Fertilization of Human Eggs in Vitro: A Defense

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The widespread debates arising from medical advances have become a familiar aspect of contemporary society, and the clinical application of man’s increasing control over his physiological and biochemical systems is bound to stimulate further controversy. This review is concerned with the current debate on one of these novel advances—the fertilization of human oocytes in vitro, and their reimplantation as cleaving embryos in the uterus of the mother. The attitudes expressed here on social and ethical values will obviously reflect the viewpoint of the writer, a scientist engaged in initiating and continuing the research and its clinical application.

Doctors, and occasionally scientists, are faced with decisions about the nature and social value of their work. An immediate issue with new clinical methods concerns the ethics of human experimentation, for if patients are to benefit, new methods have to be perfected, often with the collaboration of people unlikely to gain from the research. The impact of human research can obviously be wider than merely affecting patients and doctors, and many of the themes running through debates on fertilization in vitro also arise in connection with abortion, contraception and artificial insemination from a donor (AID). The idea of initiating human life in vitro will probably be unacceptable in principle to some people, even for the cure of infertility. This response is partly emotional and might be modified as the notion becomes more familiar and the benefits clearer, just as previous debates have led to the acceptance of new attitudes towards various other aspects of human reproduction and sexuality. Certain other well-known concepts stimulating a great deal of discussion concern the moment when human life begins and the “rights” of embryos, fetuses, and neonates, especially those growing in culture. We will now consider these issues in turn.

The Development of Clinical IVF

Like other new medical advances, studies on the cure of infertility by re-implanting cleaving embryos must pass through an initial phase where methods are being established and the prospects are assessed. Volunteers who have had a chance of ultimately benefiting from the work have been involved while the methods were being developed. Demands on these volunteers were not excessive, for treatments with gonadotropins or clomiphene were in use by many doctors to alleviate amenorrhea, and the operational risks of laparoscopy in the cure of infertility were well known and minor. Aspirating oocytes from follicles is similar to the natural events of follicular rupture during ovulation, and the ovary recovers just as quickly. The reimplantation of embryos via the cervix would demand neither anesthetic nor operation and is simple, rapid, and free from dangers such as infection, while the risks of disorders such as perforation of the uterus seem very low. These procedures are now fully practiced and performed routinely.

The application of new methods in clinical medicine usually follows a certain amount of previous work done with animals. The data published on several animal species concerning fertilization in vitro, embryo culture and transfer, and the treatment of embryos with the various agents have shown the preimplantation embryo to be highly resistant to malformation. Attempts to repeat the work on the culture of embryos using nonhuman primates have been almost a total failure, and the clinical methods have outstripped experimental studies on these species. There is disagreement among teratologists and doctors about the necessity of including such primates among the three animal species to be used before clinical trials are carried out. Thus, primates were not tested before the clinical application of either kidney transplantation, relevant data being obtained from pigs and dogs, or vasectomy. Recent data on the carcinogenetic effects of contraceptive pills have come from rats and mice, the results of studies on dogs and monkeys being yet unavailable. It is likely that all known human anomalies have been found in subprimates, including the effects of thalidomide, and in their response to some compounds the fetuses of nonhuman primates are less resistant than human fetuses. In view of the vast number of fetuses and offspring arising through embryo transfer in animals, without evidence of any increase in number or type of abnormality, there seems to be no point in delaying the clinical application of work on human infertility. This conclusion is supported by the evidence that the cleaving embryos of nonhuman primates are similar to those of sub-primates in resisting the teratogenic effects of agents applied in vivo. Many infertile couples and others with different problems would forfeit their chances of a cure if medical progress depended on verification in non-human primates.

Some prenatal diagnoses, especially the analysis of their chromosome complement, should be carried out on any fetuses arising from the reimplantation of cleaving human embryos. The chances of trisomy, i.e., individuals with an
extra chromosome, arising as the result of fertilization in vitro have not been estimated because there are few mitoses in cleaving embryos, and vast numbers would be needed to carry out this study. There is likely to be nothing novel in this respect about fertilization in vitro, because many trisomies for every human chromosome group have now been found after natural conception, and as many as 5 percent or more of all fetuses are known to be imbalanced chromosomally at three months' gestation. The incidence at fertilization is likely to be much greater for the frequency of imbalanced embryos increases as embryos earlier in pregnancy are being examined. Almost all nondiploid human embryos fail to survive, and those that do develop can be identified at four months' gestation by using amniocentesis to collect fetal cells for chromosomal examination. Other types of prenatal diagnosis could also be applied to the fetuses. Measurements of heartbeat and fetal scanning by ultrasonics can detect anomalies of the head, limbs, and other organs, and further advances are possible with three-dimensional ultrasonic images of the fetus. Amniotic fluid can be used to identify fetuses with anencephaly and other malformations, and the chances of disorders such as choriocarcinoma are determined largely by the relationship between the blood groups of the parents. The risks of abnormal offspring following human embryo transfer should thus be very small.

**Spin-Off Benefits**

The accumulation of knowledge regarding human conception should prove of considerable value to other types of clinical studies. Some of the most important contraceptive methods in use today, e.g., the safe period and the "pill," involve an understanding of human ovulation, and studies on oocyte recovery have provided the first definite indication of the moment of human ovulation. New contraceptive or sterilization methods for suppressing implantation could arise from studies on the early differentiation of the human embryo, together with a clearer understanding of the mode of action of intrauterine devices in expelling the blastocyst from the uterus. Analyses concerning the origin of various inherited or induced human malformations are even more restricted to clinical work, as shown, for example, by the rare animal counterparts of trisomy due to aging. Some inherited diseases might one day be avoided or averted by sexing blastocysts or by making chimeras in cleavage stages, for some evidence indicates that the expression of recessive genes carried on one of the cell lines is modified in mouse chimeras. On the other hand, chimeras might suffer from the combined defects of both stem lines or from interactions between them, and any embryo known to be defective would be better discarded than subjected to such methods of salvage. Human chimeras have been created at full term by injecting thymus and other hemopoietic stem cells into newborn children, and their suffering from immunological deficiency diseases has thereby been alleviated.
Benefits to Infertile Patients

The reimplantation of cleaving embryos into the uterus is the only method to help many patients who are infertile through tubal occlusion. Estimates of the numbers of these patients vary widely, partly due to ethnic or other differences in the population under study. In the United Kingdom, approximately 2 percent of all women suffer from tubal occlusion. The reconstruction of damaged oviducts might help one-fifth of them. Other forms of infertility might also be treated, including endocrine disturbances or antibodies against spermatozoa in men and women and oligospermia in men. Artificial insemination using pooled ejaculates can help some men with oligospermia, and male infertility can obviously be bypassed by using AID, i.e., using semen taken from a donor, a method now being widely used despite the ethical and legal problems it evokes. A woman without her own oocytes might be able to conceive through intercourse with her own husband if oocytes were placed in her oviduct, the similarities with AID being obvious. The recipient would carry the child through gestation, and hence both parents would help to establish their family. The legal and ethical issues involved in AID have been widely debated (Wolstenholme and Fitzsimons, 1973), and oocyte transfer should be as acceptable ethically and legally (Revillard, 1973; Stone, 1973) in the rare cases where it is needed. The number of women who lack oocytes and are still in their reproductive age is very small, and various difficulties might arise for some of them in establishing pregnancy. Congenital absence of the ovary can lead to maldevelopment of the oviduct and uterus, and some women with ovarian disorders arising in adult life have other contraindications for pregnancy. The transfer of embryos from one woman to another could alleviate infertility arising where both parents lack gametes, a very rare occurrence. There are many women, potentially fertile, who are advised against pregnancy, and the transfer of their embryos to a surrogate mother who would carry the fetus to full term would enable them to have their own children. The transfer of embryos from one woman to another is perhaps the only ethical issue requiring caution, and this form of treatment will be considered separately below.

There are clear arguments in favor of proceeding with the reimplantation of embryos into the mother for the cure of infertility, for to give a couple their own wanted child obviously needs no justification. The right to have children is stated in various international declarations on human rights. Infertility might lead to deprivation and the breakdown of a marriage, although the statistical methods supporting this view have been challenged. Adoption can satisfy the desires of some infertile couples, but fewer children are available today for adoption because of contraception, abortion, and the widespread acceptance of the illegitimate child, and many infertile couples have been unsuccessful in their attempts to adopt. The cure of infertility by reimplanting cleaving embryos does not impose intolerable treatments or surgery, or cause irreversible physical damage, and violates no canon of medical treatment. The
cost is very small, if it should be thought an important point to judge the economics of the treatment. The cure of infertility would not raise the frequency of unsuitable genes, for only a few minor causes of infertility, such as congenital occlusion or absence of the vas deferens in man and some endocrine disturbances in women, have a genetic basis, and these conditions are very rare. Even if they were successfully treated, the increase in gene frequency would be insignificant, as with the cure of other rare disorders.

The problems of population growth might ultimately erode some privileges of parenthood, although most debates stress—correctly in our view—the voluntary nature of restricting family size. Yet objections to the reimplantation of embryos as a cure of infertility have been based on the mounting pressures of population. In numbers alone, such an attitude seems mistaken, for perhaps only a small proportion of the women who could benefit will accept the treatment. More serious objections can be raised to this attitude, which implies that all forms of infertility ought to remain uncured, leaving this unfortunate minority to their own devices. Doctors dealing with infertile patients should not, and almost certainly will not, be subject to such pressures to modify their diagnoses and treatment according to events outside their consulting rooms. Strictures and regulations about procreation, if ever needed, should apply to the population as a whole and as impartially as possible.

The Meaning of Medical Treatment

Some other comments on the treatment of infertile patients appear to be equally mistaken. One remarkable opinion holds that the reimplantation of embryos to cure infertility is not therapeutic in the accepted sense, for the patient remains infertile even if transfer results in live children. What is supposedly being treated is the desire of people to have children (Kass, 1971a). A great many medical advances depend on the replacement of a deficient compound or an organ. Examples include insulin, false teeth, and spectacles: the clinical condition itself remains, but treatment modifies its expression. Patients taking advantage of these three treatments are surely receiving the correct therapeutic measures, the doctors treating the desire to be nondiabetic or to see and eat properly. In fact, most medical treatment, particularly of constitutional or genetic disorders, is similarly symptomatic in nature. Exactly the same argument applies to the cure of infertility: should patients have their desired children, the treatment would have achieved its purpose. To state the opposite is nonsense.

"Thin End of the Wedge"

Another untenable proposition is the argument based on the "thin end of the wedge" or "camel's nose," suggesting that fertilization in vitro and re-
implantation of embryos in the mother should be banned because they might lead to less desirable ends such as cloning (Kass, 1971a,b). The immediate appeal of this argument lies in its purported offer of a quick solution to difficult decisions, and in its instinctive appeal to those who are fearful or uncertain of the real issues. Its weaknesses include the pessimistic assumption that the worst will inevitably happen, and the uncritical rejection of good and bad alike. The whole edifice of the argument is fragile: thus, nuclear physics led inevitably to the atom bomb, electricity to the electric chair, air transport to bombers and hijackers, civil engineering to the gas chambers. The list is as long as the argument is fallacious for acceptance of the beginning does not imply embracing the undesirable ends.

Patients' Consent

Patients seeking treatments must be kept fully informed about the methods contemplated and the probability of success, just as in other forms of novel clinical methods. Many infertile couples urgently desire the work on fertilization and reimplantation to proceed, wish to help with it, and are fully capable of understanding their condition and the attempts to cure it. A significant proportion are doctors or the wives of doctors, scientists, solicitors, clerics, and other members of the community who are articulate, discriminating, and fully capable of analyzing and judging social and medical situations, although it is very important to avoid an "elitist" attitude in selecting patients. They are evidently aware, too, that the methods might not work, their infertility remain uncured, and that other women may be the ultimate beneficiaries of the developing methods. It is obviously hard to assess how much some patients understand; in follow-up studies after genetic counseling, one-half of the patients had fully grasped the nature of their problems, and their level of education was a significant factor in comprehension but not in their decision to limit their family. Perhaps a preferable alternative to the treatments designed to cure infertility is to persuade patients to accept their childlessness, but such advice assumes that a doctor or someone else is sufficiently authoritative to decide on the problems of the couple. Patients have the right to benefit from research, and there is no reason to believe that ethical advice from outsiders about their condition is sounder than their own judgment of it. The future child must be considered too, for there could be psychological or other problems in store for children conceived through fertilization in vitro. Most evidence would suggest an opposite conclusion: the children would give thanks to be alive, just as the rest of us do, for they would be the children of their own parents, born into a family where they are wanted for their own sake. If there is no undue risk of deformity additional to those in natural conception, and publicity is avoided, the children should grow and develop normally and be no more misfits than other children born today after some form of medical help.
**Surrogate Motherhood**

The only issue needing care seems to be the case of surrogate mothers for those women unable to carry their own children. This form of treatment could lead to conflicting claims on the child by the embryo donor and the uterine mother, and to the divided loyalty of the child itself. The surrogate mother might request an abortion or refuse to hand over the child, the donor might reject the child at birth, and the child might suffer on learning of the circumstances of its birth. Surrogate mothers could be used purely for the convenience of fertile women who wish to avoid the problems of pregnancy. At present this approach, and the use of surrogate mothers to help the infertile should, perhaps, be avoided until more consideration is given to the psychological demands on donor, host, and child, even though some existing situations do not differ greatly from this practice. Illegitimate children are often surrendered at birth, and some couples have deliberately conceived and carried babies to full term for those unable to have their own. Despite these examples, embryo transfer between women should not be encouraged until more can be deduced about the psychological relationships between parents, recipients, and children. . . .

**The Beginning of Life**

Contributions to debates on the more esoteric issues arising from fertilization in vitro have come from various quarters. Themes occurring repeatedly in these discussions include defining the moment when human life begins, the challenge of new methods of conception to established ideas on life and procreation, and the imminence of genetic engineering. The divergent viewpoints forming the basis of ethical judgements are perhaps best illustrated in attitudes expressed towards defining the moment when human life begins. Absolutists insist that full rights must be given from the instant of fertilization, partly on the grounds that the embryo is then a human being. This view is challenged on biological grounds. Fertilization is only incidental to the beginning of life, for the processes essential to development begin long before ovulation, and parthenogenetic fetuses can develop partially, and perhaps one day wholly through gestation. The potentiality for life must therefore reside in the unfertilized egg and all of its precursors. Nuclear transfer experiments are also held to weaken the absolutist case by showing that all nuclei can potentially sustain the development of an embryo. The assumption of full human rights at a single moment in a continuous developmental sequence obviously demands making arbitrary decisions that are unjustified biologically. Nevertheless, fertilization and implantation are two convenient points that are often suggested in debates on contraception and abortion, and legal guides have included quickening of the fetus and the earliest stage when neonates can survive independently (28 weeks). Granting full rights from fertilization on-
wards is sometimes combined with condoning the abortion of deformed fetuses, an outlook that is totally unrealistic, for it would lead to the justification of infanticide or euthanasia for deformed adults.

Most of the contributions by theologians to debates on fertilization in vitro and embryo transfer can be accepted and answered by laymen, for appeals and allusions to earlier Church authorities or to a “revealed ethic” are largely absent. There is no parallel between current scientific and clinical work and earlier clerical situations, and the attitudes of different theologians probably reflect their known stances on other issues, such as contraception and abortion. The Church, like other professions, represents a diverse body of opinion, even on religious issues, and will probably never give a unified decision on embryo transfer; indeed, the differences in outlook among theologians are as wide as among scientists, doctors, and others, as judged by a perusal of their published opinions.

A strict denunciation was to be expected, and duly came, from the hierarchy of the Roman Catholic Church. Their initial ruling, based on papal pronouncements, was to declare fertilization in vitro “absolutely immoral.” But absolutes are not easy to define or uphold, especially in today’s society, and this ruling was not accepted by an ethical committee of Catholic doctors, who wrote in one of their statements: (Guild of Catholic Doctors Ethical Committee, 1972, p. 242): “In vitro fertilization, with a view to transfer at an early stage to the womb of the ‘mother’ is, in principle, acceptable . . . .” Many of the views expressed in this document on other issues raised by embryo transfer coincide fairly closely with those of the present reviewer, but not the tendency to define absolutes such as giving full human rights to a fertilized egg. This belief is obviously rejected implicitly by many people, for IUDs almost certainly expel unimplanted embryos from the uterus, and abortion is legalized in many countries. The gradual acquisition of human rights during development is tacitly accepted in other situations, and is clearly illustrated by the prevalence of eugenic abortion, but not infanticide, in cases of inherited anomalies.

Procreative Arts, Child’s Consent, and Dehumanization

Some theologians still rely heavily on their own interpretations of biblical or theological concepts in judging new clinical methods, and have been described by their colleagues as “a priorists” (Fletcher, 1971a; McCormick, 1972). Reimplanting embryos was judged as unacceptable because the nature of procreation must remain as it is, divine and unchangeable. This view is astonishingly held simultaneously with an acceptance of AID, provided the sterile couple hold acts of procreation by performing intercourse (Ramsey, 1970)! It is challenged by several commentators (Guild of Catholic Doctors Ethical Committee, 1972), as summed up by one of them who writes that “these moral positions assume that only God can make a tree or a man. They ignore the fact that God has shared with us His creative power so that we may
Motives and Decision Making

Some revealing attitudes are struck in these debates. According to one commentator, the developments and the benefits of new scientific advances should not be judged by "man the technician" but rather by minds that "grasp and transform reality." This view is allied with a feeling that secret experiments detrimental to human values—especially genetic engineering—are constantly occurring so that external controls should be imposed on scientists (Crotty, 1972). Two notable aspects of this contribution are its inherent suspicion of other people's motives—reinforced by allusions to the Nazis and Hiroshima—and the belief that "a pattern of behavior is more genuinely human . . . because [it] embodies greater human values than do alternative responses." How can anyone possibly disagree with such a fine quotation, but
how far does it take us? The exact problem with many clinical advances is deciding where the great human values lie among a conflicting welter of attitudes and possibilities, and allusions to the Nazis, Hiroshima, and other cataclysms hardly helps to provide clarification. The subtleties involved in making decisions and judgments on scientific and clinical advances are well illustrated in recent symposia (Kunz and Fehr, 1972; Wolstenholme and Fitzsimons, 1973). Note, too, the attitude that “technology” (including science) is inferior to “humanity” (philosophy and theology) in helping to establish values. Some points derived from the word-centered concepts of the latter appear to be obvious and acceptable from simple reasoning; for example, the conclusion that human sexuality is an ambiguous basis for creating children, since it may be used in lust, selfishness, accident, or hatred (McNeill, 1972). McNeill considers that the ambiguity is removed by baptism, but surely love and commitment between two people are preferable.

Responsibility in Biological and Clinical Research

Research is usually divided into basic and applied science, but the borderline between them is often blurred. The distinction between them becomes almost meaningless as new methods are put into practice, and responsibility changes from the demands imposed by scientific research to those involved in the conduct of clinical trials. The problems become oriented toward patients and hence more pressing as they move to the hospital. The responsibilities of scientists in “pure” research have been debated with respect to their role in developing chemical warfare and other issues, but the primary concern of the present review involves clinical medicine.

The responsibility for applying new research methods to patients has rested traditionally on the individual doctor, often working in collaboration with scientists who are regarded as auxiliaries. This may still be the best position to adopt today, although the increased participation of non-medical men in making decisions should be recognized. The ethical and legal complexities in clinical situations can sometimes be formidable, and some commentators have advocated making committee decisions—for example, with respect to the timing of the first transfer of a human embryo. This outlook seems to be unrealistic. There are the “rights” of the patient to consider. The selection of committees and their methods of making decisions also present difficulties. Would such decisions need to be unanimous, by a majority only, or subject to veto by any single member? Can ethics be decided by a majority vote? The questions at issue—euthanasia, existence, interference with inherited characteristics—are so much more complex than those usually dealt with by most councils, and relevant opinion can come from wide sources, artistic and philosophical in addition to those outlined in this review. The chance of a united ethical and moral stance on such questions seems remote.

Individual responsibility must now cover problems additional to those de-
fined earlier. The necessity of obtaining the informed consent of patients and the establishment of clinical ethical committees in hospitals have obviously become widely accepted. Some responsibilities are novel. Doctors and scientists should understand the issues confronting each other, and both groups should familiarize themselves with the problems of the patients. Research of social significance should be published in widely read journals or articles, although the patients’ privacy must be fully protected and publicity in the press avoided. Various organizations and courses have been established to study the ever-increasing ethical questions in biology and medicine . . . , and should extend informed debate provided any bias in their constitution is recognized. The mass media have a responsibility to publicize work of public concern, but attempts at widespread discussion are often compromised by sensational press reporting, so that the standards of different professions come into conflict as control of the ensuing debate passes from doctor to journalist. Constant recourse to the Press Council is ineffective, since the damage is difficult to repair.

This review has stressed some issues raised by fertilization in vitro and the reimplantation of embryos. Many of the points raised in it are equally valid in connection with research in other areas of scientific medicine. The increasing tempo of scientific advances is occurring at a time when earlier and accepted standards of society, and the value of many scientific and technological advances are being widely questioned. There is an obvious need for continuing the debate on the value of scientific and clinical novelty, even though too much discussion can stimulate needless concern. Social priorities in clinical medicine should perhaps be listed and supported accordingly, but new avenues of scientific and clinical research will probably arise “as the acts of creation of individual geniuses, either working alone or possibly as members of teams of research workers” (Zuckerman, 1972). The widespread publicity, desired or otherwise, that now accompanies scientific and clinical advances will call for such individuals to participate in debate on social values, and equally will call for considered judgments from other professional men. There may be pitfalls and problems in the application of new methods in clinical research, yet, encouragingly, members of diverse professions can arrive at similar conclusions on complex issues.

References
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