Chapter 26

Research on preembryos: justifications and limitations

That the human condition generally has been improved through systematic biologic and medical research is undeniable. However, such research can be truly valuable only if there is careful selection of specific research objectives and strategies that emerge from identifiable individual and social needs. Often, animal studies, which carry their own need for ethical justification, have proven highly instructive in our understanding of human biology. Whenever possible, relevant mathematic models or cell and tissue culture systems should be exploited. However, if the potential benefits to mankind are judged sufficient, each of these surrogates must eventually give way to direct human study, either when balanced consideration indicates probable safety of human tests or when no adequate substitute for human studies is available or practical. In justifying or limiting research on human preembryos, we profit from the wisdom of this broader experience. Yet, the new reproductive area introduces wholly unique considerations, some involving formidable risks, others substantial benefits—often simultaneously. In chapters 8 and 9, our discussion included overt recognition that living human preembryos deserve special respect because some possess the potential to become human beings.

There are dilemmas in setting and monitoring guidelines to help clarify acceptable versus unacceptable research on human preembryos. Such deliberations must take into account that whereas a human preembryo cannot give informed consent, it is generally not regarded as a person. Nevertheless, there is wide agreement that the preembryo deserves special respect.

To be justifiable, any research on the human preembryo must provide significant and recognizable potential for generating important new knowledge—not otherwise obtainable—for benefiting human health. However, even when benefits of research on human preembryos can be anticipated, circumstances may not warrant acceptance of risk(s) of known or potential harm to persons or to society at large. Justifications and limitations of research concerning early human development must be based on thorough consideration, broad consensus, timely action, and frequent reevaluation.

In the Glossary, research on human preembryos is divided into three categories: first, the clinical trial, directed at extending a limited database that already shows favorable preliminary results in patients receiving therapy, but for which improvements in efficiency, safety, comfort, and economy are sought; second, the clinical experiment, which may have no precedent in human observations or may have only the barest clinical data, but where a potential for significant clinical advance is clearly recognizable. Often, the latter derives from persuasive data generated in animals. These distinctions in classifying research on preembryos take into account fundamental differences in the degree of previous knowledge available for assessment of potential risks and benefits. Typically, a clinical trial would carry less apparent risk than a clinical experiment; conversely, endorsement of a clinical experiment would require promise of seemingly greater accomplishment, sufficient to warrant acceptance of the somewhat greater estimated level of risk to individuals or to society generally. Inherently, because both of these undertakings constitute authentic research efforts, they—especially experiments—are not entirely predictable. In instances of clinical trials or clinical experiments, there is the foregoing intention that all viable preembryos may be transferred to the uterus with the expectation of pregnancy.

Finally, a third category is a form of preclinical basic research that cannot be effectively pursued in animals alone or by clinical trials or clinical experiments. Its principal distinction from clinical trials and clinical experiments involves prior declaration that no resulting preembryos will be transferred to the uterus, either because the preembryo is not expected to survive the experimental procedure or because there is obvious risk that abnormalities may be caused by the study procedures.

Basic research on human preembryos should be considered only when no adequate substitute is acceptable and only to procure data that are likely to
be of clinical importance. Examples might be the improvement of IVF therapy, the identification of human-specific teratogens, or diagnosis of abnormalities in the genome, as by examination of chromosomes of preembryos after cryopreservation. Certain protocols may permit the use of "extra" preembryos no longer needed for reproduction by the donors; however, the left-over preembryos may not be a representative sample, which could adversely affect the reliability of the data obtained. Other studies may require production of human preembryos as an integral part of the analysis, for example, of gamete quality or of the fertilization process itself. Assisted fertilization, including microinjection of sperm and its modifications, may contribute to the understanding of human infertility and also generate preembryos in the course of proving the utility and safety of this approach.

Besides sperm injection or the like, microtechniques used or contemplated experimentally extend to (a) removal of excessive pronuclei from the fertilizing oocyte, (b) ooplasmic transfusion, whereby metaphase II ooplasm imparts developmental potential to prophase I oocytes readied for fertilization, (c) preembryo biopsy to accommodate DNA sampling, its amplification, and nucleotide sequence analysis for specific genomic defects and identification, and (d) splitting the preembryo in order to raise the apparent statistical potential for pregnancy (in effect, duplicating preembryos), as well as any other approved micro techniques. Finally, generation of preembryos other than by studying the fertilization process, such as for treating polyspermy or for teratogenesis tests, may be justifiable in special circumstances. However, obtaining oocytes expressly for basic research on preembryos should not put the donor at significant risk.

Any deliberation for determining the acceptability or unacceptability of proposed research should assume that the principal burden for demonstration of worthiness lies with those offering the proposal. Failure to provide convincing justification should be cause for a judgment of unacceptability. This built-in bias limiting research involving human preembryos is a necessary safeguard against premature or trivial research proposals. Such a conservative posture, however, should not preclude truly innovative research directed toward important scientific or clinical advances.

Chapter 22 on the use of micro techniques for sperm insertion, oocyte diagnosis, and preembryo testing indicates that additional preembryo research would be valuable. Nonetheless, concern exists that certain experimental techniques may result in impaired offspring.

The question of creating preembryos for research purposes without the intention of transferring them for further development was considered by the early boards and committees that examined the ethics of preembryo research. Although its 1979 report was never acted upon, the Ethics Advisory Board of the U.S. Department of Health, Education, and Welfare (HEW) found that "it is acceptable from an ethical standpoint to undertake research involving human in vitro fertilization and embryo transfer provided that:

A. If the research involves human in vitro fertilization without embryo transfer, the following conditions are satisfied:

1. The research complies with all appropriate provisions of the regulations governing research with human subjects (45 CFR 46);
2. The research is designed primarily: (a) to establish the safety and efficacy of embryo transfer and, (b) to obtain important scientific information toward that end not reasonably attainable by other means;
3. Human gametes used in such research will be obtained exclusively from persons who have been informed of the nature and purpose of the research in which such materials will be used and have specifically consented to such use;
4. No embryos will be sustained in vitro beyond the stage normally associated with the completion of implantation (14 days after fertilization); and
5. All interested parties and the general public will be advised if evidence begins to show that the procedure entails risks of abnormal offspring higher than those associated with natural human reproduction.

In similar fashion, in July, 1984, the Warnock Committee in the United Kingdom (Great Britain, 1984) commented on preembryo research where transfer is not intended. A majority of the committee members concluded that the deliberate creation of preembryos for research purposes is clinically acceptable. The majority also accepted the view that preembryo research is valuable and should be permitted, provided that each research protocol is submitted to a licensing authority for prior review and approval. In fact, since 1986 there have been regular
reports of ongoing preembryo research published by the U.K. Voluntary (later, Interim) Licensing Authority. Under the terms of the 1990 Human Fertilization and Embryology Act, this area of research is now regulated by the Human Fertilization and Embryology Authority (HFEA). The first annual report of the HFEA was published in 1992.

As noted in chapter 24 of the Ethics Committee’s 1990 report, there is a need for ongoing discussion of the ethical issues in preembryo research by a visible, national deliberative body. The National Institutes of Health Human Embryo Research Panel (1994) is charged with providing guidance in this area. In addition, other national review boards should be available to review ethically controversial preembryo research protocols.

The Committee finds that in research with the use of human preembryos, the following guidelines should apply. Gametes, before fertilization, are of lesser concern than their postfertilization products. Accordingly, unfertilized oocytes are not accorded comparable worth to human preembryos at any postfertilization stage; this view recognizes that some preembryos can progress to the development of children.

The Committee concludes that it seems prudent at this time not to maintain human preembryos for research beyond the 14th day of postfertilization development. This 14-day limit was recognized by the Ethics Advisory Board (1979), the Waller Commission (Australia, 1984), an earlier Ethics Committee of The American Fertility Society (1984), and the Warnock Committee (Great Britain, 1984).

Although this limitation is somewhat arbitrary as to specific time, it recognizes that beyond this time, the definitive embryo and placenta may be structurally discriminated, individuality seems assured, and anatomic differentiation of the embryonic corpus begins. There is no reason why status with respect to research should change at this time. It can be argued that the case for research beyond this point is at least as strong as prior to it. Reservations become stronger as the embryonic period advances. This makes for a difficult, but important, issue that needs further discussion through the kind of mechanisms outlined in chapter 29.

Requests to do research on human preembryos should require especially strong justification because of the high moral value accorded to each human preembryo. In some instances, the Institutional Review Board may be well advised to seek extramural consultation in order to broaden the moral judgment to be made.*

The Committee intends that the points here considered will assist involved persons, Institutional Review Boards, local and state governmental agencies, and perhaps national policy agencies in the formulation of practical, workable guidelines for both promoting and limiting research on human preembryos. The Committee believes that we can, in this manner, achieve medical and scientific progress while protecting and preserving the essence and dignity of human generation.

* The matter is of such grave public importance that approval of preembryo research should depend on conformity with guidelines established at the national level (RAM).