

Exploiting genetic knowledge: the double helix 50 years on

Conference report from the UK

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Pharmaceutical manufacture is one of the major industries in the UK. Long experience with the “Achilles heel” of the industry – animal research activists protesting against tests of new drugs on animals – has shown commercial scientists the need to communicate effectively with the community before introducing new products onto the market. It is therefore not surprising that a conference on the commercialisation of genetic knowledge should include not only the science preceding discovery of a new drug and the steps to take that drug into the market place, but also the preparation for public acceptance of the drug through widespread community consultation on social and ethical issues.

All these topics were included in the British Council conference in Newcastle, UK on 10-14 March 2003. The 26 participants, mostly scientists, came from 17 different countries – many from the UK and other European countries, but also from Brazil, Russia, Taiwan, Thailand, New Zealand (Dr Barbara Nicholas, Senior Analyst, Ministry for Environment) and Australia (myself). Presenters included basic scientists; commercial scientists who have taken products from the market bench to the market place, seeking venture capital to develop market share; and social commentators: see Box A.

The conference was conducted under the Chatham House Rule which permits participants to use information and views received during the event but not to quote anyone specifically without their permission. This report is therefore in general terms, to provide a broad impression of issues discussed.

Box A

Presenters:

- Sir Richard Sykes, Rector Imperial College London, Glaxo Research Ltd;
- Sir John Sulston, Nobel Prize winner for physiology in 2002 and member of Professor Sydney Brenner’s group in Cambridge which did the early research on genetic regeneration of organ development;
- Dr Alison Murdoch, Chair of the British Fertility Society; Dr Frederick Wright, investment consultant on life sciences who guided Pfizer’s first recombinant-DNA derived product through FDA;
- Dr Allen Roses, Duke University Medical Centre, who led the team that identified a major susceptibility gene in Alzheimer’s disease;
- Professor Tom Meade, who chaired the expert group on the prospective study of lifestyle characteristics and genetic markers for major medical conditions, UK Biobank;
- Suzi Leather, Chair of the UK Human Fertilisation and Embryology Authority;
- two members of the Human Genetics Commission – Professor John Burn and Phillip Webb, who pioneered genetic fingerprinting for ICI, like Paul Debenham, another player in the genetic profiling market;
- social commentators, including Professor Dorothy Wertz (University of Massachusetts Medical School); Professor Derek Morgan (Law, Cardiff)
- speakers from the Policy, Ethics and Life Sciences Research Institute at the University of Newcastle (<http://www.peals.ncl.ac.uk>), including Dr Tom Shakespeare, Director of Outreach at the Institute (Co-organiser of the conference, with Dr John Burn, also at the University of Newcastle); Dr Erica Haimes; Dr Tom Wakeford, Michael Whong-Barr.

1 Current knowledge; directions of research

It is 50 years since Watson and Crick first described the double helix (and, coincidentally, 2003 is the European Year of Disabled People – a point raised at the conference). Since then, scientists have learnt a great deal about the human genome. Its structure has been mapped. We can link genes to diseases (over 1000 genes associated with disease have been identified); and scientists are exploring protein changes caused by genetic disorders that are related to disease. The focus of genetic research has now moved to proteomics, pathophysiology and pharmacogenomics.

Proteomics explores how genes are expressed in cells, producing – or failing to produce – particular proteins that are vital in the physiology of the patients. A study of genes alone will not provide this knowledge. A caterpillar and a butterfly have the same genome. What makes them different in phenotype appearance is that certain genes are “switched on” at each stage of development (the science of expression proteomics – the process of “expression” – or “switching on”, genes).

Pathophysiology is the study of the link between genotype (a person’s genetic structure) and phenotype whereby bodily factors arise from other causes, such as lifestyle and environment.

Several projects undertaking research of this kind were discussed at the conference, especially UK Biobank. This is a 45 million pound study involving 500,000 people between the ages of 45 and 69. Its aim is to study a number of common, costly conditions, such as cardio-vascular disease, cancer and diabetes: <http://www.ukbiobank.ac.uk/>. Blood samples are taken for biochemical and DNA analysis. Life-style and environmental factors (clinical, smoking, diet, exercise, etc) are obtained from a questionnaire. Participants will not be told their genetic information nor given feedback as the study proceeds (if there is a clinically significant finding, it will be publicised and all can then apply for their own test). Academic and commercial scientists will be able to gain access to samples and information for their own studies. (The Estonian population genetic database, on the other hand, will give all participants their own “gene card” when they have been tested; it will have full information on their genetic structure). The North Cumbria Genetics Project has been collecting maternal and cord blood samples, matching these with life-style information from a questionnaire completed by donors.

Pharmacogenetics is the development of drugs designed for particular individuals. One aim of the studies of the relationship between genotype and phenotype is to enable such drugs to be produced and prescribed. There are both medical and financial advantages. Drugs will be more effective as the “right drug” can be used for the “right person”. Use will be “evidence-based”. Medicines that don’t work will no longer be used (though questions may arise about whose responsibility it is to test commonly-used drugs for efficacy – who should test for aspirin, for example? And what incentive will there be for such tests if there is no market benefit?) Patients who have genetic characteristics that

make them allergic to particular drugs may take others that have fewer side-effects (4% of patients who take the drug abacavir are allergic to it and the allergic reaction may be fatal). Pharmacists may have responsibility for arranging genetic tests for patients so that the appropriate drug can be prescribed.

2 Taking new drugs and procedures to the marketplace

Initially, the principal applications of genetic technology have been in basic science (understanding the operation and significance of genes and proteins in cells); and in diagnostics (finding out which genes are associated with particular conditions. A Cambridge company has the aim: “from hospital lab to point of care: your genome in 24 hours”). Over the past 10 years, however, the major profits have been made in manufacturing the patient-specific drugs described above; and in new treatments – tissue engineering and stem cell therapies. (The US bone-marrow transplant market is estimated to be US\$15 billion per annum by 2015 – “enough to make commercial developers excited!”) Wound healing products – skin and tissue - are being developed. In future, bone replacement will be possible. A recent report on stem cell therapy was commissioned by *investment bankers*, so big business is obviously prepared to invest in this area. Future commercialisation will focus on drugs and treatments rather than diagnostics for economic reasons – a diagnostic test is used once and drug treatment for a genetic condition will be ongoing or long term. This makes it more difficult for commercial scientists to raise venture capital to develop diagnostic kits. Investors outside the NHS see greater profits for drugs for long-term use.

Gene therapy, although it may have potential, is not being developed because of safety concerns – problems associated with retroviral and adenoviral vectors (these are the viruses used to introduce new DNA into a person’s body to try to correct a genetic disorder). In the UK, children with severe combined immunodeficiency (SCID – the “bubble” children) have developed leukaemia. Thus, despite the potential advantage of gene therapy in “correcting” a genetic defect so that the person no longer needs to take drug treatment throughout life, this research is not being pursued at present.

3 Commercialisation to date

In addition to new diagnostics, drugs and treatment, there have been other uses of genetic knowledge. Genetic fingerprinting, first developed in 1989, is now widely used in the UK (as in other countries), especially in criminal trials and for paternity tests. Results are now much more accurate than the earlier blood-grouping or tissue typing and the genetic “bar-code” is far clearer for examination in court. Tests are cheaper (average about £100); and they can be conducted on saliva or hair (with root attached) as well as blood. The UK Child Support Agency, the government body overseeing maintenance payments, relies on DNA tests. A Code of Practice and Guidance on Genetic Paternity Services has been developed in the UK, covering validation and control of samples; accreditation of testers; consent; and strong avoidance of “motherless” tests: <http://www.doh.gov.uk/pdfs/geneticspaternity.pdf>

Everyone arrested for a criminal offence for which imprisonment may be imposed is DNA-tested and the sample is held in the national DNA database, even if the person is later acquitted. This is the largest database of this type in the world, with over 2 million offender profiles on it.

DNA testing has also been done on birds and animals. For example, three Blue Hyacinth parrots, alleged to have been illegally imported into the UK, were the DNA tested to refute the owner's claim that these birds were the progeny of birds that he had bred in captivity and so could be legally imported.

4 Community concerns about genetic technology

Concerns about more widespread use of genetic tests and treatment include the following:

- Public awe of genetics – people think genetic results are definitive and do not understand the impact of lifestyle and environmental factors;
- Management of the “worried well” – those who know their genetic risk and worry about it long before symptoms appear;
- Costs of increased genetic testing, especially for the NHS;
- Should “genetic” tests (or assisted reproductive technology) be subjected to specific regulation?
- Globalisation: scientists move to a more favourable regulatory climate. As Lee Silver said, “the marketplace – not government or society - will control cloning. [I]f cloning is banned in one place, it will be made available somewhere else – perhaps on an underdeveloped island country happy to receive the tax revenue”. The UK is attractive for the development of stem cell research because embryos can lawfully be allowed to develop up to 14 days. Infertile couples resort to “reproductive tourism” – a person seeking an identified gamete donor cannot find one in the UK but can in the US; internet genetic tests. “Motherless” tests of a child to check paternity are not commonly done in the UK but overseas providers advertise non-consensual tests on the internet. On the other hand, globalisation may be an inducement for commercial scientists to take account of community concerns before taking a product to market. The UK experience of Monsanto in attempting to sell genetically modified food products in the UK shows the importance of “market preparation”. If companies do this in many countries, taking account of all concerns raised for market purposes, this may encourage a uniform approach even if the regulatory requirements are different in each country.
- Non-consensual access to genetic information by insurers – in the UK, insurers have agreed not to use any genetic information from research studies in setting premiums;

- The use of pre-implantation and pre-natal genetic testing to produce a "sorting society" – people wanting the "perfect" child, especially if starting a family late and anticipating only one or two children. Should genetic tests be limited to "serious" conditions (cystic fibrosis, Down syndrome, Achondroplasia (dwarfism), profound deafness?) – and, if so, how should this be determined? And by whom? (In the US, 60% of patients in a survey said that patients should be allowed to have tests for any genetic condition if they pay for it themselves; on the other hand, 50% world-wide in the same survey said they would support a woman who decides not to terminate her pregnancy despite the very serious genetic condition, Fragile X syndrome. Also, the spectre of "designer babies" seems to be overrated – most women don't want to conceive by assisted reproductive technology and will use it only for strong medical reasons;
- Privacy of genetic information. People in the UK apparently sometimes seek genetic tests directly rather than through their family doctor so the results will not appear on their medical records; or they use a pseudonym;
- The number and width of genetic patents; patents of whole organisms. Should genetic patents be for shorter periods? Could they be subject to variation by the World Trade Organisation to benefit poor countries?
- The problems that inevitably arise with international instruments – they are drafted in broad terms (such as "human dignity") to secure agreement but need much more specific wording if they are to be uniformly implemented in each country.

5 Consultation and policy development

Presenters and participants described new methods of community consultation – stressing the need for a "bottom-up" approach – responding to other people's "lived experience" and what the public want to know, rather than information provided by scientists and government authorities. The UK Committee for the Public Understanding of Science (COPUS), through which scientists explained science to the people, was disbanded last year, due partly to public scepticism that government wanted to *appear to* consult them about their attitudes to GM foods rather than a real interest in their views. (One change made after community consultation on the Biobank project described above was to reject the original name "Biobank UK", which the public considered too commercial, and to replace it with "UK Biobank"!)

The UK Human Genetics Commission was established in 1999 with about 20 part-time members – half clinical, science and commercial genetics; half "lay"- ethics, consumer, sociology, disability: <http://www.hgc.gov.uk>. One method it uses to consult the community is a panel of people with genetic conditions, or their representatives. All drafts are sent to this Panel for comment.

Other presenters described similar processes of patient consultation in which people with genetic conditions were asked to describe the process of their condition and decision making concerning treatment – talking about “illness” (experience of patients) rather than “disease (diagnosed by doctors). One presenter found that cystic fibrosis patients thought that others were not aware of the “moral good” of disease or disability – that one can “learn from” illness; deaf people worried about the deaf culture being eradicated by prenatal genetic decisions; people with achondroplasia were concerned about the spread of eugenic attitudes. Pregnant women are apparently far less willing to terminate pregnancies for genetic reasons than many geneticists believe, even for “severe” conditions like cystic fibrosis, Down syndrome, Achondroplasia and sickle cell disease.

In explaining scientific issues to the public, scientists do not always understand what people want to know. Regarding embryonic stem cell research, for example, people want to know not only what research involves and what it may achieve in future, but also about whether there are any alternative means to achieve these results without destroying embryos.

Initiatives for engaging the community in discussions concerning science that were discussed at the conference included the following:

- **Cafés Scientifique** – regular, informal discussions in a public venue, free to the public, on issues like genetically modified crops and biological warfare. A Wellcome Trust grant has enabled this popular movement to spread around Britain. Many European countries have similar cafés but they are an outreach of universities. Demographic surveys show that most people attending these cafés are university-educated, so they are not representative of the whole community. Also, the debates do not change people’s minds. However, people are empowered by the opportunity to discuss the issues openly, to confront scientific experts about the wider implications of their work. They may understand the complexities of the issues in greater depth. And the scientific presenters will know the reservations that the lay community have about their research and where it might lead.
- **Citizens’ juries** to canvas attitudes of small farmers in India to three potential agricultural developments – GM crops, growing organic crops for export; and agricultural practices for self-sufficiency: see www.prajateerpu.com
- **Extended peer review** of research proposals. Instead of the usual approval and monitoring of research protocols by ethics committees, the UK Alzheimer’s Society invited 150 “consumers” (patients’ families or representatives) to participate in considering, ranking and monitoring research. These people are involved in each research project, visiting researchers and presenting an independent report at the end of the project: see www.qrd.ion.ucl.ac.uk

It should be noted, however, that others are sceptical about attempts to “democratise” decision making about medical and scientific matters. Even people who have been directly involved in a research project, providing their “informed consent” for it, often do not really understand what it involves. When the comprehension of participants in the North Cumbria Genetics Project, mentioned above, was investigated by a survey, it was found that most had a “murky idea” of the nature and aims of the study and had not thought about future uses of the samples, confidentiality, access by insurers, feedback etc. When these issues were raised, the donors were concerned about them. Thus, consultation had an educative function but might also cause alarm.

There are also concerns about the *weight* to be attached to community views. “Moral majoritarianism” cannot be accepted – that is not “doing ethics”. The vast majority of the population believe in capital punishment but their opinions do not dictate that this should be the law.