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# BUILT-IN OBSOLESCENCE: WOMEN, EMBRYO PRODUCTION, AND GENETIC ENGINEERING*

DITTA BARTELS
School of Science and Technology Studies, University of New South Wales, Kensington, NSW, 2033, Australia

**Synopsis** — The ultimate control over the genetic constitution of offspring will be achieved when the embryos in all pregnancies are quality tested and those found to be defective are corrected. As yet, the science required for this ultimate control has not been perfected. But, as this article shows, experts in in-vitro fertilization (IVF) and genetic engineering are working to ensure that "progress" is being made rapidly in several areas that pertain directly to this ultimate control.

First, they are conducting research into the *genetic diagnosis* of early embryos. These are embryos generated outside the body by IVF or embryo flushing, and they are yet to be transferred into the uterus. While this research is being actively pursued, at present it is somewhat hampered by a shortage of experimental embryos. But the researchers are also working hard to overcome this temporary limitation. They are developing the technology for *egg maturation in vitro,* and with this technology in place, they will be able to generate thousands of research embryos without any active participation by women. The third step along is the correction of genetic "defects" in embryos. I argue that with a plentiful supply of embryos available for research, little will stand in the way of molecular biologists wishing to apply the results already obtained with animals to humans.

The three developments discussed here — embryo genetic diagnosis, egg maturation, and embryo gene insertions — will bring science several steps closer to the ultimate control over the genetic constitution of all offspring.

> We must rid ourselves of preconceptions based on our traditional behaviours in matters of parentage, and open our minds to the new possibilities offered by our scientific knowledge and techniques . . . We can do so by bringing our influence to bear not on the number of children in a family, but on their genetic composition (Muller, 1963).

Herman J. Muller, the highly influential geneticist and Nobel Prize winner, made this statement about fifteen years before the new technologies of in-vitro fertilization (IVF) and genetic engineering were first put into practice. On the whole, IVF and genetic engineering started off with their own separate spheres of application: IVF was to deal with infertility, while genetic engineering was to lead to a wide range of bacterial strains producing chemicals for commercial sale. But this separation of domains was not kept up for very long. Ten years of development have brought IVF and genetic engineering into close proximity. Moreover, this proximity is now related quite explicitly to Muller's prophetic statement of twenty–five years ago. In the late 1980s, the time has come for a new crop of joint experts in both IVF and genetic engineering to feel confident that they have the science in hand with which to control the genetic constitution of our children.

The control over the genetic constitution of the offspring can be exerted at several different stages during reproduction. In the last ten years, the main emphasis has been on the detection of genetically defined "defects" by amniocentesis and on the abortion of the identified defects late in

*Throughout the article, I use the terms "defects" and "defective" in describing embryos because this is the language of medical and scientific workers in human reproduction. I do not accept these terms as correct or morally defensible. "Defects" implies nondefects; or normal and deviant. These dichotomies are the justificatory basis of modern medicine and science and the point of this article is to discuss scientific and technological developments based on these rationalizations.

pregnancy (Rothman, 1986). But increasingly, the genetic control over reproduction is shifting to embryos that are kept separate from the bodies of women, that is to say, to embryos cultured and grown in vitro.

In this article, I focus on the recent developments in the area of genetic engineering of in-vitro embryos. It is essential to note also the means by which the scientific experts gain access to the embryos for this genetic engineering work and the fact that ultimately the embryos come from women. What we find is that to fulfill their demand for research embryos, the scientists are pushing the problematic reproductive technologies of superovulation, IVF, and embryo flushing out of the context of infertility and into that of genetic engineering.

## HOW SCIENTISTS GAIN ACCESS TO RESEARCH EMBRYOS

Before IVF came on to the scene, early human embryos were simply not available for research, since they split and developed well inside women's bodies, out of sight and without anyone even knowing that they were there. But IVF changed all that. Henceforth, at least in principle, early embryos could be generated by scientists in their laboratories at will. The only limitation was that the eggs had to be collected from women, and egg collection was far from simple. To start with, the eggs had to be *cut out* of the bodies of women, and this was considerably more cumbersome than the straightforward collection of sperm. But more problematically still, to base everything on the slim chance of collecting one lone egg per woman per month required patience and perseverance beyond the call of duty (Edwards and Steptoe, 1980).

There was, however, a technological way around this early difficulty of the IVF enterprise. With the simple technology of *superovulation,* a large number of eggs could be extracted from each woman at one hit. The required drugs were by then well known to fertility experts – they were clomiphene citrate, marketed, for example, by the pharmaceutical company Merrell Dow as Clomid, and menopausal gonadotrophins, which was being obtained out of the urine of nuns in Italy.[1] As soon as superovulation became a regular concomitant of IVF programs, research with human embryos became a distinct possibility. But for the women involved, superovulation can be dangerous.

First, there have been a number of reports in the medical literature detailing the history of women who have been treated with superovulation hormones and who developed cancers of the ovaries (Bamford and Steele, 1982; Carter and Joyce, 1987). Second, Dr. G. R. Cunha and his colleagues at the University of California, San Francisco, have recently published a paper showing that clomiphene citrate causes serious structural defects to occur in various parts of the *developing* human female reproductive tract (Cunha *et al.,* 1987). In Cunha's experiments, tiny reproductive organs were cut out of human female fetuses that had been aborted late in pregnancy. These fetal organs were transplanted into three types of mice: untreated controls and experimental animals with either implanted capsules of clomiphene citrate or of diethylstilbestrol (DES). DES is, of course, well known to have caused a large range of structural abnormalities as well as cancers in the reproductive organs of the *daughters* of women who were treated with the drug. In Cunha's experimental systems, the clinical effects of DES were mirrored in that the transplanted fetal human ovaries, Fallopian tubes, and uteri developed in abnormal ways in the DES-treated mice. These mice, together with the human fetal tissue transplanted into them, thus constituted the so-called "positive controls" in the experiment, that is to say, that part of the experiment that is designed to test the effectiveness of the experimental system itself.

Now, feminist critics of IVF such as Anita Direcks, Helen B. Holmes, and Robyn Rowland have argued before that since the chemical structure of clomiphene citrate is similar to that of DES and since DES has a well-known range of associated problems, chances are that clomiphene could also result in reproductive problems in the daughters of women who take the drug (Direcks and Holmes, 1986). Cunha's experimental findings now provide hard data with which to back up these predictions. The point is that in the comparable mouse transplantation experiments, DES and clomiphene citrate acted in exactly the same way. Both compounds were found to cause structural deformities in developing female reproductive systems.[2]

Thus there are now two separate lines of evidence pointing to hazards associated with superovulation: cancers in women who have taken the superovulation drugs and abnormalities in the developing reproductive systems of the daughters of superovulated women. But the use of superovulation technology has not diminished so far. Let us then examine who the women are who undergo superovulation for purposes of generating embryos in vitro. I shall distinguish the following groups:

1. Women who enter IVF programs with the aim of having babies and who are infertile;
2. Women who enter IVF programs with the aim of having babies and who are fertile;
3. Fertile women who wish to be sterilized and who are coopted to act as "volunteer egg donors";
4. Fertile women who are paid to act as embryo donors.

In most discussions on IVF, particularly in discussions by the practitioners involved, the women in the first group are highlighted and the assumption is made that these are the only women who undergo superovulation. This provides an easy copout with regard to the concern that superovulation is hazardous. The argument presented by the proponents of IVF runs along the following lines: first, the women are desperate to have babies and they are physiologically incapable of having them; second, science can step in to help them fulfill their deepest ambitions; and third, the risk that they run with superovulation is minor in any case.

Conveniently, the proponents of IVF omit two significant facts in addition to downplaying the hazards of superovulation. On one hand, many of the infertile women in question are actually infertile because of previous rounds of medical interventions (including DES) that caused them to end up with structural defects in their reproductive systems (Corea, 1985; Rowland, 1987). On the other hand, quite often women are *defined* to be infertile when they are actually quite capable of giving birth to healthy babies without the intervention of any kind of technology (Collins *et al.,* 1983; Gomel and McComb, 1981). These two considerations change the focus of the debate considerably on whether the hazards of superovulation are acceptable or not even for those women whom I have fitted into the first group above.

Moving on to the second group of women on IVF programs, we come to those women who are perfectly healthy and fertile but who enter IVF programs for purposes of overcoming the fertility defects of their husbands. Submitting these women to superovulation and its associated hazards is even less responsible than in the case of the women comprising the first group.

Third, we come to the so-called volunteer egg donors. These are fertile and perfectly healthy women who seek to be sterilized because they do not wish to have any more babies. Instead of just proceeding with the task at hand – the requested sterilization operation – the gynecologists consulted by these women recommend that the women participate in planned embryo research projects. The idea is that before the women are admitted to their surgery, they take a course of superovulation hormones so that about a

dozen eggs ripen in their ovaries. During the women's surgery, these ripe eggs are then collected and subsequently fertilized in the laboratory. In spite of the hazards of superovulation, in Britain the recent trend has been to obtain research embryos from volunteer egg donors in this way, particularly at the top three embryo research centers located at the Universities of Edinburgh, Cambridge, and Aberdeen (Braude *et al.,* 1984; Messinis *et al.,* 1986).

Apart from the IVF route, early embryos can also be made available for laboratory work through a technique called *embryo flushing*. This technique was developed by researchers from the University of California at Los Angeles and commercialized and patented by the Chicago–based company Fertility and Genetics Research (Buster *et al.,* 1983). Here, the embryos are produced *inside* the bodies of women, generally following superovulation and artificial insemination. But before the embryos have a chance to attach themselves to the uterus they are flushed out of the bodies of their mothers. As with IVF, initially the technique of embryo flushing was developed to deal with infertility, in this case infertility due to ovarian failure. But here again, once the technique has been made available and permits access to early embryos in the laboratory, the opportunity also arises for the use of these embryos in research.

Embryo flushing presents considerable hazards for the women involved. Quite apart from the already-mentioned problems of superovulation, with embryo flushing there is the additional danger of an unwanted pregnancy, of infection, or worse still, of an ectopic pregnancy.[3] Nevertheless, in Britain there has been considerable discussion about the use of embryo flushing in conjunction with the development of techniques for the genetic diagnosis of embryos. For example, the dominant British embryo research group at the University of Edinburgh, as well as Anne McLaren who is Britain's foremost spokesperson for embryo research, have expressed an interest in obtaining embryos for genetic testing purposes by means of embryo flushing (McLaren, 1987; West *et al.,* 1987).

This concludes my discussion of the four different groups of women who are submitted to the dangerous practice of superovulation so that early human embryos can be generated in the laboratory. But are all these in-vitro embryos actually available to researchers for experimental purposes, including genetic engineering work?

In spite of there being a range of approaches for the production of in-vitro embryos, there is, in fact, currently a worldwide shortage of such embryos available for research. This is not to say that there are not many thousands of frozen embryos stored in the various IVF centers around the world.[4] But on the whole, the IVF clinics seem to treat the frozen embryos as the property of their IVF clients. Many of these clients are quite possessive about their frozen embryos, which is perfectly understandable in view of the problems that they faced in even getting that far in the IVF cycle. What I mean by possessive is that the IVF clients would much rather have their embryos kept in deep–freezer storage than make them available to researchers for experimental work. Furthermore, the number of those women who are prepared to act as volunteer egg donors or as volunteer embryo donors is also quite limited. As a consequence, the embryo research scientists have had to devote a lot of their energy on the ongoing search for their experimental material. This has made some of them quite frustrated.[5]

But there is a glimmer of hope on the horizon for these scientists. What they are working towards is the maturation of eggs in vitro and once this technique becomes perfected, there will be an unlimited supply of early human embryos available for research. At that stage, the production of human embryos will have become completely severed from any input by women. It is consequently important that we examine this future technology a little

more closely.[6] In the natural menstrual cycle, as well as in the superovulation cycle, the maturation of eggs takes place in the follicles on the surface of the ovaries. Part of this maturation process involves the splitting in half of the chromosome number so as to yield an egg with 23 chromosomes. By contrast to such an egg that is physiologically ready for fertilization, the thousands of eggs found in the ovary contain 46 chromosomes and are not ready to be fertilized. They are referred to as "immature." For years, experiments have been performed with mouse and sheep ovaries to determine the appropriate culture conditions for the transformation in vitro of immature eggs into mature ones (Moor and Trounson, 1977). By 1983, this work was sufficiently advanced for a committee of the Royal Society in Britain to proclaim (1983: 5):

> Recent progress in maturing eggs from rodents and other mammals *in vitro* raises the possibility that human ovarian tissue obtained from cadavers or removed during surgery undertaken for other purposes, might provide an alternative source of material. This would considerably enhance the scope for research on human fertilisation and embryology.

In the last five years the required "breakthrough" with the eggs of women has not yet happened. But the technology has been advanced further during this period and also adapted to cattle production (Vines, 1987b). Moreover, the three most prominent IVF research groups in Britain are actively working on the human system.[7] In the light of this intense research pressure and its applicability in the profitable enterprise of animal husbandry, it will probably not take much longer before it will be possible to mature in vitro not only animal eggs but the eggs of women as well. When this happens, researchers will be able to mature at will thousands of eggs taken from ovaries removed either from women who have just died or from women who undergo gynecological surgery. At that stage, there will be an abundance not only of in-vitro embryos, but of *research embryos* as well. Women will then no longer have any say at all in regard to what happens with embryos in IVF clinics. After all, they will no longer "own" these embryos even in the limited sense that applies at present. Furthermore, judging by the direction of current developments, we can predict that the primary goal of the work with the newly generated mass of research embryos will be in the area of genetic engineering.

## THE NATURE OF GENETIC DEFECTS AND WAYS OF TESTING FOR THEM

The objective of human genetic engineering is to prevent the occurrence of, as well as to treat, those diseases that are defined to have a genetic basis. Currently, molecular biologists go to great lengths to distinguish several categories of genetic diseases (Weatherall *et al.,* 1986). First, there are the straightforward cases of single–gene conditions with a known biochemical basis such as phenylketonuria, thalassemia, sickle–cell anemia, the Lesch–Nyhan syndrome, and Tay–Sachs disease. Then there are the conditions that are inherited in a Mendelian manner, but where the biochemical fault has not yet been characterized; examples are Huntington's chorea and cystic fibrosis. The next group are chromosomal disorders such as Down's syndrome with an extra chromosome 21, Turner's syndrome with an XO chromosomal constitution, and the ill–famed XYY condition. In the 1970s, geneticists alleged that this chromosomal pattern was linked with criminal behavior, but by the end of the decade there was a complete turnaround and now the consensus is that there is no link between XYY and criminality.

In addition to all these conditions, in the last few years molecular biologists have also identified specific gene markers which they associate with manic depression and with schizophrenia

(Robertson, 1987). This is actually quite a threatening development, since what it means is that the psychopathologies that are clearly related to the social environment, are being brought once again into the hereditarian picture. Finally, specific genes have also been linked to cancers as well as to cardiovascular disease, and thus these two major disease types are increasingly seen by researchers in the light of genetics.

I shall now consider some of the recent attempts by molecular biologists to study how all these various conditions can be *prevented* from occurring in the next generation of offspring. Prevention of a genetic condition generally means its detection in a fetus and the abortion of the affected fetus. Amniocentesis, where fetal cells are removed from the amniotic sac at about 16 weeks of pregnancy, is still the dominant mode of genetic testing. But a few years ago, a technique was introduced that can be performed much earlier in pregnancy, at about 8 weeks. This is called chorionic villus biopsy and its obvious advantage over amniocentesis is that if a termination is deemed to be necessary, it can be performed in the first trimester of pregnancy.

However, there are problems as well in the introduction of chorionic villus biopsy. First, the testing procedure at times leads to a miscarriage, and the rate for this is higher with chorionic villus biopsy than with amniocentesis. Second, there is some evidence that the chorionic villus tissue is not quite representative of the fetus from which it is derived in that it contains a greater number of chromosomal abnormalities (Vines, 1987a). This means that the diagnostic test can show up a chromosomal defect when there is actually nothing wrong with the fetus. In both these cases – the induced miscarriage and the false positive test result – a wanted pregnancy with a perfectly normal fetus is lost *because* the pregnancy was genetically tested.

With these hazards associated with chorionic villus diagnosis, it would obviously be a good idea to restrict the diagnostic procedure to cases of serious risk. That, however, is not really in the nature of high technology medicine. In general, it is the case that medical technologies come to be applied to a much wider range of patients than is envisaged when the technique in question is first developed (Taylor, 1979). But, in addition to this general pattern, there is a further factor that comes into play in the special case of genetic testing. This is that the *range* of conditions that can be tested prenatally is increasing rapidly. A few years ago, genetic testing was largely restricted to Down's syndrome, spina bifida, and Tay–Sachs disease. Now, recombinant DNA–based gene probes also make it possible to test for sickle cell anemia, thalassemia, cystic fibrosis, Huntington's chorea, muscular dystrophy, and hemophilia. It stands to reason that as more and more conditions can be diagnosed prenatally, and indeed, relatively early on in the pregnancy, increasingly larger numbers of pregnancies will be assessed. Furthermore, the recombinant DNA test kits employed in genetic diagnosis are produced commercially by entrepreneurial biotechnology companies such as Integrated Genetics, Collaborative Research, Cetus, and Genentech, and these companies are exerting their own pressure for increasing the usage of genetic testing (Klein, 1987b; Saltus, 1986).

So what we have is a climate in which the genetic testing repertoire increases month by month and abortion is being offered earlier and earlier in pregnancy. As a consequence, increasingly larger numbers of pregnant women are having their babies "quality tested" prenatally by genetic diagnosis. But the proponents of genetic testing–both the scientists and the companies involved – still have a problem in that genetic diagnosis is stigmatised by its association with abortion. This has contributed to the view that it would be better still if the testing process could be shifted even closer to the beginning of pregnancy, preferably before the

pregnancy starts. This is where human embryo research enters the picture. The idea is that the *embryo itself* could be genetically tested before it has a chance to implant in the uterus. Thus, the trend of replacing amniocentesis by chorionic villus biopsy looks like being continued with the replacement of chorionic villus biopsy by *embryo biopsy.*

In this technique, the objective is to remove one or two cells from the early embryo and to assess these cells using the genetic test kits that have been developed for amniocentesis and chorionic villus biopsy. Only those biopsied embryos that pass the genetic diagnosis test will be inserted into the uterus. When this technology is perfected, then, at least in principle, there will be no further need to conduct abortions for the prevention of genetic defects. Genetic diagnosis by means of embryo biopsy (also referred to as preimplantation diagnosis) is currently the hottest topic for embryo researchers in Britain, with the groups at the Universities of Edinburgh and Cambridge and at the Hammersmith Hospital in London competing in this field.[8] So far, the major breakthrough for the use of gene probes at the level of embryo diagnosis has come from the laboratory of Professor David Baird at the University of Edinburgh. There a group of researchers under the leadership of John West have shown that it is possible to determine the sex of an early embryo using a commercially produced gene probe (West *et al.,* 1987). At the press conference announcing this work, West said: "It certainly would not be ethical to use this method to choose the sex of a baby. But we could not prevent the technique being used that way" (Johnston, 1987).

To use genetic diagnosis by embryo biopsy, the clients would have to go either through the IVF route of reproduction or through embryo flushing. Either way, the beginning of pregnancy would become highly medicalized. At this stage, when the techniques needed for the genetic diagnosis of the early embryo are only in their experimental phase, the extent of application of embryo biopsy cannot yet be foreseen clearly. But if we take the introduction of amniocentesis and chorionic villus biopsy as a guide, we note that the fear in the community of producing a child with a genetic defect is so great, that genetic testing becomes associated with a large number of pregnancies, most of which are not at serious risk at all (Rothman, 1986). It can, therefore, *be predicted that* genetic diagnosis by embryo biopsy will become quite prevalent when the science is perfected. What this means is that many pregnancies will start off with a genetically tested embryo. Moreover, this development will probably not take all that long. As I noted, there is a tremendous research pressure in the field and an additional commercial pressure that comes from the biotechnology companies that produce and market the test kits.

In addition to pregnancies starting off with embryos that have been quality tested for genetic defects, these embryos will also have had their sex determined. A number of writers have discussed the implications of sex determination on the sex balance in the population and on sex stereotyping (Etzioni, 1973; Holmes and Hoskins, 1985; Kishwar, 1985; Rothman, 1986; Rowland, 1985; Warren, 1986). What has received far less attention is that the preoccupation with the detection of genetic defects and their eradication is in fact a *eugenic* enterprise, in many ways analogous to the eugenic programs conducted in a number of countries before and during World War II. As we have seen, the direction of genetic research using embryos is towards an increase in quality control of those embryos that are allowed to give rise to offspring, and towards an increase in the involvement of experts at the start of pregnancy, even for couples who are not infertile. These planned interventions in reproduction are undoubtedly eugenic, and this aspect of the technological advances will need a great deal more careful scrutiny.

## EMBRYO GENE THERAPY

Considering the significant advances that have occurred recently in detecting genetic defects in early embryos, the question arises whether there is any point in even talking about fixing up defective embryos. Many geneticists at the forefront of research into genetic diagnosis, for example, Bob Williamson and Anne McLaren in London, David Wetherall in Oxford, and David Danks in Melbourne, say they cannot see the point. For them, genetic engineering of human embryos that involves the insertion of genes into defective embryos for purposes of correcting the defect makes no sense at all. They argue that once it is known which embryos are genetically defective, it is much more rational to discard the defective ones and implant into women only those that have passed the "quality control test." This attitude is also reflected in a recent report of the Australian National Health and Medical Research Council (National Health and Medical Research Council, 1987) on human genetic engineering for which Professor Danks acted as consultant (1987).

But before dismissing quite so quickly the possibility of gene insertions into human embryos for purposes of correcting genetic defects, we should note the recent pace of development in regard to the insertion of genes into animal embryos.[9] In the last few years, a whole range of genes have been introduced into the embryos of mice, sheep, and pigs to generate so-called *transgenic animals.* The introduced genes have included those coding for growth hormone, milk proteins, cancer proteins, the blood clotting agent TPA (tissue plasminogen activator), and even the AIDS virus. Generally, the genes have been introduced into normal embryos. But as a special sophistication, the technology of transgenic animals has now proceeded to the creation of mutant animals that are genetically analogous to humans who suffer from genetic diseases such as thalassemia or Lesch–Nyham syndrome. With the creation of such mutant mice, the next step is to proceed to their *correction* by means of further gene insertions into early embryos. Recently, a spate of articles on corrections of genetic defects in animal embryos have been published (Constantini *et al.,* 1986; Doetschman *et al.* ,1987; Readhead *et al.*, 1987).

So without a doubt there have been significant advances made recently in regard to the genetic engineering of animal in-vitro embryos. Nevertheless, there seems to be a reluctance among researchers to proceed to similar work with human in-vitro embryos. What might the reasons be? In part, the reluctance is due to the reasoning I have described above, which holds that if defective embryos can be weeded out effectively, there is no need to repair them. In addition, the present limited supply of human embryos available for research probably affects gene insertion experiments more than it affects genetic diagnosis experiments. The reason is that the diagnostic experiments can be portrayed as helping those women who are already on IVF programs. For example, women in their late thirties who fear a Down's syndrome child and who find the thought of having an abortion unacceptable, could be quite willing to have their IVF embryos tested with a gene probe for Down's syndrome. By contrast, at this stage, gene insertion studies would have to depend almost entirely on embryos produced specifically for research purposes. As I have argued before, such embryos are produced primarily from the eggs of women who can be coopted to act as volunteer egg donors, and not all that many women are prepared to go along with the necessary procedures, including superovulation. Consequently, at present, research embryos available for gene insertion studies are in particularly short supply. Finally, the climate of opinion among molecular biologists currently holds that gene additions to embryos are problematic from an ethical point of view, because the genetic alterations would be passed on to

the next generation.

It seems to me that in the *current climate* where there is both rapid development in the area of gene diagnosis by embryo biopsy and a shortage of research embryos, gene insertion experiments analogous to those conducted with animal embryos will not be carried out extensively with human in-vitro embryos. But if the research that I have discussed into the in-vitro maturation of human eggs is successful, and human research embryos become plentiful, then the situation will change dramatically. The temptation will then be considerably greater to repeat with human embryos what can be achieved so readily with animal material, particularly in regard to the correction of genetic mutations (Constantini *et al.,* 1986; Doetschman *et al.,* 1987; Readhead *et al.,* 1987).

Furthermore, in the technological progression from amniocentesis to chorionic villus biopsy and then to embryo biopsy, the driving force has been that science ought to be able to provide something better than aborting a defective fetus in an established pregnancy. Logically, this argument can be extended further from embryo biopsy to embryo gene insertion: science ought to be able to provide something better than the discarding of defective in-vitro embryos. Robert Edwards, the British pioneer of IVF technology, has in fact called attention to this rationale and coined the term "abortion in vitro" for the discarding of embryos found to be defective by genetic testing.[10] Similarly, a number of philosophers, such as Peter Singer in Australia, Hans–Martin Sass in Germany, and John Fletcher in the United States, have already pointed to this rationale and argued in favor of human embryo genetic engineering *on behalf of* scientists (Fletcher, 1985; Sass, 1987; Singer, 1984).

Nevertheless, the scientists themselves have as yet generally not canvassed to any great extent for studies of gene insertions into human in-vitro embryos. But a change in outlook could be underway in 1988. An editorial in the prestigious science journal *Nature* has suggested that from an ethical point of view there is, in fact, nothing wrong in attempting to correct genetic defects in embryos (Editorial, 1988). The apparent anomaly that the scientists themselves have not yet pushed for embryo gene therapy can be explained quite easily: scientists are generally realists to whom their dependence on research resources looms large. With a limited supply of research embryos, they will be unlikely to use them up in gene insertion experiments, particularly since this is likely to strike up fears and opposition in the general public. It is much better to work on embryo biopsy and to concentrate on the research that leads to the quality control of embryos, at least for the time being.

## REGULATION AND LEGISLATION–WHAT IS PERMITTED?

I have argued that at present a considerable amount of work is proceeding on the detection of genetic defects in early embryos in spite of a shortage of embryos available for research. I have also drawn attention to the scientific efforts to develop an in-vitro maturation system for the immature eggs cut out of the ovaries of women who have just died or undergone surgery. Third, I have suggested that when these experimental egg maturation studies are completed, vast numbers of research embryos will become available and that this will push ahead gene insertion studies into human embryos. At that stage, we will be faced with full-scale human genetic engineering at the level of embryos.

At present, however, in the absence of in-vitro maturation of human eggs, there is a limitation on such genetic engineering in terms of a restricted supply of research material. In addition, there could be a further limitation at work due to laws imposed upon research scientists to prohibit the genetic engineering of human

embryos. To determine whether this is in fact the case, I shall look briefly at appropriate regulations and legislations in various countries.

*Britain*

The publication of the Warnock Committee report in July 1984 (Warnock, 1985) was followed by two years of operation under the guidelines of the Voluntary Licensing Authority (1987). In late 1987, the government released its long-awaited White Paper on embryo research (Department of Health, 1987). According to this paper, the major decision on whether embryo research can continue in Britain will be resolved in Parliament. If the vote is against experimentation, then research will cease on the detection of genetic defects in embryos as well as on gene insertions for correcting defective embryos. However, if the Parliament votes for limited and regulated embryo research, then the government recommendation is for a prohibition on gene insertion studies. On this scenario, embryo biopsy research would continue, and this is the position that most British embryo research scientists are currently lobbying for. The Parliamentary vote is expected in November 1988.

*West Germany*

There have been two major reports in relation to embryo research and genetic engineering: that of the Benda Commission released in December 1985 (Bundesministerium, 1985) and that of the Parliamentary Commission into genetic engineering completed in July 1987 (Enquete, 1987). The government's response to these commissions is still being finalized, but it appears that legislation will be passed to control embryo research, with a prohibition on gene insertions into embryos (Dickman, 1987). On present indications, research leading to the detection of genetic defects in early embryos will not be prohibited.

*France*

Following the report of the National Ethics Commission, the government has imposed a three–year moratorium on gene insertions into human embryos (Nau, 1986). Embryo biopsy work can be conducted.

*United States*

The Office of Technology Assessment is currently completing a major study on infertility. The Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health (NIH) has issued guidelines on gene insertion into adults and children, but has left gene insertion into embryos in the "too–hard basket." The radical science body, the Committee for Responsible Genetics, has tried to push the RAC to come out openly against embryo gene insertion, but the RAC has refused to do so. Furthermore, the NIH does not fund embryo research, and so experimental work with human embryos is financially limited by having to be supported by nongovernment funds. Overall, in the United States there is no legislation in sight to limit embryo research. Thus, both embryo biopsy and gene insertion into embryos can be carried out as long as they are privately funded.

*Australia*

*Victoria.* According to the Infertility Medical Procedures Act passed in 1984, each embryo research project in this state must be submitted for approval by the Standing Review and Advisory Committee on Infertility. Failure to do so could lead to a jail sentence of up to four years. In addition, the legislation permits research only on "spare" embryos produced in clinical IVF programs, but not on embryos created specially for research purposes.[11] So far permission has not been sought from the Committee in respect of embryo biopsy or embryo gene transfer work. It is interesting to note that while this law stands, progress in the domain of *in vitro* egg maturation makes no difference to plans on embryo research. In other words, in Victoria the present limitation in research resources is encoded in law. With this limitation in place, there

are not many embryos available for genetic diagnostic work either.

*National Health and Medical Research Council.* This is a body dominated by scientists and it has recommended that gene insertions into embryos should not be conducted (1987). However, genetic diagnostic research on embryos is well within the guidelines, which simply limit embryo research to 14 days past fertilization. These quite unspecific guidelines apply only to institutions funded by the federal government.

*The Senate.* A committee of inquiry comprising seven senators recommended in its report published in October 1986 that only "therapeutic" experiments should be permitted, namely those which would further the chances of survival for the embryos experimented on (Bartels, 1987; Senate Committee, 1986). Late in 1987, the federal government responded to the Senate Committee with a rejection of the recommendation to limit embryo research to therapeutic experiments. The Parliament will debate the issue in 1988, but at the moment there is no planned Australia-wide legislation in sight to control embryo research, with the exception of the state of Victoria.

## CONCLUSION

In this article, I have dealt with five main issues: the dangers of superovulation for women, the present and likely future availability of human embryos for research, scientific developments in the genetic diagnosis of embryos, the factors currently inhibiting research on gene insertions into embryos, and legislative moves in several countries to regulate embryo research. What emerges from my analysis is that in spite of a present shortage of human embryos as research material, considerable advances have been made in regard to the genetic testing of embryos and that the pace of this development is likely to increase further. The reproductive technologies that produce in-vitro embryos, namely superovulation, IVF and embryo flushing, have therefore obviously moved out of the context of infertility and into that of genetic engineering. At this stage the genetic engineering is by way of genetic diagnosisrather than through the insertion of additional DNA into embryos.

The scientists have argued that this represents a rather restrained intervention in human genetic material. But with the foreseen advances in genetic diagnosis that I have discussed, the mechanism is certainly there for a great deal of control over reproduction so as to eliminate all those conditions which are defined as genetically based defects. That can be done most effectively with the technique of embryo biopsy and the use of commercially marketed diagnostic kits.

In addition, research is proceeding at a fast pace to determine the laboratory conditions for the maturation in-vitro of immature eggs. When this work is completed, scientists will have effected the obsolescence of women in regard to the production of research embryos. Of course, slices of ovaries from women's bodies will still be needed in order to collect the immature eggs. But as I have pointed out, these ovaries will come from women who have just died or from women who are undergoing gynecological surgery. Either way, it will not prove difficult for researchers to obtain their required ovarian tissue. Once the eggs are cut out of this tissue and matured in-vitro, it takes only a short laboratory step to produce embryos out of them. Thus, immature eggs will be turned into research embryos, and these will then be available to scientists in large numbers for full-scale genetic engineering work.

## ENDNOTES

1. Conveyed by Bob Seamark, Department of Obstetrics and Gynecology, University of Adelaide, at the 56th ANZAAS Congress, held in Palmerston North, New Zealand, in January 1987.

2. It is still an open question what concentrations of clomiphene citrate would bring about such deformities in human developing fetuses (Rodell, 1988).

3. Gena Corea reported on the case of Alejandra Muñoz, a young Mexican woman, who was smuggled into the United States to act as an

embryo donor. One of Muñoz' embryos did not dislodge in the flushing procedure and she became pregnant. During her pregnancy, she was intimidated about being an illegal resident in the United States and kept in hiding. Muñoz wished to raise her baby, but she was prevented from doing so by the contracting couple (Corea, 1987).

4. According to Andrew Veitch, reporter at *The Guardian* (London), there are over 10,000 frozen embryos stockpiled in IVF centers around the world (5 October, 1987, p. 4).

5. The sense of frustration about an acute shortage of embryos available for research was expressed by Alan Trounson of the Monash University IVF Centre, at the Conference of the Victorian Standing Review and Advisory Committee on Infertility, *Embryo Experimentation and Beyond: What Does The Future Hold for Our Children,* held in Melbourne on 29 September, 1987. Alan Trounson claimed that only seven research embryos were available in all of Melbourne at that time.

6. Also see Klein (1987a, 1987b, 1988) for a discussion of the maturation of immature eggs in vitro and the development of techniques for the detection of genetic defects.

7. These are the IVF research groups of Robert Edwards at Bourn Hall in Cambridge; the IVF center of Professor Templeton at the University of Aberdeen; and the IVF research unit at the University of Edinburgh under the direction of Professor David Baird (Voluntary Licensing Authority, 1987).

8. Information on IVF research in progress in Britain is gathered and published by the Voluntary Licensing Authority (ibid.).

9. Many aspects of this work are covered in Ewing (1988).

10. Discussion at the Symposium *Human Embryo Research: Yes or No?* (CIBA Foundation, 1986, p. 78).

11. This legislation has been designed to limit experimentation with human embryos and thereby to benefit women. But it has also been argued that the legislation could in fact have a detrimental effect on the women in IVF programs (Klein, 1987b; Rowland, 1987).

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