellectual pessimism.

But a spate of home-grown catastrophes has in this one medium sized European country generated intense public debate about risk. Dunblane, Milford Haven. BSE (mad cow disease) and GM foods have aroused very different feelings: the shared grief of an entire nation at the killing of the children and their teacher, the tired disgust at yet another oil spill, together with the knowledge that even the experts do not know whether or when nature can heal herself, to disbelief that any government and industry could so mismanage the food chain that the risk of Creuzfeld-Jakob's Disease in humans is now hideously real but of an incalculable incidence. But what is new in the public discussion is the question of how can society better manage the risks posed by incessant technological change. The consumer revolt against GM foods has forced both huge agro-biotechnology industries and gung ho governments to pull back. What ever one thinks about the pros and cons of GM - unquestionably this huge struggle has put into a new political context.

For a country which by and large does not see social theorists as part of its public intellectuals, it has been fascinating to see that they are at last seen as having something useful to say about risk, so we find Ulrick Beck and Tony Giddens discussed by the broadsheet newspapers. The cultural contrast with the Torrey Canyon oil disaster of the 1960s could not be more complete, for then the government of the day turned to the Royal Society. The assumption then was that the élite of British science was the ultimate repository of Truth about Nature, and as such the culturally authorised group to speak to Power. Whether the Fellows of the Royal Society actually knew anything about marine ecology, oil or risk was all rather secondary.

A number of disasters later, from Bhopal to Chernobyl, we all know it's a bit more complicated. It is not necessary to buy into the wholesale deconstruction of truth at the hands of postmodernism to acknowledge that generally within society the claims of the élite natural scientists are seen as rather more limited. Instead of élite knowers of Truth we look for competent experts. Today there is another difference, for it is not only sociologists who are inclined to think that people, as the human part of a local ecological system, have potentially something intelligent to say about both the prevention of risk and the management of disaster. Increasingly the media represents the voices of local people as providing trustworthy accounts to be set alongside the accounts from scientific experts. What is newer is to find the media discussing the arguments of social theory that risk has to be understood as integral to late modernity. The question becomes, not only how do we understand and respond to a particular disaster, but how do we understand and manage risk as integral to a technologically innovatory society.

The new genetics

The new genetics is central to today's techno-economic project. Thus while the leading scientific ideologues of the Human Genome Project (HGP) as its international institutional expression, claim its potential contribution to medicine and to knowledge, most have shares in biotechnology companies. Not only does the HGP mark the moment when the life sciences entered Big, that is industrialised, Science (De Solla Price 1963) it is also the moment when they made a new relationship to capital. As only the joint support of capital and the state could underwrite this long term investment, this required selling the new genetics to diverse audiences.

One sales pitch was to re-enchant fundamental science; thus we saw metaphors of the Genome as 'the Holy Grail' and the 'Code of Codes' routinely evoked in the discourse of the molecular biological elite as they sought to capture cultural support. The second, made by the geneticists, in alliance with the molecular biologists, was the power-charged claim of genetic therapy. In what has to be one of the most quoted editorials in Science, one of the two most influential scientific journals in the world, gene therapy was promised, not only for well recognised genetic disorders, but also for cancer and heart disease. And as if this was not enough, the editorial went on to promise to solve alcoholism and homelessnessii2.

The new genetics are potent for they shape society both as culture and as artefact. As the science of difference human genetics has had a long and frequently negative association with eugenics (Kevles 1985), for the science of difference has never taken place in the context of an egalitarian society but always in the historical context of strong social hierarchies. A newly massively funded new genetics thus intensifies the risk of exacerbating and naturalising social hierarchies. The initial gungho promise of gene therapy fundamentally modelled itself on single gene defects, argued that with the powerful and reductive tools of molecular biology, the new genetics would to able to find and fix faulty genes. The media swiftly picked up the claim and aired the possibilities and the ethical desirability of the 'perfect baby' and 'designer genes'. Science critics were rather more concerned with the political problem of who was going to decide what was a 'faulty' gene and who was to decide what was 'normal' let alone 'perfect' (Keller 1992). There was also a widespread public questioning about both the safety and also the morality of 'tampering with nature'.

Promise was unable to deliver therapeutic performance. Human Genome research ran into a number of technical problems, notably that closing the gap between the first approximation of the 'faulty' gene - the marker- and the gene itself , turned out to be slow and difficult. Then even single genes turned out to be complex and unstable. What had been understood as one condition with one gene sometimes became a set of similar conditions associated with slightly different genes. Despite a cascade of short lived claims reported with uncritical enthusiasm by the media, a recent report to the US government, concludes that after a decade of research, there are currently no effective genetic therapies. Instead we have proliferating

numbers of genetic diagnostics. Culturally these bring science into medicine in a new and dangerous way (Nelkin and Tancredi 1989), and while science and medicine are close they are not identical. Thus science holds that knowledge, in itself, is a social good; medicine, by contrast, is interested in knowledge which helps prevent, treat or manage conditions. Indeed clinicians have long held an ethic of not adding to the burdens of patients by sharing knowledge of conditions which they cannot treat. Today this paternalistic ethic is giving way as patients demand to share doctors' knowledge, but this new torrent of diagnostic information without therapy is qualitatively different from such negotiations.

The new diagnostics claim to be able to tell us, if we have the gene for the neuro-degenerative disease Huntington's, when it will express itself and how severely. However science's enthusiasm for knowledge is not evenly shared by people from families at risk of Huntington's. Many refuse this offer of certainty and prefer to live with uncertainty. Similarly a study I was engaged in, of people with genetically produced high cholesterol, revealed almost certainly affected kin who refused to enter the risk discourse of disembodied knowledge, even though in this case there was the possibility of therapy. These fragments of resistance underline the material power of this new techno-science to reach into our most intimate lives disturbing our created narrative of the self as going forward, uncertainly in time but always hoping to reach a good old age.

What energises these new material powers is the determinant cultural shift which informs the new genetics. While geneticists formally say that genes are not determinant, the unambiguous cultural message that comes through is that they are. Thus when Michel Foucault wrote in his history of sexuality, of that general biomedical project which searches 'in the depths of the organism' (1978:44), today's molecular biology insists on searching ever deeper and weakening the possibility of our narrative of self. In this discourse of the molecular biologists the organism itself, never mind about culture, is reduced to the sequenced four letters of the genetic code. Strings of sequenced DNA 'R' us.

Geneticists rarely publically resist this cultural determinism. When the Human Genome project was being proposed to Europe under the name 'Predictive Medicine', it was not the geneticists or molecular biologists who mobilised against this title as inappropriately determinant, but the German Greens and eventually the European Parliament. The cartoonists are well aware of this new determinism; one shows Madam Rosa, crystal ball gazer, being driven out of business by the new rival, a genetic diagnostician, setting up shop next door.

In turn the cultural determinism is then reinforced by the claimed performativity of the technologies. In the increasingly marketised and individualised society which loses each day a little more collectivity, the new genetics as diagnostics can produce a new form of cultural terror. I

speak of terror because genetic diagnostics in the context of hard Anglo-saxon capitalism works to mobilise fear and to deny space for scepticism and social trust3.The best way that I can convey the problems of risk, trust and scepticism is through an iconic tale of two sisters. They are American. One is diagnosed as having cancer and subsequent testing indicates that she has the BRCA- 1 gene. She 'chooses' to have double radical mastectomy. Her sister who shares the gene but who has no diagnosis of cancer 'chooses' to follow her example. These women are not isolates, some 20,000 US women have accepted this genetic risk assessment and surgical intervention.

But what underlies these 'choices'? Do these risk assessments and surgical choices which produce extreme bodily mutilation indicate trust in science and surgery? Or do they conversely speak of the lack of trust felt by these women in the capacity and willingness of American society to take care of women with either cancer or the threat of cancer? Is their 'choice' biologically cruel but ' socially smart' - based on an unglamourized reading of the US medical care scene?

I read these 'chosen' double mastectomies, not as the choices of cultural dopes, but as acts of grim social rationality faced with a medical care system based on private insurance, where 30 million Americans are without health care and where long term, or chronic illness can destroy the security of even the well insured individual or family. Resisting genetic pre-destinationism in a marketised context is particularly difficult. Theoretical opposition has come from feminist biologists such as Ruth Hubbard who argues that such determinism is both bad biology and also harmful to women. Empirical opposition has been launched by the recent publication of detailed epidemiological studies tracking family histories of breast cancer which provide the evidential basis for rejecting determinism. Given that alternative models have more cultural efficacy in displacing 'bad science'than mere criticism, such studies may help to weaken the currently iron genetic determinism.

1 Cf Rose and Rose (1969)
2 Editorial, Science, 246. (1989)p.189
3 One study reported that those without insurance were four times less likely to request BRCA-1 testing. White (1996) 'Notebook' Women's Journal of Health 5, 5, pp 415-20

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The last lecture took the history of genetics from Mendel's peas to Crick and Watson's discovery of the double helix structure of DNA. Genes, once hidden determinants, abstract accounting factors, had become real material objects, sequences of nucleotide bases arranged along the giant molecule of DNA. Let's just recap briefly how Mendelian inheritance works.

(transparency)

Now lets see how that might be translated into the language of DNA

(transparencies)

But that still doesn't tell us how we might get from DNA to phenotypic characters. After all, DNA as we have said is a pretty inert molecule. The molecules that do the work in the cell are proteins, and last time we referred to what Crick called the "central dogma" of molecular genetics, that "DNA makes RNA makes protein." As we hinted – but we will come to in the next lecture in more detail, things are now known to be rather more complicated. But without getting into too much detailed biochemistry, let's just look at how one does get from DNA to protein. Each strand of DNA consists of a linked sequence, many thousands of units long, of four molecules – called bases, which we can just call by their initials, A,C,G,T (of course also the initials used in the film GATTACA). (One complexity, just to help clarify the transparencies, is that en route to coding for protein, the DNA is transcribed into RNA, and the four bases in RNA are slightly different – ACG and U – so for U in RNA read T in DNA)

Proteins consist of linked chains of another type of molecule – amino acids, of which there are twenty different types. Crick, Sydney Brenner and others in the

decade from the mid-fifties to the mid-sixties recognised that the problem of protein synthesis was in part a problem of a *code*. How could sequences of four bases 'code for' protein sequences containing 20 different types of amino acid? If each amino acid is recognised by just one base, then only four types would be possible; if each required 2 bases, then 4X4 or 16 were possible. To recognise 20 different types you needed 3 bases – 4X4X4 – making 64 possible combinations in all – seemingly too many.

(transparency)

We won't go into how the problem was solved, but by the back end of the sixties it was realised that this was indeed the mechanism, and that the code was so-called degenerate – that is more than one combination of three bases were available for each amino acid. Other triplets are instructions about starting and stopping copying.

(transparency)

Of course you need a lot more than just DNA to make the proteins – the DNA is transcribed into RNA and then translated into protein in a complex set of reactions which involve a multitude of enzymes, lots of precursor chemicals, and a considerable supply of energy, all packed into individual cells – although the process can be mimicked in the test-tube. But again, lets take all that for granted for the moment.

So what are mutations? In the simplest case, a piece of the DNA code is swapped. A triplet which to produce the 'normal' protein should read, say, ACT (threonine)gets miscopied to read AGT (serine) instead. Or one base in the DNA chain might just be deleted, so that the sequence ACTAGTG (THREONINE-SERINE-) becomes ACTGTG (THREONINE-VALINE) – so the triplet code is now read quite differently; the whole of the sequence following is misread. Thus malformed proteins are made – or in some cases, no protein at all because the message has become so garbled. Mutations can be caused by radiation, or by

certain chemicals, or many other causes. But once they are present, they will tend to get copied fom cell to cell as cells divide and multiply, or during reproduction.

Now let's see how that bit of biochemistry might relate to the issues that Hilary began by discussing, and take a case which is pretty well understood, the disease called sickle cell anaemia. In this disease, which is inherited, something has gone wrong with the haemoglobin of the body's red blood cells. Haemoglobin functions to carry the oxygen from the lungs to the body tissues, but in sickle cell its chemistry is disordered – it is unable to bind so much oxygen, and indeed when there is too little oxygen being breathed in the round red cells themselves collapse into a sickle shape. Haemoglobin is a complex protein, one whose chains is some 300 amino acids long, and it turns out that swapping just one of these amino acids for another – a valine for a glutamate is enough to change its structure and produce the sickling. The mutation couldn't be simpler – a T has been substituted for an A within the section of DNA coding for the protein. So this means that there has been some mutation in the DNA code for that particular amino acid.
Remember that each cell in the body contains two copies of each gene, one inherited from the mother, one from the father. (Each of the two copies is called an ***allele***). If only one copy has the mutation (heterozygous) the person carrying it is both weakened by the disease and can of course transmit it to his or her offspring. If he or she has two copies though, one from each parent (homozygous) then they are in serious danger of dying young from the disease. Such inborn errors in the structure of haemoglobin are by far the commonest of all single gene disorders, and one person in 15, worldwide, is now a carrier. But this simplicity turns out to be misplaced; there are now known to be hundreds of different mutations which affect haemoglobin producing diseases which are in outcome rather similar but have quite distinct genetic origins.

That seems to be a clear-cut case of a single gene disorder, inherited in a proper Mendelian way, in which carrying the sickling gene seems to almost inevitably produce the condition. Sickle cell is unusual because the affected protein, haemoglobin occurs in just one type of mature body cell – the red blood cell, so

the mutation has relatively specific effects. The biochemistry of haemoglobin is well understood, and, the links between the disordered biochemistry and its physiological consequences for the fate of the red cell and hence a person's health are easy to understand, at least in principle. There is also some evidence as to why such a seemingly deleterious mutation should persist. It turns out that heterozygotes, carrying just one copy of the gene, are less at risk for malaria *(expand if there is time – unless Frank wants to!)* and therefore are favoured in malaria-prone areas.

There are many other single gene disorders, some relatively common, others affecting only one family in half a million or so. The US geneticist Victor McKusick' s list of such disorders now runs to getting on to 4000. However in the overwhelming majority the links between what goes on at the level of the gene or protein, and how it affects an individual's health are much less well understood. Take for example Huntington's disease, a disorder caused by a single dominant gene. Sufferers from the disease only begin to experience the symptoms in their middle years, when they steadily begin to lose muscular co-ordination and mental capacity. The gene responsible for the disease produces a protein called, unsurprisingly, huntingtin, which within its chain contains strings of the amino acid glutamine, coded for by the triplet sequence CAG. Some abnormality in the synthesis of the gene occasionally results in long repeated sequences of CAGCAGCAG and hence the protein contains long strings of glutamine – up to a hundred or more sometimes. The severity of the disease and its age of onset depend on the numbers of glutamine repeats – though no-one quite knows why.

Another example is phenylketonuria, a recessive single gene disorder which affects about 40 children born in the UK each year. Children born with this condition excrete large quantities of abnormal substances in their urine. It turns out that this is because a genetic mutation prevents the synthesis of a key enzyme required for the breakdown of one of the amino acids normally present in the diet, phenylalanine. Toxic products accumulate in the blood, and these result in turn in a wide range of damage in many body tissues, including irreversible brain damage. The mutated gene is said to be pleiotropic, having

many different effects. But the links between the specificity of the genetic condition and the widespread body effects remain obscure. Incidentally, it is also possible ***partially*** to alleviate the effects of the mutation if the affected child is fed on a phenylalanine-free diet.

Other single gene disorders – cystic fibrosis, Duchenne muscular dystrophy, FH – mention briefly depending on what is in Hilary's half.

To summarise the key points so far. Mutated genes can give rise to specific diseases. However genes aren't automatically 'good' or 'bad' – as in the heterozygous advantage in malarial areas for sickle cell. Furthermore, how a gene is expressed depends on the environment – the effects of the gene responsible for phenylketonuria are quite dramatically affected by the environment in which the child carrying that gene develops. The great population geneticist Theodosius Dobzhansky generalised this argument. Rather than simply assuming that each gene led to a specific and unmodifiable phenotypic consequence, as if one gene = one character, Dobzhansky pointed out that genes show what he called a 'norm of reaction' to the environment. How they are expressed depends on the environment in which they are expressed.

((transparencies)

The simple view of the gene sees a straightforward linear relationship between the presence of the gene in the fused sperm and egg following conception and the appearance of some phenotypic character in the adult. However, between fertilised egg and adult there are years of development to produce the hundred trillion cells that go to constitute each one of us. And each cell contains perhaps a hundred thousand genes, switched on and off in sequence during development. To add to the complexity, as with the haemoglobins, there are many different mutations along the sequence of DNA bases that code for the protein (or that control when the gene acts – a topic we will come to next time) that can result in a dysfunctional protein. Because to produce a fully developed organism, the genes have to work in concert, rather than independently, the environment for

any gene includes all the other 99,999. So if one gene is perhaps defective in some way, the activity of many of the others may be diverted or modified so as to overcome the defect. This is called developmental plasticity and when we come to discuss genetic engineering – of crops or animals or even humans its importance will become even clearer.

The consequence is that in no case is it ever possible to say that the presence or absence of a particular gene or gene mutation ***absolutely*** determines whether a particular disease will result and how severe it will be. Even in Huntington's disease, because the gene product, the protein huntingtin, has to exert its effect by interacting with other proteins, produced by other genes, the properties of those proteins will influence the outcome for the individual. The link between gene and phenotype is complex and non-linear.

This is why it is increasingly the case that instead of referring to genes as causing disease, one describes them as risk factors for the disease, increasing or decreasing the probability that a person will succumb to it. And so far we have been talking about diseases for which single genes have been implicated. But most common diseases are multifactorial – that is there are many different factors which contribute to whether or not one is susceptible to the disease. There may be dozens of different genes a defect in any one of which may slightly increase the risk of the disease, as well of course as many different environmental conditions which may either protect or precipitate – just as is also the case for infectious diseases.

To take another disease that is being increasingly intensively studied, Alzheimer's. This is a degenerative brain disease, which primarily affects older people – some 600,000 in the UK today. In the disease, nerve cells die and the brain is full of strangely tangled protein deposits, called amyloid, broken off sections of a protein called the amyloid precursor protein which is normally involved in holding the cells together in proper patterns and in memory formation. There is no one single causative factor for Alzheimer's disease – the best predictor is simply growing old! However there are a number of

environmental factors – such as having suffered from concussion, or been subject to general anaesthesia - which contribute to the risk. And there is a small subset – some 5% - of Alzheimer's patients who contract the disease early, and in which it is inherited in something like a Mendelian fashion. Other genes are also risk factors, For example one gene, coding for a protein called ApoE, exists in four different forms, one of which ApoE4, significantly increases the risk of a person becoming diseased, and another, ApoE2, which significantly reduces the risk. At present, no-one knows why.

The hope of some geneticists – ands you'll still read it in the newspapers – has been that in the long run, when we knew enough genetics, it will become ***predictive*** – that is, if you decoded a person's genes, you would be able to read their life history from them, knowing which diseases they would get and when they would be likely to die. Fortunately, for reasons we have begun to explore in this lecture, and will become yet more apparent next time, such dreams – or nightmares – are far from being achieved. But the consequences of living with knowledge of genetic risk, as Hilary has emphasised, are profoundly changing how we feel about ourselves and the way we live.

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