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Embryo research: yes or no?

Warnock legislation begins in the House of Lords

The government bill on human fertilisation and embryology (p 1355), which it has presented more than five years after the publication of the Warnock report,[1] gives clinicians and medical scientists engaged in assisted conception cause for concern.

The bill will affect radically the way that assisted conception procedures are practised by removing anonymity for sperm donors, restricting the time for which frozen pre-embryos or gametes may be cryopreserved, and passing on to the consumer the costs of a statutory licensing authority, thus further penalising the subfertile—for whom there are already limited facilities. These issues seem likely, however, to be overshadowed by the debate on whether preimplantation embryo research should continue or not[2] and may be clouded further by confusion of embryo research with the arguments about abortion. There is a definite risk that both the present benefits for the patients and those likely from further research[3] will be restricted by legislative proposals that put clinicians practising in vitro fertilisation (IVF) directly under threat of criminal prosecution.

The bill gives to members of both houses of parliament a free vote on whether research using preimplantation embryos should be allowed to continue under licence from a statutory licensing authority or whether research should be disallowed completely unless proved to be of direct benefit to the embryo itself. No restriction is placed on "allowing the embryo to perish," though in what circumstances this may occur and exactly what constitutes "research" is unclear.

What has research on human preimplantation embryos shown so far? What potential benefits may accrue? And what may be lost if restrictive legislation is passed?

Improvement of assisted conception techniques

Human fertilisation in vitro was first achieved 20 years ago.[4] Its development to give the first live birth[5] and the improvements that have made it a universally accepted method for the alleviation of infertility were achieved by research on human conceptuses in vitro.[6] Yet the cost-benefit ratio of IVF is still too low. According to the most recent report from the Interim Licensing Authority, the overall live birth rate was little more than 10% per treatment cycle.[7] Though the reasons for failure are still obscure, recent research with human eggs and cleavage stage preimplantation embryos surplus to therapeutic IVF and gamete intrafallopian transfer (GIFT) programmes has given some clues. Fewer than half of all oocytes fertilised in vitro are able to develop to the blastocyst stage in culture, most suffering cleavage arrest after the four cell to eight cell stage.[8,9] This coincides with the time of activation of the embryonic genome,[10,11] but whether the arrest is caused by failure of activation, is a consequence of activation and changing requirements, or is purely coincidental remains unclear. A surprisingly high proportion (30-40%) of human conceptuses resulting from IVF are chromosomally abnormal.[12] One possible explanation has come from recent work on human oocytes, which have been found to be particularly sensitive to fluctuations in temperature.[13,14] Transient cooling of oocytes during GIFT or IVF procedures may induce abnormalities in the meiotic spindle that would lead to abnormal chromosomal segregation at fertilisation and thus be incompatible with embryonic survival. The simple expedient of strict temperature control during aspiration of oocytes and GIFT replacement procedures may provide an immediate benefit from such research.

The ability to freeze and store human oocytes would greatly benefit patients needing medically assisted conception and reduce the costs to the health service substantially.[15,16] Assisted conception procedures are associated with high perinatal losses, largely consequent on multiple pregnancy, which inevitably occurs after some IVF and GIFT procedures even as practised according to current guidelines.[17] In 1987, one quarter of all IVF and GIFT pregnancies were multiple, and these procedures accounted for half of all the higher order multiple pregnancies in the United Kingdom.[7] If oocytes could be frozen and thawed successfully it would be possible to fertilise them singly and then replace them in natural cycles. This would not only avoid multiple pregnancy after IVF but might also lead to higher success rates, as any adverse effects of superovulation on the endometrium would be avoided. However, though freezing of oocytes and the birth of live young has been achieved in mice,[18] freezing human oocytes has proved much more difficult.[19] Research on human oocytes has shown substantial differences in the cytoskeleton of human and mouse oocytes,[20] which may in part explain their differences in response to cryoprotectants and to freezing and thawing protocols. Because of these differences attempts to apply cryopreservation techniques therapeutically should be preceded by an examination of the effects of cryoprotectant agents and freeze-thaw protocols on human as well as murine oocytes. The resulting embryos should also be examined in vitro for their developmental normality.

Similarly, new techniques to help achieve pregnancies for

infertile couples in which the male partner suffers from severe oligozoospermia need to be assessed for safety and feasibility on human rather than animal oocytes alone. For example, "drilling" a hole through the zona pellucida to facilitate access of spermatozoa is usually done by a procedure that has been shown recently to give a high frequency of parthenogenetic activation of human oocytes.[21] Restrictive legislation forbidding fertilisation of human oocytes in vitro for research purposes would remove one further element of safety in developing these promising techniques.

Preimplantation diagnosis of genetic disease

Most people still see IVF solely as a technique for helping the infertile, but its benefits are wider than this. Couples who are at risk of transmitting a genetic disease often ask for some form of prenatal diagnosis such as amniocentesis or chorionic villus biopsy, with the understanding that diagnosis of a defect in the fetus may leave them faced with the difficult decision of whether to proceed with a late therapeutic abortion. For some couples the risk of an affected child is so high that they have undergone multiple abortions with the attendant emotional and medical sequelae. A realistic alternative for these patients would be diagnosis of the disorder before implantation from biopsy specimens taken from cleavage stage embryos developed in vitro followed by selective replacement of unaffected embryos.[22] A single cell can be removed at three days of development from an eight cell stage embryo without affecting the development of the remaining cells.[23] This single cell can then be assessed for the presence of the defect, and if unaffected the embryo can then be replaced. If a suitable genetic probe is available this analysis can be made at the DNA level by using the polymerase chain reaction[24] to amplify the small amount of DNA in the biopsy specimen.[25] Alternatively, if the defect is an enzyme deficiency, such as in Tay-Sachs disease, the Lesch-Nyhan syndrome,[26,27] or severe combined immunodeficiency disease[28] direct enzyme microassay may be undertaken. Clearly, tests of efficacy and safety would be needed, and though these may be, and have been, met initially by experiments on animals and animal embryos, it does not follow that the techniques developed for one species can be transferred reliably to humans. The responsible approach would be to test the techniques on human preimplantation embryos not destined for transfer before applying them to preimplantation embryos that are to be replaced in a patient.

This cautious approach has proved to be well founded. Experiments on a mouse model gave good reason to be optimistic about the application to the human of the technique for preimplantation diagnosis of the Lesch-Nyhan syndrome at the eight cell and blastocyst stages. Experiments using the same enzyme microassay for hypoxanthine phosphoribosyltransferase in spare human preimplantation embryos and oocytes has, however, shown that the kinetics of activity of the enzyme in the human are so different from those in the mouse than direct application of the technique is unreliable for clinical use.[29] This responsible progression from animal model to tests on human preimplantation embryos in vitro will not be possible if restrictive legislation is imposed. Without the intermediate testing stage failure of the transfer of the technique would have manifested with the birth of an affected child.

A similar responsible attitude to the sexing of human preimplantation embryos by the polymerase chain reaction on single blastomere biopsy specimens for sex linked genetic diseases has had positive benefits. The sensitivity and reliability of that particular probe and the normality of development after biopsy had both been shown in surplus human preimplantation embryos[23]; it is reasonably safe, therefore, to put this method into clinical trials with some expectation of success.

Contraception

Many of the problems in the world stem from inexorably rising birth rates and the difficulty of providing acceptable methods for safe and reversible medium to long term contraception. In Edinburgh Aitken and his colleagues are developing a contraceptive vaccine based on an antibody that reacts with the human zona pellucida.[30] This is effective in preventing pregnancy in marmosets, but tests of the ability of the antibody to prevent spermatozoal penetration of the human zona pellucida in vitro are being conducted before field trials on humans can be undertaken. Although salt stored human zonae have been used to show the efficacy of the antibody in preventing sperm-zona binding,[31] the properties of the zonae pellucidae of fresh oocytes seem to be different, thus requiring modification of the antibody for greater efficacy and safety. As the consequence of failure of the antibody to act in vitro is the creation of a fertilised egg restrictive legislation that prevents the fertilisation of human oocytes for research presumably would prevent this type of testing even though fertilisation was the consequence rather than the intention of the experiment.

In the deliberations about the pros and cons of research on preimplantation human embryos we need to consider what there is to lose by a total ban on research and what the consequences of that ban might be. A ban could not stop but will severely impair progress in the treatment of infertility, preimplantation diagnosis of genetic diseases, the development of new contraceptive agents as well as our understanding of the causes of pregnancy failure,[32] and the generation of placental tumours.[33] The imposition of a ban will reduce the safety of that research and change the subjects of experimentation. Instead of conducting research on small groups of living cells in culture it will be the women seeking treatment by these means who will themselves become the subjects of the experiment. By trial and error, over a longer period, success may eventually be attained. In the process many more late abortions will be induced and many more preimplantation embryos will be lost.

The Royal Society and the Medical Research Council have spoken clearly and unambiguously in support of patients and research. Individual clinicians and their representative royal colleges need to consider which alternative they believe to be medically and ethically proper for their patients and make their views known to the parliamentarians.

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Child health surveillance

New report highlights value of parental observations

The foundations of our current child health services were laid at the beginning of this century. In 1922, the county medical officer for Nottingham wrote in his annual report: "In 1897 no interest had begun to be taken in Child Welfare, and the community was content that 152 out of every 1000 children born should die within the year. Three years later the numbers reached 161. Last year only 69 children died out of every thousand born. But in the meantime, two doctors, 10 wholetime women Health Visitors and 15 part time Health Visitors have been appointed and are working in connection with 13 Child Welfare Centres."

Sixty seven years later infant mortality is less than 10 per 1000 births, and the number of doctors and nurses working in child health surveillance is 10 times higher. I, too, would like to believe that our child health services are a major force in this improvement, but proof is difficult to obtain. In 1922 the emphasis of the service was to "provide medical and especially hygiene advice."[1] From this developed a system of regular checks on children that we now call child health surveillance. In the Sheldon Report the functions of the child health service were listed as routine medical examinations of children presumed to be healthy; infant nutrition and hygiene; detection of defects—physical disorders, mental retardation, and emotional health; parental counselling; health education; measurements; immunisation and vaccination; and the sale of welfare and proprietary foods.[2]

The series of checks recommended in this 1967 report has been repeated with almost unquestioning faith ever since. Some changes have been made in terms of less frequent checks, but what was once innovation has become tradition and sometimes seemingly immune to improvements in our knowledge or to the type of critical thought or original ideas that led to the birth of our child health services.

At last, however, we have a new and welcome review of child health surveillance. *Health for All Children* is the result of two years' work by a joint working party representing the British Paediatric Association, the Royal College of General Practitioners, the General Medical Services Committee of the British Medical Association, the Health Visitors' Association, and the Royal College of Nurses.[3]

The report has three broad thrusts. Firstly, it argues that the content of the screening programme should be determined by our state of knowledge about the conditions sought, the effectiveness of the test, and the availability of programmes for management. Secondly, it emphasises the good evidence that parents are far more effective than professionals in the early diagnosis of a wide range of handicaps.[4-7] Thirdly, the report underlines and clarifies the health education content of the surveillance programme.

For each section of the report the working party reviewed current evidence and made recommendations for practice and research. The package of recommendations is condensed into checks at birth, at discharge from hospital, 6 weeks, 8 months, 21 months, 39 months, and 5 years and school age.

In physical examination the report recommends the continuation of screening for congenital dislocation of the hip, congenital heart disease, and undescended testes. The case for these is strong, but successful programmes depend on clinical skills and a good organisational framework. Even for these conditions the report points to our lack of information on aspects such as the natural course of congenital dislocation of the hip or the assumed value of repeated examinations in reducing late diagnosis. Screening is not recommended for hypertension, asthma, and adolescent scoliosis. Screening for hypertension is a very blunt instrument for identifying children with secondary hypertension, and we have no accepted treatment to offer for other causes of hypertension.[8] For asthma it is argued that general awareness would be more effective than screening, as the children are already brought to medical attention by their parents.[9] For adolescent scoliosis more research is needed on the natural course and to improve the predictive value of examinations.

In laboratory and radiological tests only the well established programmes for phenylketonuria and hypothyroidism receive full support. The common problem of iron deficiency anaemia might seem a reasonable target for a screening programme, yet important questions remain to be answered about the acceptability of screening, the effectiveness of intervention programmes, and the part of health education in prevention.[10 11] Screening for haemoglobinopathies is supported, but the working party acknowledges that more resources and organisation will be required to deliver such a programme.[12]

Monitoring of growth might be regarded as a foundation stone of the child health clinic. Yet the report reminds us that the practice may well not justify the effort if measurements are inaccurate and are not plotted on growth charts and if those who work in clinics are not trained in their interpretation. Weighing at each clinic visit and measuring height at 3 years and between 4 and 5 years are both recommended.

For testing vision in the young child the evidence is that our efforts are ineffective and that we do better to rely on careful inspection of the eyes and the child's visual behaviour and to recognise the importance of parental observations.[4 13-15] At