Future ethical challenges in biology

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In recent times, the life sciences have gone through a rapid growth and development fuelled by successes such as the sequencing of the human genome, the discovery of stem cells and their possible benefits in healthcare, and the advent of cloning technologies. The beginning of the 21st century is fast becoming the 'bio' era. This rapid technological and scientific development of the biosciences has parallels with the nuclear age. The unlocking of the secrets of the atom led to innovation and development in the field of nuclear physics. Nuclear power stations were to make power cheap for everyone and radiation would be used to cure us of our cancers. However, as Pugwashites, we know that the nuclear revolution was used in more nefarious ways with the design of nuclear weapons and their subsequent use in Second World War. Similarly, new technologies in the biosciences have the potential to be used irresponsibly. The following sections outline some of the areas for concern. However, most importantly of all, I think we are in a position to learn from what has taken place before and we must now try to pre-empt problems arising from the misuse of science.

The dangers of new reproductive technologies.

The clashes of culture in scientific endeavour, between what is scientifically possible and what is deemed to be 'ethically and morally' correct, are exemplified by the developments of new reproductive technologies such as in-vitro fertilisation, and pre-implantation genetic diagnosis. In-vitro fertilisation (IVF) is the technique for conception of a human embryo outside the mother's body and is one of the methods used to help people with fertility problems to conceive. In this technique, several ova, or eggs are removed from the mother's body and combined with sperm from the father in a dish containing a nutrient medium; they are then cultured in an incubator. Upon successful fertilisation of the egg by a sperm, the fertilised egg is allowed to grow for several cell divisions and the resultant embryo is either transferred to the mother's (or a surrogate mother's) body for normal development in the uterus or frozen for later implantation. These frozen embryos are kept in liquid nitrogen and may be transferred to the uterus at a later date if the mother fails to conceive during the first cycle, or if after successfully becoming pregnant she wishes to try for another child in the future.

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The first 'test-tube baby' was born in 1978, and by 2000 over 50,000 such babies had been born the UK. According to the National Health Service (NHS), the publicly-funded healthcare system in the UK, 6,000 babies are currently born as a result of IVF each year in the UK [1].

A major complication surrounding IVF treatment is the increased chance of multiple births occurring due to several embryos being implanted at once to increase chances of a successful pregnancy. Women who become pregnant through IVF have a 25-30% chance of having twins, compared to 1 in 90 of the general population [2]. Multiple births lead to increased risk to the babies and the mother because there is a higher chance of stillbirth, miscarriage, and premature delivery. Welfare and financial implications may also arise due to the parents having to provide for more than one child.

Due to improvements in the technique, implanted embryos are more likely to come to term than in the past. Accordingly, since March 2004, regulations stipulate that a maximum of two embryos can be implanted in women under 40. Women over 40 may have a maximum of 3, as they have a smaller chance of conceiving [3]. This is the case in the UK but we are unaware if there are similar limits imposed in other countries. In those where the technique is less developed, there may not be limits on the number of embryos implanted at one time.

Recent cases have arisen where women in their fifties and sixties have become pregnant through IVF. Although the menopause sets a natural barrier to conception it has been possible to implant an embryo into the womb if the woman has taken special hormones. The women are surrogate mothers and not genetically related to the child they give birth to. In January 2005, a 66 year old woman from Romania became the oldest recorded mother after undergoing fertility treatment for 9 months. Both the ovum and sperm came from anonymous donors [4]. In 2003 a 65 year old Indian woman gave birth to a baby boy.

These cases, and the likelihood of them becoming increasingly common in the future, raise several important questions. How is the welfare of a child affected by being brought up by elderly parents who may have less physical energy to invest in them? The welfare of the parents is also at stake, because although the baby comes as a blessing, the effort that is required in bringing up young children is high. The psychological effects on the child of not being genetically related to their birth mother and unable to find out the identity of their genetic mother and father should also be investigated [5].

Should IVF be available with public money? How should public funds be invested – is IVF a more pressing need than, say, research into cancer? According to the NHS the typical cost of one IVF cycle at a private clinic is £2,000 but from April 2005 it says that Primary Care Trusts should be offering at least one cycle of IVF treatment on the NHS to infertile couples. Women must be aged between 23 and 39 to qualify for free treatment. In addition, they must either have been unable to conceive for three years despite regular intercourse and no identifiable problem or have a specific problem such as absence of sperm or blocked fallopian tubes. The National Institute for Clinical Excellence (NICE) recommends that three free cycles of IVF should be offered, but a timescale for implementing these guidelines has not yet been announced [6]. If the treatment is not free or is limited, then the technique will only be available to the rich, and not to those who can't afford it. This leads to a further question, namely whether genetic parenthood is such a fundamental human need that individuals can demand public funding of treatment.

It seems that although IVF treatments are becoming a standard procedure, there are still debates and ethical issues to be addressed.

One step on from IVF

IVF therapy has laid the foundations for more advanced interventions. By culturing the embryo for a time outside of the uterus, that embryo can be observed microscopically for any gross anatomical defect and, using modern genetic tests, more detailed characterisation of the embryo can be undertaken before implantation. These developments have produced the technique of pre-implantation genetic diagnosis (PGD). PGD is a procedure that allows for an embryo that has been created in vitro to be screened for a number of genetic disorders prior to implantation into the uterus. The embryos undergo a biopsy procedure in which one or two cells are removed and tested for the specific disorder either by looking at the structure of the chromosomes in the cell or by extracting the DNA from the cell and looking for specific mutations in their genes. If the cells are determined to be unaffected, the embryo from which they came can be implanted into the mother's uterus; if, on the other hand, they are found to be carrying a disease, the embryos are not implanted and are subsequently destroyed. This introduces selection on the basis of genetic phenotype. Selection of embryos has always been a part of IVF treatments in that embryos are examined under the microscope and only those that appear anatomically normal are used, as embryos that appear abnormal are unlikely to implant and produce a child. PGD is an extension of this selection from an anatomic level to a genetic level.

Pre-implantation genetic diagnosis is used in cases where the parents know that they are at risk of passing on a serious genetic disease on to the child. The Human Fertilisation and Embryology Authority (HFEA) in the UK currently licences PGD of cystic fibrosis, haemophilia, beta -thalessaaemia, sickle cell disease and Huntington's amongst others [7]. These diseases are characterised by a very high penetrance (the genetic defect leads to disease in almost all cases) and a severe phenotype often resulting in death. In addition, this high penetrance is due to a small number of mutations whose genetic interactions are relatively simple. Simply put, very closely defined changes in the genome lead to disease. Most genetic interactions are more complicated than this and while it is indeed possible to diagnose certain disorders such as Huntington's, for many other common genetic diseases the complex genetic interactions are less well understood. While the severity of the disease may still be high, the penetrance of any given mutation may be lower and so when screened a given embryo will have a percentage chance of resulting in a diseased child. This raises the question: At what level of probability should an embryo be discarded, if at all, if it is in danger of suffering from a debilitating disease at some point in its life? For many disorders it may be possible to diagnose the probability of contraction but the age of onset and severity may not be so clear.

While PGD is not a commonly used technology (during the 1990s in the UK, 900 children were tested) we must consider the societal impacts of PGD, if it were to become more commonplace and the range of disorders diagnosed for was to increase. While the desire for a healthy child is understandable, the possibility must be addressed that as the technology becomes more advanced the criteria for a 'healthy' child may change. A fear is that compassion for diversity will decline as it becomes possible to ensure your child is free from genetic disease. The risk is that the technology will become so normalised that society is pushed into a certain set of beliefs. With so many potentially conflicting interests – parents, disability awareness groups, right-to-life groups - the ethical situation becomes increasingly complex. While PGD procedures are comprehensibly legislated for in the UK and available only for a few

medical conditions, already people have sought this procedure abroad. Could this be the beginning of 'genetic tourism'?

The genetic tests used in PGD are not limited to use in the IVF situation. Prenatal diagnosis can be used to determine the disease status during pregnancy. The methods for prenatal diagnosis include ultrasound imaging, chorionic villus sampling (CVS) and amniocentesis. Ultrasound imaging, in a similar way to the microscopic examination of embryos before implantation in IVF, examines the foetus for gross abnormalities. CVS involves analysing a tiny tissue sample from outside the foetal sac and amniocentesis involves taking a small sample of amniotic fluid. These samples can then be tested for genetic and chromosomal abnormalities as described in PGD. CVS and amniocentesis are not routinely offered to all pregnant women as it carries a small risk of miscarriage but may be offered to parents who have a high risk of passing on a genetic disease to their child, or when the mother's age may be a risk factor [8]. Currently in the UK, if it is discovered that there is a genetic disease, then the pregnancy may be terminated. In addition, if there is risk of a severe disability, then a termination can be carried out after the 24 weeks mark that is the usual abortion limit in the UK.

By testing the embryo in the womb, the selection choice is not asking should this embryo be implanted or not, as in PGD, but rather do we terminate this existing implanted embryo.

Selection on the basis of gender

Technologies such as PGD and prenatal diagnosis are used to produce children free from a given genetic disease. However, selection on the basis of sex is also possible and in fact is commonplace in India and China where unborn female babies are aborted simply on account of their sex. This has led in India to a nationwide ratio of 933 women for every 1000 men and in Delhi, where the practice is prevalent, to a ratio of 814 females to every 1000 males (the world average of male-to-female ratio is 1000 males for every 1036 females) [9]. Although a law has come into force that makes it illegal to use ultrasound examinations for sex determination, the practice continues, albeit underground. Doctors who disclose such information are punishable by suspension but also stand to gain by, in some cases substantial, under-the-table fees from the expectant parents. No case has yet been brought to court and it has been argued that the medical fraternity is not sufficiently regulated and the law is impossible to enforce.

UNICEF has warned of some of the social impacts of this practice – gaps in the workforce, men unable to find brides and an increase in the trafficking of women. A preference for boys over girls can be explained by India's dowry tradition which makes having a girl an expensive burden for poor families. But the problem has not disappeared even in Delhi's prospering suburbs and continues despite growing affluence.

Sex selection is currently illegal in the UK. Termination on the basis of sex, and selection of an IVF embryo to be implanted solely on the basis of gender are illegal, unless the child will suffer from certain sex-linked illness's. It is also illegal to carry out procedures such as 'sperm sorting' which increase the probability of one sex being conceived over another during fertility treatment. This has upset a small number of parents who wish to use this treatment for 'family balance'. In the US these treatments are available, however most clinics insist that you already have one child of the opposite gender before carrying out the procedure. While the expense of

these treatments mean it is unlikely to become a universal method for sex selection, the potential for gender-imbalance such as in India cannot be ignored.

The increasing possibilities in reproduction made possible by the technologies outlined above are creating new ethical and moral challenges not only for prospective parents and the counsellors advising them, but also for society as a whole. It goes to the heart of societies' conceptions of what is seen as 'healthy', 'normal', a 'balanced family' and may bring social pressure to conform to this norm and decreased acceptance of difference, because technology has made it possible. Those who provide genetic counselling have been depicted as contemporary eugenicists by encouraging practices that result in the termination of foetuses with disabilities. By supporting the choice of the patient, they have been perceived as discriminating against people with disabilities and have been labelled as 'playing God' and turning children into consumer goods.

Issues surrounding the derivation of stem cells

Recent advances in biology have created many possibilities for novel treatments for disease and leading the way in these new technologies are stem cells. The usefulness of stem cells lies in the fact that they are undifferentiated cells with the ability both to multiply and to differentiate into specific kinds of cells. Tissues in the human body are being continually turned over; for example red blood cells have a lifespan of only 120 days. New cells need to be produced and this is the job of the stem cell. New red blood cells are produced in bone marrow from specific stem cells; these cells divide many times, then mature into blood cells. Similarly there are stem cells in the skin which continually produce new layers of skin to replace the old skin as it is lost.

The property of stem cells to divide and differentiate into many different tissues is what is so unique. In the case of stem cells in bone marrow, a stem cell can become either a red blood cell or one of many different types of white blood cell depending on the signals that it receives. Such a stem cell is said to be multipotent, that is that it has multiple possible destinations within some constraints (i.e., 'bone marrow stem cells do not want to produce skin'). Other stem cells are not constrained at all and can become any type of cell given the correct signals. These cells are found in the early stage of life shortly after fertilization when the embryo contains only a few cells which must go on to produce the whole array of cells in a fully developed organism. These cells are known as totipotent stem cells.

From a biomedical point of view, stem cells hold the promise of enabling scientists to grow specialized cells or tissues, which could then be used to treat injuries or disease. For example, diabetes can be caused by the loss of insulin producing cells in the pancreas. Stem cell therapy could one day produce new pancreatic cells which when injected into the patient would give normal insulin production, thereby curing the diabetes. Other possible treatments include using stem cells to produce new nerve tissue which could be used to repair damage from spinal injury possibly reversing serious paralysis.

However, stem cell research is controversial because the best source of totipotent stem cells is human fetal tissue. By harvesting stem cells, the embryo is destroyed and many see this as morally problematic. Efforts are underway to try to turn multipotent stem cells into totipotent cells by removing the constraints put on the multipotent cells. This would negate the

need for embryonic stem cells and while progress in this area is being made, the current consensus seems to be that embryonic stem cells are the most promising.

Embryonic material to produce stem cells is available from several sources, each having its own ethical concerns. Stem cells can be harvested from aborted fetuses. This is seen as sanctioning the act of abortion and ties in stem cells with the controversy surrounding abortion.

Surplus embryos that are a consequence of the *in vitro* fertilisation technologies mentioned previously can be used to derive embryonic stem cells. Ethical concerns centre on the status of the embryo itself and the controversial issue of how much respect should be given to a human embryo. On one side, the embryo is viewed as a genetically human and a potential person and therefore should be granted protection. On the other side of the argument, while the embryo may be genetically human, in the early stages of development it does not possess any of the characteristics of being human; rather it is a simple cluster of cells and hence should not be given an independent ethical status. There are numerous compromises between these two views suggesting that although in the early stages of life the embryo is not a person, it is to be respected and given a degree of protection as befits the starting point of a human life. It is a prerequisite that IVF clinics may only use spare embryos for research work if the embryo donors have given their informed consent.

Embryos can be created from donated eggs and sperm solely for the purpose of extracting stem cells. Again the same issues regarding the ethical position towards the embryo are raised here as was the case for spare embryos from IVF treatment, along with new concerns over the deliberate creation of an embryo in order for it to be ultimately destroyed. Spare embryos from IVF therapy were created with the intention to produce a child but were not used and would therefore be discarded. It could be argued that this is ethically a stronger position to use spare embryos destined to be destroyed rather than creating new embryos which do not have the chance to become a child but are simply to be used produce stem cells. However, it can also be argued that creating embryos with the sole aim of deriving stem cells is less of an ethical problem precisely because the embryos are not created to be implanted in a woman and so are not intended to produce children.

While stem cells for research purposes can be generated in the three ways described above, any treatments developed from them will face the problem of immune rejection by the patient. In a similar way in which organ transplants are rejected by the recipient's body, stem cells injected into a patient will be treated as foreign by the immune system and attacked. Patients will have to be treated with drugs to suppress the immune system from attacking the stem cells. However, there is the possibility to get around this problem by producing stem cells using cloning technologies. In order for the patient's body not to reject the stem cell therapy, the cells need to be identical to the patient's cells. This can be achieved by replacing the genetic material from an egg cell with the patients cell's DNA and producing an embryo from the egg. The embryo will then have exactly the same genes as the patient, i.e. will be a clone of that individual and stem cells derived from that embryo should be tolerated by the immune system without the need for powerful and potentially dangerous immunosuppressive drugs.

This technology is faced with the same ethical issue of creating an embryo, simply to be destroyed as was the case for creating embryos for research using donated sperm and eggs. There is the consideration that this process if used, once therapies are developed, for personal

betterment, i.e. a woman donates her own eggs to produce an embryo to cure her own diabetes, then it is a personal matter akin to donating a kidney.

The ethics of biomedical research

Ethics is generally defined as that branch of the study of value and quality in philosophy that deals with the nature of morality. Thus, it has to do with defining what is right and wrong. There is no universally applicable and objectively determinable 'right' and 'wrong'. What is deemed right and wrong in a society is 'negotiated' over time by the members of that society. Culture thus plays an important role. Not all members have equal power to influence these 'negotiations' of what is to be considered right and wrong, but in most societies there is an attempt to balance the interests of the 'stakeholders' in an issue. In the case of bioethics – concerned with what is right and wrong (i.e. moral) when it comes to bioscience and technology- stakeholders can be identified on several levels.

At the *individual level* we identify the individual who benefits or suffers from biomedical related issues, the doctor/health worker who administers or has to make decisions related to biomedical issues and the scientist who do research. These actors/stakeholders have needs, rights, interests and responsibilities. Some would argue the unborn child should also be considered as a stakeholder with rights.

At the *societal level*, we identify groups in society affected by these issues or feeling that they have a stake in these issues, such as religious groups or groups with disabilities who mobilize around their collective interests. We also identify the category 'society as a whole', for example, bearing the economic cost of IVF. On this level, issues relating to the conception of society or future impacts on the development of society, often arise. Is PGD a step in the direction of designer babies and what would be the impact on society.

The *national level* often corresponds with 'society as a whole', but involves the state or government and therefore refers to the level on which policy is made. Laws regulate the biosciences and technologies. Policies are plans of action to execute legislation. When policy programs are designed, they take as sub-text the recognition that budgetary resources are finite and that socio-economic imperatives are generally in competition. Money spent on IVF, for example, cannot be spent on malaria research.

At the *international/global level*, we look beyond a narrowly conceived society (e.g. a nation-state) to other societies as well. In an era of increased globalization (through travel, information technology, research exchanges etc.) biomedical questions cross state borders in diverse ways, whether through bio-medical tourism, international negotiations of a bio-ethics framework, and issues about intellectual property rights in biotechnologies that may benefit one society (nation) at the expense of another.

Controversies develop between the interests and responsibilities of actors on the various levels. Most notably the question arises: which of these levels is the most appropriate one to make decisions about biomedicine? Should individuals be allowed to make decisions about PGD or should societal groups' interests be considered too? Is it possible to identify norms on the international level established enough to sustain an international framework of bioethics or would societies be more inclined to govern biomedical choices within their borders as currently the case?

The social 'negotiation' of what is right and wrong in the field of biomedical ethics evokes emotive responses and, mildly put, is a very complex process where multiple actors engage with each other. It is not only important to contextualize issues as far as possible, but also to see them holistically, i.e. amidst other issues, such as the gaps between rich and poor, gender imbalances and the responsibility owed to future generations.

Science and Scientists need to play their own part in keeping to the highest ethical and moral standards, especially as the discipline of science has suffered from a series of public relations disasters of late and because of this scientists are gaining a bad reputation. This exemplified most recently by the scandal involving faked research by the team of Korean stem cell scientists led by Hwang Woo-Suk [10]. Science and technology are powerful players in the modern world and therefore, as the practitioners of these disciplines, we need to be responsible and enlightened in both how we actually use these tools and how we are perceived to be using them.

Open debate about all these biomedical issues must occur if we are to develop ethical judgments about the use and abuse of these technologies within our own countries. However, this debate will be almost impossible while the language we use to represent the issues is so emotive, e.g. unborn baby vs. foetus. It seems that only by educating people about the pros and cons of these technologies will we be able to carry out these necessary debates.

Even then, as countries reach different ethical decisions based on their cultural and moral creed, the possibility of an international framework of biomedical ethics seems remote. At present, the best approach would seem to follow the one we are advocating for nuclear awareness: education, education, education. Without an understanding of all the issues and their implications we will be unable to make correct ethical decisions and the potential for the misuse of this technology will continue to increase.

Notes

1. See http://www.nhsdirect.UK/en.asp?TopicID=641.
2. See http://www.babycentre.co.UK/refcap/4094.html.
3. See http://www.babycentre.co.UK/refcap/4094.html.
4. See http://www.chinadaily.com.cn/english/doc/2005-01/07/content_406794.htm.
5. See http://www.marchofdimes.com/professionals/681_1165.asp.
6. See http://www.nhsdirect.UK/en.asp?TopicID=641.
7. See http://www.hfea.gov.UK/Abouthfea/hfeaPolicy/Preimplantationgeneticdiagnosis.
8. See http://www.marchofdimes.com/professionals/681_1165.asp.
9. See http://www.genetics-and-society.org/newsdisp.asp?id=756.
10. See http://news.bbc.co.UK/2/hi/asia-pacific/4608352.stm.