IVF methods come under the microscope in France

A team of French biologists, who last year created two children using a controversial *in vitro* fertilization (IVF) technique that involved the direct injection of oocytes with spermatids, the round unflagellated precursor cells of spermatozoa, are now under fire for allegedly having bypassed regulations governing medically assisted reproductive techniques and for proceeding with human studies without adequate prior animal studies. But the allegations have triggered counterclaims from many reproductive biologists that the guidelines and procedures now in place to regulate experiments involving humans are ill-suited to the regulation of these new reproductive techniques, and that, furthermore, such techniques fall outside the competence of existing authorities.

The controversy itself centers on research published in the *New England Journal of Medicine* last August (**333**, 525; 1995), which was carried out by Jan Tesarik at the American Hospital in Paris, in collaboration with Carmen Mendoza of the University of Grenada in Spain and Jacques Testart, head of INSERM's gamete maturity and fertilization laboratory in Paris. Tesarik and his colleagues extended the technique of microinjecting oocytes with individual spermatozoa — so-called intracytoplasmic sperm injection — to the injection of spermatids taken from the ejaculates of men lacking spermatozoa, a condition known as azoospermia. Of the seven women implanted with embyros produced using this technique, two later gave birth in June and September of last year.

Critics of the research, such as Bernard Jégou, head of INSERM's laboratory of male reproduction in Rennes, argue, however, that the recent spermatid studies expose a worrying trend of applying new — and potentially risky — medically assisted reproductive techniques to humans, without first having carried out adequate animal experiments. The few tests of the original intracytoplasmic sperm injection technique that were carried out in cattle and rabbits before being applied to humans in 1992, for example, were largely unsuccessful. Proponents of the technique say they therefore felt justified in moving to humans. But Jégou points out, however, that the method was later shown to work well in mice. He also believes that there were insufficient data of intracytoplasmic injection methods using spermatids in mice and rabbits to warrant extending the technique to humans.

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Light microscope view of *in vitro* fertilization in which an ovum is being microinjected with a spermatozoa — the technique has now been extended to allow the microinjection of spermatids, precursor cells of spermatozoa.

Such concerns have been vociferously taken up by Axel Kahn, head of INSERM's genetics and molecular pathology laboratory at the Cochin Hospital in Paris, and vice-president of the national consultative bioethics committee. But what concerns Kahn and others the most is that the spermatid studies could be undertaken without formal authorization.

In particular, Testart, who is also head of the laboratory of reproductive biology at the American Hospital in Paris, did not seek authorization from the local regulatory body for the spermatid experiments. Approval by these so-called Consultative Committees for the Protection of Persons in Biomedical Research is compulsory for all research involving human subjects under the 1988 Huriet law.

Testart claims, however, that approval by such committees was unnecessary because the injection of spermatids is not "research" as such, but merely an improvement of an existing technique. Moreover, he and his colleagues question the relevance of the consultative committees, set up originally for the protection of persons involved in clinical trials, to techniques involving human embryos or gametes. In general, such committees require statistically valid comparisons of new treatments with either other treatments or placebos. Such comparisons are impossible to make in the case of medically assisted reproductive techniques, Testart and others argue. Moreover, they say that in the past, decisions by these committees have not always been consistent where these new reproductive techniques have been concerned.

The government has so far failed to clarify the situation. More than two years ago, the National Federation of Biologists of Laboratories for the Study of Fertilization and Egg Conservation wrote to the then junior health minister, Philippe Douste-Blazy, asking him to rule on whether the intracytoplasmic sperm injection technique fell within the purview of the consultative committees. The government has still not replied, according to the Federation's Chairman Bernard Sèle.

In a separate but related action, the national bioethics committee concluded in 1994 that intracytoplasmic sperm injection needs to be supported by adequate animal data and its practice rigorously evaluated. The bioethics committee also recommended that the technique should be available only at specialized centers and that parents contemplating a pregnancy using intracytoplasmic sperm injection methods be clearly informed of the technique's experimental nature.

Many biologists argue that these recommendations are too vague to be of any practical use. Jacques Montagut from a privately run center for medically assisted reproduction in Toulouse also says that the bioethics committee's deliberations are not keeping pace with the rapid advances being made in the area of medically assisted reproduction. What is needed, Pierre Jouannet of the Cochin Hospital says, is an oversight body that can anticipate the development of such new techniques and how they might best be applied in practice.

Some feel that the gap in oversight of these new techniques could be filled by the National Biological and Medical Commission for Reproduction and Prenatal Diagnosis, set up last November by the Ministry of Health to provide operating licenses to IVF clinics. Simone Zerah, who is head of the privately run La Dhues Clinic near Paris, and who is also a member of the commission, expects it eventually to do just that, overseeing all practices in reproductive biology, including the use of new medically assisted reproductive techniques. Even so, many question whether an authority that licenses clinics is an appropriate body for making judgments about the scientific and ethical issues raised by these new techniques, not least because of the potential conflict of interest given that most commission members are also reproductive biologists.

CATHERINE TASTEMAIN
Paris