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From genetics to revelation?

There has been no shortage of meetings in recent years to discuss the daunting implications for society of advances in molecular medicine and the human genome project. Yet there is still precious little agreement about the issues of genetic privacy, diagnosis and therapy, as well as related matters such as embryo research and insurance. One such meeting* was convened recently by the Institute of Religion and the Baylor College of Medicine in Houston to examine these ethical problems. Sadly, while illustrating many exciting developments in genetics, the meeting provided little consensus as to how society should respond.

Molecular diagnostic technology is moving so rapidly that society is having difficulty absorbing the impact of the changes

More than 20 years after the first successful allogenic bone marrow transplant was performed on a patient with X-linked severe combined immune deficiency (the patient now has twin sons who have 'lost' the rogue gene), gene therapy is a reality. The first recipient, a young girl suffering from adenosine deaminase (ADA) deficiency, was treated in 1990 by Michael Blaise, Steven Rosenberg and W. French Anderson at the National Institutes of Health, and the early indications are that the therapy is working well.

With an increasing number of gene therapy proposals receiving approval, and *in vivo* therapy for melanoma about to begin, questions on the types of treatment allowable are being addressed. Despite general agreement that safe, appropriate somatic cell therapy is acceptable, what about germline therapy? Are there cases in which enhancement of certain features would be permissible? Such a notion is not apparently discounted by the general public. In Houston, bioethicist LeRoy Walters from Georgetown University quoted an opinion poll conducted a few years ago in which 44% of those surveyed approved of genetic enhancement and 76% were comfortable with the idea of germline intervention to prevent disease. And how does one distinguish between disease prevention and enhancement of a capability? What if, Walters mused, a way was found to boost the immune system to ward off disease? Or if sleep requirement could be halved from eight to four hours a night with no side-effects, or long-term memory could be rendered more efficient? Treatment for deficiency, or enhancement of a capability? Walters and others did emphasize the need to correct social ills before rushing to explain every trait in genetic terms. Even so, and in marked contrast apparently to the public, few academics consider enhancement acceptable.

The current controversy over fetal tissue transplantation is vividly illustrated by the saga of the Reverend Guy Walden's family. The Waldens lost two children to Hurler's syndrome, a rare fatal genetic disorder. Opposed to abortion, they nevertheless sought help through *in utero* fetal tissue transplantation when their unborn child was diagnosed as having the disease two years ago. Because of the US federal ban on human fetal transplants, the operation (using tissue from an ectopic pregnancy terminated due to the risk to the mother) was performed in a doctor's office under

*Genetics, Religion and Ethics Conference: Implications of the Human Genome Project for Medicine, Theology, Ethics and Policy. M.D. Anderson Cancer Center, Houston, Texas, 13–15 March, 1992.

local anaesthetic. Their son Nathan shows signs of producing the missing enzyme, but the long-term success of the therapy is uncertain. Ironically, while fetal transplants in animal experiments are condoned, their potential to alleviate human suffering is being ignored. The gulf of opinion in religious circles, even among Baptists like the Waldens, is enormous. Some feel that the use of fetal tissue sanctions abortion, while others view embryo and fetal research as having as much of a moral mandate as other forms of therapy.

Molecular diagnostic technology is moving so rapidly that society is having difficulty absorbing the impact of the changes. A few examples were provided by Tom Caskey of the Baylor College of Medicine: a cocktail of eight polymerase chain reaction (PCR) primers aids diagnosis of Duchenne muscular dystrophy in 250 centres worldwide; automated DNA sequencing has become the method of choice for screening Lesch-Nyhan disease; and barely two months after the elucidation of the defect in myotonic dystrophy, the Baylor clinic had performed 15 prenatal diagnoses by direct assay of the unstable region. There are some surprises also, such as a pregnant woman with two active male partners who is interested in sustaining the pregnancy depending on the father's identity. And in seven rape victims who had subsequently become pregnant, *in utero* testing revealed that five of the fetuses were fathered by the husband, not the rapist.

The latest *in vitro* fertilization techniques, which have produced 15,000 births worldwide, will have a major impact on prenatal diagnosis. Mark Hughes, from Baylor, and his UK collaborators affectionately refer to this technology as BABI (Blastomere Analysis Before Implantation), in which PCR analysis is performed on DNA from one cell prised from eight-cell blastomeres which have been fertilized *in vitro*. Early applications include sex testing for risk of X-linked diseases, and specific diagnosis of common mutations in cystic fibrosis (CF). Only two embryos are reintroduced to avoid complications, but they will sometimes include a heterozygote carrier if healthy homozygotes are not available. Of 660 pre-embryos that have been reimplanted, 33% gave rise to successful pregnancies (21% single births, 12% twins and 0.3% triplets). The first reimplanted pre-embryo, which had been screened for CF, was born recently in the United Kingdom (and is a normal homozygote). Now the Genetics and IVF Institute in Virginia is offering a similar 'embryo biopsy' service for CF, X-linked disorders and a number of other genetic diseases, at a reported cost of $13,000.

This work raises many familiar questions: what of the fate of the spare, normal embryos? Do late-onset but fatal disorders constitute a serious genetic disease? Consider adult polycystic kidney disease, which affects more than 1 in 1,000 births. Symptoms do not appear until adulthood, notably cysts, hypertension, chronic renal failure and early death. DNA markers near the (unknown) gene permit accurate genetic diagnosis long before the onset of physical symptoms (and reproductive decisions). In the United States, an estimated 500,000 people are at risk, and the annual cost of treatment is nearly $700 million. Yet should insurance companies be allowed access to this information and deny coverage, which could ultimately save them millions of dollars? Caskey suggests that positive but presymptomatic diagnosis should not be termed a disease (or what the health insurance industry terms a pre-existing condition, which prohibits private health insurance). Examples of discrimination against persons who harbour genetic defects are growing, such as the director of a US Fragile X Resource Center whose health insurance was cancelled because although herself only a carrier, two of her children developed fragile X syndrome. More and more people seem destined to experience a similar fate.

Can society cope with the explosion of sequence information and new technologies? To some, the motives underlying the genome initiative are either misguided or flawed — 97% of the genome is allegedly 'junk', and the tedium of large-scale sequencing conflicts with the best examples of scientific endeavour. But the genome project is not going to go away, nor are the ethical dilemmas posed by gene therapy. Most religious leaders would agree that there is more to 'humanness' than the mere sequence of 3 billion nucleotides so 'correcting' some of them does not necessarily pose an ethical problem. But where does it end? And what good are regulations in certain countries if the spectre of less stringent 'offshore ethics' becomes a reality? It is only right that genome project funds have been diverted for consideration of such ethical issues, but the time is rapidly approaching when society must seek resolutions, especially in embryo research and insurance.