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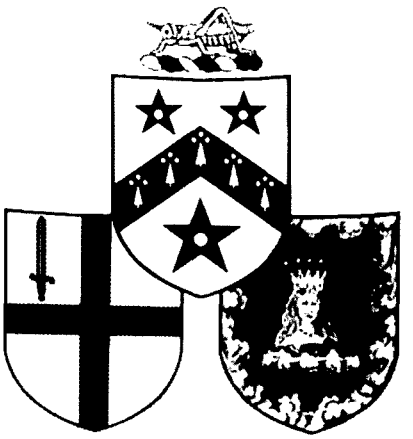

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CONFLICT AND CONSENSUS IN THE AGE OF THE NEW GENETICS

Lecture 5

TAILOR-MADE DRUGS?

by

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Tailor-Made Drugs?

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June 26th. 2000. A transatlantic press conference addressed by Bill Clinton and Tony Blair announces that the rival teams racing to sequence the human genome – the three billion letters of each person's DNA code – have completed their task. Politicians, scientists and the press go hyperbolic. Depending who you listen to, decoding the 'book of life' is the greatest invention since the wheel or the discovery of fire. Ageing, disease and human misery will be abolished. The essence of humanity will be laid bare for all to see, each of us will have our own personal DVD carrying our unique genetic signature.

There were, inevitably, just a few snags. First, the genome was not really yet fully decoded – it was only a 'rough draft.' The press conference was a skilled political balancing act to salvage the amour propre of the rivals – the publicly funded Human Genome Project led by the US's Francis Collins but also massively supported in the UK by the wealthy UK based Wellcome Trust, and the entrepreneurial team run by the much vilified Craig Venter. A 'gold standard' version of the genome is still a couple of years off. Second, the much hyped benefits to human health from the immense sequencing efforts are still only promises. DNA technology enables genes to be identified and potential diseases diagnosed, but possible therapies still lie in the future. For the moment the only beneficiaries are those who hold shares in the many exotically named biotech companies which have rushed to patent almost every conceivable (and some highly improbable) DNA sequences.

Herein lies the key to understanding why there should have been a 'race' at all. After all, would it really have mattered if the whole exercise had been delayed a couple of years – or even ten – to be sure to get it right? Even though we scientists can get quite competitive, most of the time we work, if not collaboratively, at least in comfortable parallel with one another. Of course there have always been priority disputes, but the idea of racing, of beating one's fellows to a solution, seemed a peculiar product of the American psyche, shockingly demonstrated when one of the two co-discoverers of the structure of DNA, Jim Watson, published his candid account of *The Double Helix* back in 1968. (That Crick considered suing his collaborator speaks for the scandal that the book generated).

What seemed then a vulgar aberration was transformed by a series of decisions by the US Patent Office to allow patents, first on genetically engineered life forms, and subsequently on genes themselves. (British pressure finally pursuaded a reluctant Europe to follow suit). It was whilst Venter was still a US government employee that he was central to an attempt to patent a vast number of short DNA sequences, isolated experimentally but with as yet no known biological function. The initial attempt failed, but it opened up a wide rift both in the molecular biological community and amongst ethicists and lawyers. Could and should what are essentially extracted body parts - so clearly "discoveries' and not "inventions' - be patented, or are they part of a universal human birthright whose study and use should lie in the public domain?

Wellcome, the UK's Medical Research Council and the US National Institutes of Health, backed public access to the gene sequences – interestingly supported by many of the big drug companies, who wanted to be able to draw freely on the sequences to support their own – clearly patentable – drug development programmes. Venter, backed by substantial venture capital investment, went his own way, founding a series of institutes and companies dedicated to fast sequencing and where possible patenting 'interesting' genetic fragments. The stage was set

for intense rivalry. The original target set for the complete sequencing of the human genome – 2005, at a cost initially estimated at some $3billion - was dragged forward; the public sequencing centres started releasing their data every 24hrs, making it unpatentable, whilst the innovative Venter developed constantly faster techniques to speed up his private effort.

By February 12th of this year, the public and private teams made a further simultaneous announcement, the public one in Nature, the private one in Science. A further stage of the sequencing had been completed and it was now possible to estimate more precisely the total number of genes it contained. Once set at around a hundred thousand, the number is now revised down to about thirty to forty thousand – only about twice that of, say, the fruit fly Drosophila. More than 98% of the laboriously sequenced genome has no known function – the so called introns, or intervening sequences we discussed last year. But dismissing this as nothing other than junk or repetitive or selfish DNA might seem just a tad incautious.

So how can the same number of genes specify either a fruit fly or a human? The answer is that they can't. Our bodies may contain up to a hundred thousand different proteins, for a start. Our brains contain a hundred billion nerve cells, and up to a hundred trillion connections between them. Such complexity cannot be specified by so few genes. This is where the simple idea of one gene, one protein, one phenotype, falls down. First as we have discussed, there is really no such thing as 'a' gene any more. Different DNA sequences can be patched together in many different ways, and even read differently; the code has multiple reading frames. And it is the power of combinatorics, of the myriad ways in which genes can be expressed and permuted, shaped by environmental and developmental contingencies, which results in the phenotypic outcome. This is why the new buzzword is no longer genetics or genomics alone, but something called functional genomics – that is, the study of what the genes are actually permitted to do by the cell in which they are embedded. It is against this background that we have to judge the claims that the new genetics will enable us to understand and hence transform our lives.

A few years ago the assumption was that the new genetic knowledge would enable genetic engineering – the elimination of genes with undesirable effects or the insertion of genes with desirable ones, either within the lifetime of an individual (somatic gene therapy) or into the germ line itself (germ line gene therapy) hence passing the transformed or manipulated gene onto the offspring – a procedure which is still banned. As unforseen technical difficulties have prevented even somatic gene therapy being successful, the goalposts have been radically shifted. The intention now is to use the new genetic knowledge to understand the biochemical mechanisms that go awry in particular diseases and on this basis to design drugs which can modulate these mechanisms. Hence two new terms have entered the vocabulary: pharmacogenomics and pharmacogenetics. These are the prospects which have underpinned the development of the genetic data bases of the type represented by the Icelandic company DeCode, the subject of Hilary's research that we discussed last month. In this lecture, we propose to look a little more closely at the genetic and health claims and possibilities offered by these new technologies.

First a little more background on the genetic code and its sequencing. What has been sequenced is in fact an 'average' genome, a combination sequence from a few unknown individuals. In Venter's case interestingly he has let it be known that these included both Americans of European origin, Afro- and Asian Americans, and pointed out that they were indistinguishable, thus emphasising the biological meaninglessness of the term 'race.' The sequence any one of us carries in unique to us (and if we have one, any identical twin). This is partly because of the gene shuffling that occurs during sexual reproduction; recall that each of us carries two copies of each gene (called alleles), one inherited from each parent. Which particular allele we get is the result of that shuffling. The two alleles of the same gene may differ from one another as a result of inherited mutations. The effects of such mutations may be

dramatic (as in the single nucleotide swap in the haemoglobin gene that results in sickle cell anaemia) or they may be minor or neutral – part of the vast reservoir of hidden genetic variance within the population. As well as major genetic differences, there are a whole raft of minor ones – ones in which a single nucleotide has been swapped for another without obvious effect on a person's phenotype. To distinguish them from mutations (the term generally implies some observable phenotypic difference, but it is a bit vague) these are called single nucleotide polymorphisms, or SNPs. On average each of us differs from our neighbour by at least three million individual nucleotides. Such differences form the basis for, for instance, genetic fingerprinting techniques.

There are a very large number of diseases and disorders which are attributable to the malfunctioning of a single gene, and which are therefore inherited in a relatively simple Mendelian way, even when they are sex-linked. Some 5000 of such different diseases have been recorded, many of them with severe or lethal consequences and most extremely rare, affecting only a few families in the population. But most of the common diseases, such as atherosclerosis, cancer, multiple sclerosis, Alzheimer's or psychiatric conditions such as manic depression, schizophrenia or autism, even where there may be a genetic 'predisposition' to the condition, there is no single gene which may be responsible. Rather there are likely to be many genes each of which may act as a 'risk factor' contributing to some small extent to the condition. Or, another possibility: there may be several genes any one of which could have a major predisposing effect, but some people carry one such, others another, so that no clear link can be constructed responsible for the disease in everyone who suffers from it.

This is where the DNA and health data bases of the DeCode type are supposed to come in. Take a population of, say Iceland's size, of around 250-300,000 people. Within this population, there will be many whose medical records list them as suffering from disease X – multiple sclerosis, let's say. If one now compares the DNA sequences from all those who suffer from X with those who do not, the assumption is that one will begin to pick up certain regularities. Certain SNPs will be more frequent in the sufferers than those who are free of the condition. If one has the family records – of who is related to who – then the associations can be matched more precisely. Particular diseases will be found to be linked to particular SNPs, or chromosomal locations. This doesn't of course mean that the SNP is responsible for the disease or disorder, it may –most likely is – not in a gene at all but in an intron close by. However, it will be a *marker* for that gene, segregating with it during sexual reproduction, and will therefore in principle indicate a gene which may be associated with the disease and whose functions can then be studied. . Such genetic loci are technically known as Quantitative Trait Loci (QTLs). Even so the gene is unlikely to be the single 'cause' of the disorder for the reasons indicated above. It is most likely to be a risk factor that contributes a small percentage to the chance of a person having the disease. The ApoE alleles, one of which is a risk factor for Alzheimer's disease, are good examples of this. And, once the gene is identified, it becomes feasible to examine just how it may contribute to the development of the disease or disorder.

The hope of pharmacogenomics therefore, is that the DNA data bases now being collected – in Iceland, in Estonia, in Sweden, the UK, and in many other countries – combined with medical records, will begin to make it possible to identify, say, the ten or twenty genes most closely associated with the development of the disease. The question that remains open, however, is just how useful such information will turn out to be. Just suppose that gene X is identified, and in the best possible case the biochemical mechanisms that it is associated with are interpreted and that malfunctioning of these mechanisms represents a 5% risk factor for the disease. What should one do about it? Gene therapy isn't on the cards – and certainly not for such a low risk situation. Nor can one envisage putting a person on a lifetime drug regime for such a low risk. So what does one do? At best identify other risk factors for the disease and be particularly

careful about avoiding them (like going on a low saturated fat diet if one has a genetic propensity to hyperlipidaemia). On the other hand the potential damage that such knowledge can result in cannot be discounted. Suppose a parent is told their child has a 5% increased risk of suffering from schizophrenia. Every action of that child will be that much more carefully scrutinised in case it means the condition is beginning to manifest itself. The chances of exacerbating rather than diminishing the risk by generating such potentially self-fulfilling prophecies are obvious.

The other possible scenario that the data base could generate is slightly more positive though. Suppose it turns out that for a condition – say essential hypertension – there are five or so different genes each of which may separately predispose towards the condition. Each gene may be a strong risk factor but may not have been identified by classical genetics because of the fact that it is but one of a cluster of such genes within the population. Then identification may help lead to rational drug therapy. This moves us into the terrain of pharmacogenetics. Pharmacogenetics has a very different and more grounded rationale than pharmacogenomics. It starts with the observations (a) a drug which helps alleviate symptoms or even cure one individual may be without beneficial effect in another, whilst (b) many people suffer adverse effects from one drug whilst responding favourably to a closely related one. Why should this be? One possibility is that one gene is associated with the disorder in one person, and a different one in another, or that one person carries a combination of genes that interact badly with one type of drug but not with another. Then determining an individual's genetic profile might reveal which drug they should be prescribed, or which they should avoid. Hypertension is a case in point. There are at least three different classes of drugs prescribed to lower blood pressure – beta blockers, ACE inhibitors and calcium channel blockers. Each produces adverse effects in some people but not others (beta-blockers can result in impotence, ACE inhibitors in hacking coughs, etc.). Drugs to treat high cholesterol levels have similar problems; some work better than others, some produce serious muscle pains in some people, and so on. Currently which drug you get prescribed first is a hit-or-miss affair, depending on your GP, and often you have to be sample several before hitting on the most effective and least damaging. The hope here is that a genetic profile – your DNA on a chip, as it is fantasised – will enable the right drug to be chosen first time around, saving you needless suffering and the health service a significant drug bill.

However, it should be emphasised that individual tailoring, Saville Row style, it is not. It is more like buying a T-shirt in one of three sizes, small, medium or large. Thus even on the best assumption, the 'fit' between the genetic profile and the drug class will be loose fitting.

Well, no-one knows yet whether such a pharmacogenetic vision will turn out to be practical. What is clear is the big drug companies are beginning to invest heavily in it, and we can be sure that it will form one part of tomorrow's high-tech medicine. Whether it will be more beneficial than harmful remains to be seen. What will happen to those whose genetic profile doesn't quite fit any of the available drugs? Will a cash-strapped health service simply triage them out of care, rather like post-code prescribing and ageism does now? And technically, will the pharmacogenetic vision really work. The simplistic genetic idea that for each diagnosis there is a specific gene has long gone out of the window. But now that even the hardest line genetic determinists are beginning to see that it is not individual genes but the combinatorial properties of many genes expressed in complex and shifting environments which need to be understood, even pharmacogenetics may prove too blunt an instrument to deal with human variability.

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