

# ETHICS AND EMBRYOLOGY

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In 1978 the world's first "test tube baby" was born in Oldham, United Kingdom. Until this time most people, apart from doctors, knew little or nothing about embryology; and although years of research and failed attempts to fertilize human eggs in the laboratory preceded this, few people had ever heard of in vitro fertilization. The very first reaction of the popular press was to welcome the baby, Louise Brown, as a miracle; the men who had worked the miracle, Patrick Steptoe, a surgeon, and Bob Edwards, a research scientist, were hailed as heroes. However it soon became clear that the practice of IVF was by no means universally welcomed. Infertile couples were of course given fresh hope (often to be sadly disappointed, for the early success rates were very low, and not all types of infertility were suitable for this remedy); but on the other hand there were many who found the whole idea vaguely distasteful or "unnatural," and the forces of the Roman Catholic Church were violently opposed to it, as were orthodox Jews.

Now that so many thousands of babies have been born by IVF all over the world, it is difficult to think back to that time. It is perhaps especially hard to understand the people who simply reacted with horror or disgust at the 'unnatural' character of the procedure. But right from the start there were those who invoked the analogy of Frankenstein and the monster he

created in the laboratory (a science-fiction figure invented in the 19<sup>th</sup> century by Mary Shelley); and then, more seriously, there was moral opposition from some, but not all, religious bodies, and especially from the Roman Catholic Church. This opposition has remained, to attach itself firmly to all the further uses of embryology that have been developed in the last 35 years.

Strict Catholics objected to the fact that IVF involved a man masturbating to produce the sperm that was to be inserted into his partner's fallopian tube, and this was a sin that no desirable end could justify. But even those who did not take this purist line had far greater objections, namely that IVF entailed the destruction of human embryos. For first, if the practice of IVF were to become an established treatment for infertility, its success rate must be improved, and this involved experimentation. Research had to be undertaken into the best composition and temperature of the fluid in which the egg was to be fertilized, and into the best way of freezing and storing sperm and embryos, and, later, eggs. Every element in such research meant the destruction of the embryos that had been used in the trials. They could not safely be placed in the uterus of an infertile woman in case they had been damaged. So, as we often heard, they were thrown down the sink, an outrage to the sanctity of human life. Secondly, apart from research, it was then part of the procedure of IVF to give the woman super-ovulating drugs at the proper time of her menstrual cycle so that she would produce a large number of eggs, of which as many as possible were fertilized in vitro. The healthiest were chosen for insertion and the rest destroyed, unless they were offered for donation to a woman who could not produce eggs. So, again, after every IVF procedure there were surplus embryos that would be discarded, contrary to the doctrine of the sanctity of life.

The Roman Catholic Church had always forbidden abortion, so when the time for legislation approached in the late 1980s, they had to make clear

to members of the Church what line they should take on IVF; what, in fact, was to be the moral status of the human embryo alive in the laboratory—an entity, after all, which was new and had never existed before 1978. Thus in 1989 an Instruction was issued by the Vatican asserting that human life was to be treated as an inviolable right to its possessor from the “moment of conception,” that is from the moment that the human egg was fertilized, whether in utero or in vitro. This was also the view of the then Chief Rabbi. It was the line taken as well by a group called The Society for the Protection of the Unborn Child, many, but not all, of whom were religious, and who were equally vocal in their campaigns to criminalize abortion.

In the course of our deliberations in the Committee of Inquiry, we had naturally foreseen the ethical disagreements that would arise; indeed we had people of different moral views and different religions as members. We could not fairly have been accused of packing the committee with scientific or medical people, or those unduly sympathetic to the infertile, though we often had such allegations leveled against us, as the ethical debate spread with the approach of legislation. In fact the composition of the committee fairly well reflected the divisions of opinion in society at large, as we discovered from the evidence we took.

I devote some attention to the detailed workings of the committee, not because it got everything right, nor even because I am proud to have chaired it, but because it was the first of its kind in the world, and therefore it had considerable influence on subsequent thinking about the ethics of embryology, perhaps world-wide, but certainly in Europe. The non-medical members of the committee, and that was the majority including myself, were astonishingly ignorant of the natural development of the embryo; so before we could advise Ministers on the matter of possible legislation, we had to learn as much as we could about the subject-matter. We decided early on that we were minded not to prohibit

IVF absolutely, even though we knew that we should not get agreement throughout the membership on this point. But the great majority held that the balance of benefits over harm was too great. We did not think that to remedy infertility was a trivial matter; and in any case it was becoming clear by now that IVF might be used for fertile couples at risk of having children with genetically inherited diseases, where the mother's eggs could be fertilized in vitro, and the resulting embryos screened, only the healthy ones being selected for implantation (I return to the ethical objections raised against this practice below). But because we were about to make recommendations that were plainly moral rather than merely legal or political we had to learn the facts; moral judgments cannot be based on ignorance, though this is not always recognized. Luckily we had a brilliant physiologist, the late Dame Anne McLaren, among our number, who was not only a great scientist but a great teacher. She taught us that, on fertilization, the embryo consists of a loosely conjoined collection of cells (a zygote) which multiplies to four then sixteen undifferentiated cells. An undifferentiated cell may develop into any one of the 120 types of cell that make up the human body, such as skin, muscle, etc.; and some would not become part of the body at all, but of the placenta or the umbilical cord. From about the 14<sup>th</sup> day, however, there begins to appear, among this collection of cells, a sort of thickening in the centre, known as the Primitive Streak. After this the embryo develops fast, the primitive streak becoming the beginnings of the spinal cord, and the central nervous system starts to form. This is the last stage at which twins may split off, and develop as two embryos. We therefore decided that until 14 days from fertilization, the embryo could not be regarded in the same way as a later foetus (or two fetuses), but rather as a collection of human cells which could not yet have any experiences, having no vestige of a nervous system to organize them. Its use in research and subsequent destruction could therefore be morally justified, as long as the whole procedure had a beneficial purpose. However, to keep an embryo alive in the laboratory for longer than 14 days from fertilization was to be a serious criminal offence.

I have labored this decision because it has been of the greatest significance in the acceptability world-wide of IVF and other research using human embryos. The Fourteen-Day Rule has been incorporated into most if not all European legislation. The legal position is less clear-cut in the United States, largely because of the influence of fundamentalist religious views on federal legislation, as well as the freedom from regulation of much private medical practice.

The question of the moral status that should be accorded the live human embryo in vitro was and remains the single most fundamental source of ethical disagreement in general embryology since the 1970s. But, even within the narrower sphere of IVF, many other social issues have proved controversial. Because IVF, though now more or less routine, still requires complex surgical intervention, questions have arisen about whether doctors are entitled to refuse to treat some categories of people. Should those who are not married be treated? Should single women, or women who are part of a lesbian couple be treated, with donor sperm? Should women be treated if they are acting as surrogate mothers for single men or homosexual couples? On the whole, in my view rightly, the medical profession is unwilling to make moral judgments about those who present themselves for treatment, or long-term judgments about the effects on society of unusual families. So they are generally prepared to treat anyone who is clinically fit to be treated and who can pay for the treatment; the extent to which insurance companies or nationalized health services should cover costs is another moral or political issue, but hardly a matter of embryology. However, the concept of clinical fitness leads to a further ethical question. Is it morally acceptable to treat post-menopausal women? Will being the child of someone old enough to be his grandmother be physically or psychologically damaging to a child, or merely occasionally embarrassing? Answers to such questions must be hypothetical and, without supporting evidence, judgments cannot be reached with confidence. Perhaps, to form a judgment, a doctor would

need to enquire into the motives of the would-be mother (there was an elderly IVF mother in France whose motive turned out to be that of securing an inheritance, and depriving her sister of it).

More immediate than such ethical speculation is the anxiety now widely expressed about the risk of multiple pregnancies that IVF carries. In the 20<sup>th</sup> century, when IVF was new, it was generally accepted that to insert as many as four embryos in the uterus in any one cycle gave the greatest chance of successful implantation and resulting pregnancy. A multiple pregnancy was a risk, but one worth taking. Would not a hitherto infertile couple prefer to have two or three babies than none? Now, however, further studies have cast doubt on the effectiveness of inserting more than one embryo; also that the ill effects of multiple births, both on the mother (and probably the father) and the babies, is too serious to be lightly incurred. Perhaps legislation is needed in this area, or at least strongly worded guidelines.

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Finally, as I have already mentioned, moral doubts have been expressed about the ethics of pre-implantation screening of IVF embryos. Some disabled people hold that to attempt to eliminate the risk of a child being born with, say, cystic fibrosis is derogatory to the disabled. I regard this as such a bad argument that I shall not discuss it further. But some people also argue that such a process may be abused: parents, they argue, may want another baby with a particular blood-group, as a “savior sibling” to save the life, by organ transplant, of a fatally sick brother or sister. This

would entail, they think, that the second child was not loved for his own sake, but only as a means to an end. I regard this as a weak argument as well. Someone may be loved for himself and even more because he is a possible savior of his brother. Finally it is argued that pre-implantation selection may be used to select the preferred gender of a child (sex-selection); and that this would inevitably lead to a preponderance of boy babies over girls. However I do not think this is a genuine threat. Most people will not go through the painful and exhausting process of IVF just to have a baby of the chosen sex (though I can just about imagine doing so if this was likely to be your only child, or if you already had many daughters, and wanted a male heir). But to discuss such matters more thoroughly would be to encroach on the other ethical topic to be covered in this volume, that of so-called Designer Babies and other forms of enhancement.

There have been enormous advances in embryology since the 1970s. Probably the most notable has been the discovery that embryos might be formed by means other than the fertilization of eggs by sperm: a form of cloning. Cloning is a form of non-sexual reproduction in which all the offspring are genetically identical to the parent from which they are derived and to one another. All the identical organisms are collectively a clone; and each individual in the collection is a clone of all the others, parent and offspring alike. Many plants, such as strawberries, reproduce both sexually by spreading seeds and by putting out suckers which become plants that are really extensions of the parent plant. Human beings have long intervened in the reproduction of plants by taking cuttings, which are clones.

Research had been going on for many years to investigate the possibility of artificially cloning farm animals with a view to finding a quick way to reproduce a particularly successful strain of cattle or sheep. More than 50 years ago, a biologist called John Gurden had, after many failures,

transferred cells from tadpoles into frog's eggs from which the nucleus had been removed, and had produced new tadpoles which survived to maturity. But it was comparatively easy to work with frogs or salamanders which have large eggs, and where fertilization and development takes place outside the body. It was long believed that mammalian cloning was impossible. When in 1990 the United Kingdom, as part of the Human Fertilization and Embryology Act, made human cloning a criminal offence, they were thinking of the possibility of splitting a human embryo in the laboratory to produce artificially two embryos out of one zygote, that is, to produce identical twins.

But in 1997 scientists at the Roslin Institute in Scotland announced that they had successfully cloned a lamb, named Dolly, by a different method. They had taken a mammary cell from an adult ewe and cultured it in the laboratory so that it began to divide; meanwhile they harvested an egg from a second ewe and extracted its nucleus, using a pipette. They then insert the whole dividing cell of the first ewe into the enucleated 'shell' of the egg from the second ewe, and by means of briefly exposing it to an electric current, they got it to fuse into an embryo, which they then inserted into the uterus of a third ewe, a surrogate mother, where it implanted, and the pregnancy proceeded to term. However, the resulting lamb was not completely genetically identical to the first ewe, as naturally formed identical twins are to one another, because she inherited from the second ewe a small but significant amount of DNA contained in the mitochondrial cells that had continued to line the "shell" of her egg, and that are always passed in this way through the mother's line. The whole procedure was fraught with difficulty, the reconstructed embryos being exceedingly fragile. At Roslin, the scientists reconstructed 277 embryos. Only 29 of these were thought strong enough to be transferred to surrogate mothers, of whom 13 were used. Out of all these, only one was carried to term. Dolly grew into an adult ewe, somewhat overweight, and suffering from arthritis in her later years. She died at the age of six, which is late middle-age for a sheep.



As soon as the birth of Dolly was announced, speculation began about the possibility of cloning other mammals, including human beings (techniques have improved in the last 25 years, and many cloned cattle and sheep have been produced, some of them genetically modified at the embryonic stage, for particular medical or husbandry purposes). The idea of cloning human beings gives rise to widespread, though not universal, moral outrage. Immediately after the birth of Dolly, and before new prohibitive legislation had been passed, an Italian obstetrician, already notorious for bringing about an IVF pregnancy for a post-menopausal woman, announced that he was coming to England to make human clones, and that he already had 200 women lined up to act as surrogate mothers for the reconstructed embryos. The British government immediately rushed through legislation to prohibit human cloning, for although it had been prohibited under the 1990 Human Fertilization and Embryology Act, or so everyone assumed, an organization devoted to preventing the use of any human embryos in science or medicine took the issue to court. There a judge, rather surprisingly, ruled that a reconstructed human embryo would not be an embryo under the meaning of the 1990 Act, which covered only embryos created by the fertilization of eggs by sperm, that is, by normal means, though outside the body. So fresh legislation was deemed necessary (the judge later reversed his judgment).

If the procedure of producing cloned embryos by cell nuclear transfer became safe, I, for my part, can imagine cases where its use might be justified as a remedy for certain kinds of human infertility, so that a couple might have a child who was at least in part genetically theirs. I do not take very seriously the arguments of those who claim that a child born as a clone would be less than human, or would necessarily suffer from being genetically nearly identical to someone of a different generation. Such a child, after all, would be brought up and educated in quite different, and contemporary, circumstances. If someone wanted, as

some apparently do, to reproduce himself for the benefit of future generations, such arrogance alone would make such an outcome undesirable, even if it were both safe, and within the law. However, I suspect that the ethical revulsion that many people feel with regard to human reproductive cloning is largely explained by the sense that it is of all things the most contrary to Nature. Nature demands that, for a child to exist, it must have been conceived, and for it to be conceived, there must be a father and a mother. Nothing is more deeply ingrained in us than this belief. But Dolly had no father. A child with no father would be an unnatural monster, like Frankenstein's famous creation.

Arguments based on the supposition that what is natural is good, what is unnatural bad, have been common at least since the time of Jean-Jacques Rousseau. But they are flawed by the fact that "natural" and "unnatural" are capable of such widely differing interpretations. Especially in the field of medical interventions, hardly anyone believes that Nature should be allowed to take its course if someone is suffering from acute appendicitis, to be remedied by surgery, or from heart failure, where a pace-maker can be inserted. So it is irrational to object to asexual human reproduction solely on the grounds that it is not Nature's way.

And, as I shall explain, there are very good reasons to permit it, provided that it is not carried right through to the point of implantation in the human uterus. We must distinguish here between reproductive and therapeutic cloning. Reproductive cloning is the process already described, such as led to the birth of Dolly. Therapeutic cloning, as its name implies, is the creation of embryos solely with a view to developing therapies based on the use of cells before they have differentiated, following extraction from embryos a few days after being created. These are known as stem cells. Stem cells are characterized by two main properties: they have the capacity to renew themselves indefinitely; and they are not yet differentiated. However, they have the capacity to turn

into different specific types of cell. In nature, they do differentiate gradually this way, starting from four or five days after fertilization; but if they are taken from an embryo at this very early stage of development, they may be induced to develop into any one of the kinds of cell that might be needed to take over from and replace cells in a person's body that have been damaged by disease or injury. This would be known as cell transplant, to which concept I shall return in a moment.

Stem cells that are taken from early embryos are capable of being made to differentiate into any type of cell. They are also easy to obtain, whether from a "spare" embryo, which has been produced by fertilization in the laboratory in the course of an IVF treatment but not needed for implantation, or by cell nuclear transfer, the method that produced Dolly. But there are other sources of stem cells as all adults retain some stem cells in their bodies. However, adult stem cells have already partially differentiated and are capable of being made to develop into only a few of the types of cells of which the body is composed; and in any case they are difficult to obtain. There are stem cells to be found in the umbilical cord and the placenta and in aborted fetuses, but none of these is as versatile as those to be found in early embryos. Those people who are opposed in principle to the use of human embryos in research, and who hold that no embryo should be created in the laboratory which is not implanted in the uterus, so that it has at least a chance of being born, believe, understandably, that these drawbacks must be accepted as the price to be paid for the protection of embryonic life. They, reluctantly, prefer the use of "spare" embryos as the source of stem cells to the deliberate creation of embryos for the sole purpose of harvesting cells; but they do not approve of that either. And so they urge that, if cell transplant is to be pursued as a therapeutic goal, it should be confined to the use of adult stem cells (or cord and placental stem cells).

But cell transplant, like organ transplant, carries with it the risk of rejection by the recipient. Cells, like whole organs, carry a unique DNA makeup, and

must, like an organ for transplant, be as nearly as possible “matched” to the DNA of the recipient, who will probably have to take immune-suppressant drugs in order to avoid rejection by his or her immune system. Nevertheless, the possibility of the transplanted cells being turned into, say, bone-marrow cells that regenerate the bone-marrow cells of the recipient is an exciting medical development, and it is already being brought about in practice. And in the United Kingdom, at least, embryonic stem cell lines are being created and deposited in a stem cell bank, under the supervisory powers of the British Medical Council, for use in research or therapy.

The next step is to overcome the problem of rejection in a radical way. It is possible, at least in theory, to take a cell, any ordinary somatic cell, from a patient suffering, say, from spinal-cord injury or heart failure, culture this cell and treat it in such a way that “the clock is turned back” and the cell reverts to an earlier, undifferentiated, form of being. It can then be made to differentiate and become a cell of the required type; but it would be a cell from the body of the patient himself, so there would be no question of rejection. If this were to become a practical and usable therapy, there would be no need to extract stem cells from newly-created embryos. Stem cells could be, as it were, created artificially and individually, according to each patient’s needs. If this kind of procedure were to become widely available, it would be a huge step forward in medicine.

This is undoubtedly the way forward for stem-cell research and its applications. It is difficult to ascertain the progress that has been made globally. But one of the many merits of such amazing advances is that it no longer involves the creation by conception in vitro or by cell nuclear transfer of human embryos in the laboratory. But meanwhile, until such an advance can be hailed as routine, or be taken for granted, research using embryos continues to be a part of medical research, if only in order to enable us to better understand the details of cell differentiation (and

de-differentiation) within them. And obviously for the purposes of the remedying of infertility by IVF, embryos must be created by conception in vitro, and surplus embryos discarded. And so the ethical problems will in the end remain the same as they were in the beginning. What moral status ought we to accord to the human embryo at its very early stages? I think it would be true to say that in most developed countries, even some that are predominantly Roman Catholic, such as Ireland, in vitro fertilization has been accepted, and this means that the creation and destruction of early embryos is regarded as an acceptable, inevitable, routine procedure. This in turn means that the Instruction of the Vatican has, to all intents and purposes, been disregarded (though of course no one can be compelled either to undergo IVF treatment or to practice it, any more than they can be compelled to undergo an abortion, or use contraception). Such widespread disregard may be taken as a sign of the general secularization of society, which in turn means that people must increasingly find justifications other than religious dogma for their ethical judgments. That is, they need to find arguments that will convince the atheists.

## **The possibility of the transplanted cells being turned into cells that regenerate the cells of the recipient is an exciting medical development**

There are many who welcome this. The ethical status of any measure, including any scientific research or medical procedure, must be judged according to the criterion of whether it does more good than harm to society at large, in other words according to the criterion of the Common Good. Legislators have always been obliged to use this criterion when deciding whether to prohibit some practice, regulate it, or allow it to be freely practiced. It is never easy to make such a judgment, and it may turn out to have been a bad decision, with consequences so obviously bad that

it has to be reversed. But those who broadly welcome the advance of scientific knowledge and the increase in medical and therapeutic technology, or who are interested in their own country's reputation in scientific research, recognize that risks must be taken if there are too many barriers to it. On the other hand there are some who fear that if society becomes accustomed to the use of human embryos in infertility treatment, it will seem no different from the use of other human tissue (such as, for example, the use of blood in blood transfusions); then something important will have been lost. This unease need have nothing to do with any religious belief. It may arise from the reflection that all civilized human societies must hold the protection of human life among their very highest values; and early embryos, however they are created, by conception or otherwise, are human and alive and have the potential, in the right environment, to develop into full human beings. If this respect for human life is allowed to be eroded, they fear, society will inevitably suffer, becoming less sensitive, more indifferent and ultimately barbarous. This anxiety is serious and must be taken seriously.

We thus come back to the beginning. There are, as I hope I have shown, a number of social problems which have to be solved by practitioners of, or beneficiaries from, advanced embryology; yet the fundamental ethical question remains that of the moral status a society should accord the very early human embryo. There are two considerations that might bring some comfort to those who are inclined to think we should turn our back on the whole thing, give up deploying IVF to remedy infertility, and go no further in the pursuit of therapy derived from embryonic stem cells. The first consideration is this: scientists who use and then destroy human embryos, thus wasting potential human life, are not alone. Nature itself is almost incredibly profligate in the creation and destruction not only of sperm and eggs but of actual embryos which come into being and are aborted so early that the woman herself who bears them does not know that they existed. The second consideration is more serious, perhaps. If

research is allowed to proceed towards its present goal, when cells from an adult may be taken, treated so as to turn them into totipotent cells and then used to repair damaged cells in that adult's own body, then the need for the use of embryos will come to an end. That, though far distant, is the ultimate aim of embryonic stem-cell research, and of course it can never be attained unless that research is allowed to continue. In my view, this is the justification for permitting such research, despite the ethical issues that at present it raises.

This study has necessarily been based on experience within the United Kingdom. It isn't difficult to discover how far stem-cell research has progressed in other parts of the world. (It is probably less advanced in other European countries, which have been more hesitant than the United Kingdom in bringing forward regulatory legislation). In the United States, there is no federal funding for new research that would stock cell banks with cell-lines other than those produced before 2002, many of which were not particularly useful. So, in effect, whatever stem-cell research is done must be privately funded, and about such research it is quite difficult to find reliable reports. There is little but rumour to tell us how advanced such research or indeed such therapy may be in South America, Singapore or China. But wherever embryos are used in research, and by whatever techniques the embryos are brought into being, the fundamental ethical question is the same: how are we to value these tiny entities, morally? Are they like babies who have been born or more like scraps of human tissue? My belief is that we should hold them to be more like human tissue, on the grounds that they can no more feel pain or pleasure than can a discarded piece of fingernail or a hair from a human head. And therefore we do not injure them by depriving them of life in the way that we would injure a baby who had been born, but whom we decided to destroy. The moral status that we accord them is based on developmental biology.





>> Almost 35 years after the birth of the first “test tube baby”, the controversy surrounding IVF treatment has greatly diminished, yet the ethics of embryology remain complex. What moral status should be accorded to the live human embryo in vitro? More recent discoveries involving cloning have provoked widespread, though not universal, moral outrage. But there are very good reasons for permitting the therapeutic cloning: the possibilities opening up through stem cell research could revolutionize medicine. The future may well bring cloning techniques that remove the need for embryos. Whatever may happen, the undifferentiated cells of the human embryo should be accorded a moral status based on developmental biology.

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