Joint Committee on Health Care
Vice Chairman John Stefanini
State House
Boston, MA. 02133

Re: House 2863
March 4, 1997

Testimony in Support of An Act Relative to the Treatment of Infertility

Dear Committee Member

With the news of the world still focused on the stunning announcements of sheep and monkey cloning, this 6th annual review of House 2863 couldn't be more timely. Just this past weekend, it was announced that a monkey had been cloned 7 months ago; and last week it was announced that a sheep had been cloned 7 months ago. Will we read tomorrow that a human had been cloned - years ago?

In light of these recent headlines, the potential for human cloning has been raised in the media and by the experts - and all have denounced this potential as unlikely and unacceptable. And all have been silent on the 1993 cloning of abnormal human embryos by Dr. Jerry Hall at George Washington University (Gelman, Springen, 1993). Admittedly, Dr Hall's successful human embryo cloning was not done by nuclear transfer ... but, semantics aside - a clone is a clone is a clone.

Enucleation of human eggs and human ova fertilized with nuclear replacement (of spermatogonia nuclei) were performed by Dr. Shettles in 1979. Since those early years, an explosion in reproductive tinkering followed, which continues to mushroom to this day - without any regulation, enforceable standards, or national discussion. Fertility clinics can do whatever they want to do, and 'anything goes'. The specter of reproductive and genetic engineering is among us, and, in my opinion it has gone out of control.

The fertility industry, while avoiding oversight due to lack of funding for the Fertility Clinic Success Rate and Certification Act of 1992, continues to verbalize that self-regulation is possible and preferable. Many memorable headlines should spotlight this industry's credibility: Dr. Cecil Jacobson's substitution of his own sperm for that of the woman's partner resulted in excess of 75 offspring; eggs and embryos have been stolen from and surreptitiously 'donated' to unsuspecting women; eggs were stolen from women for purposes of research; *abnormal embryos have been implanted into women undergoing* IVF (Munne, Cohen, et al., 1995).

The 'right to procreate' has been crafted into a legitimate means to support any and all types of human/embryo experimentation, yet "ethically required informed consent is lacking" (Macklin, 1995). "Incomplete and misleading information is given to women"

(Baird, 1995), and John Robertson, who has served as a member of the American Fertility Society's Ethics Committee has stated: "as more personnel become involved in handling gametes and embryos, the number of embryos lost because of negligent handling or accidents in the laboratory may increase. Often couples may not learn of these mishaps, but be told that "oocytes did not fertilize", that zygotes "did not cleave," or that "your embryos were not viable" (Robertson, 1996, p.11).

The lack of disclosure of the known, suspected, and unknown health risks to women and offspring associated with the burgeoning reproductive technologies (IVF, GIFT, ZIFT, TET, FET, ICSI, SUZI, ROSI, PGD, SFR) and fertility drugs (synthetic, hormonal, recombinant, and "other") is reprehensible. Even though "present scientific evidence *does not support* the use of IVF for indications other than tubal blockage" (Buitendijk, 1995, p.901), and despite the lack of safety and efficacy data ... the indications for IVF and its variants have exponentiated: endometriosis, subfertility, polycystic ovarian disease, unexplained infertility, *male* factor infertility, egg donation, surrogacy, preimplantation diagnosis, postmenopausal pregnancies, or simply to verify that fertilization takes place.

Ovarian,' breast, and endometrial cancers, visceral, vascular and neurological injuries, adverse neurological symptoms, memory loss, bone loss, infections, and death are but a few of the known risks associated with fertility treatment and/or fertility drugs. Bacterial contamination following egg retrieval "appears to occur commonly", as does the "common phenomenon" of bacterial contamination in semen (Cottell, et al., 1997). The lack of mandatory screening of sperm has resulted in at least 7 cases of women contracting HIV from anonymous donors. "That superovulation is a problem that results in many abnormal embryos is universally recognized in animal breeding" (Moor, et al., 1985, p.171). Despite the media's glare on the recent sheep and monkey cloning, no mention has been made that the oocytes used in this research were obtained following superovulation with fertility drugs - the long term effects of which remain unknown.

Fertility clinics that are associated with hospitals and/or universities can claim that their procedure(s) and protocol(s) are subject to review by an Institutional Review Board - yet, as one local reproductive endocrinologist recently stated: "Institutional review boards have served an exemplary role as a universal vehicle to develop technology." (Seibel, 1996, p.671). The inherent profits in human embryo research was spelled out clearly in the 1994 National Institutes of Health's Human Embryo Research Panel: Therapeutic agents, vaccines, hormones, proteins, stem cells, gene therapy, cell lines, chimeras, patents, etc., were all deliberated as potential b(u)yproducts of human embryo research. 'Hundreds of products are being developed or marketed now, the beginnings of which depended on the availability of human embryos" (Shearer, 1988, p.132).

In fact, "relative value units" is the measure upon by which physician reimbursement is decided. And only those procedures that are not experimental or investigational are accepted into the 'Current Procedural Terminology' code (Hill, 1996) - hence the exorbitant out of pocket expenses for consumers and the "creative coding" seen throughout fertility practices (Soules, 1996). Dr. Soules, Professor and Director of the Division of Reproductive Endocrinology and Infertility in Seattle, Washington states: "...

patients generally pay cash in advance for a procedure that most likely will fail." (Ibid, p.695).

It was perhaps best stated by Dr. Barbieri of Brigham & Women's Department of Reproductive Biology - "The opportunities to perform ... research in reproductive medicine have never been greater" (Barbieri, Hill, 1996, p.690). The latter ellipses omitted just one word: "meaningful". I can find no meaning or justification for the unethical and criminal exposure of woman and potential and actual embryos/offspring to an agent such as lupron (leuprolide acetate) - a known teratogen, carrying the label 'Pregnancy Category X drug' by the Food and Drug Administration, all the while acknowledged as the most widely used 'adjunct to ovarian hyperstimulation'.

Jacques Cohen, who "has visited a hundred labs worldwide" (Talan, 1990, p.11) has noted that 'Lupron embryos were different. They grew faster, developed more rapidly. They were more fragile when frozen and less likely to survive thawing. Nobody knew why or what it meant for the long-term health of the woman or any resulting child." (Hotz, 1991, p.67). In a recent study of twenty-three women who conceived with lupron, there was a 43.5% incidence of adverse pregnancy outcome - "higher than previously reported in the literature." (Karande, et al., 1996, p.A27)

Women undergoing lupron treatment are not aware of this or other information. For example, women are not told by their fertility doctor or clinic that there is a National Lupron Victims Network (NLVN) - a germane fact. Why is that women who contact the NLVN (because of health problems), learn from the NLVN - and not their doctor - that symptom/disease X, Y, Z, is listed as an acknowledged adverse event to lupron by the FDA. Despite lupron being used for well over a decade, the occurrence of bone pain and bone loss has largely been ignored: Bone pain has been attributed to osteoporosis, yet osteoporosis is “the silent disease“ and as such is painless until fracture; and bone loss has been described as secondary to menopause and reversible, yet menopausal bone loss is not reversible.

Only recently has it been acknowledged that GnRH analogs (such as lupron) causes irreversible bone loss. After some 15 years of experimentation on women, in 1995 someone decided to do a bone biopsy and examine what the effects of lupron are on the bone: the conclusion was "severe disruption of the cancellous microstructure which are unlikely to be reversed". Women, who for example use lupron in four fertility cycles in one year - what is her cumulative bone loss... and is it being tracked? "(T)here are no published studies examining such recovery more than 1 year after GnRH agonist treatment is stopped."(Dawood, 1993; Abbott, personal communication, 1995). "It is increasingly apparent that [GnRH analogs] do not just affect the gonadal hormones, but are powerful modulators of autonomic neural function." (Mathias, 1995, p.1406). And lupron has been shown to "shut down blood flow to the frontal lobes of the brain" (Hale, 1994).

How would a fertility patient be aware of any of this information? RESOLVE, a national organization boasting tens of thousands of members, a corporate structure, and

ample seed-money from pharmaceutical companies ($247,930 from Serono alone in 1995, according to RESOLVE's Annual Report filed with the Attorney General's Office) is not sharing this type of data with its paying members. Yet, it only takes a grassroots effort to ferret out this information, and two women to distribute it on the internet free? That is pathetic, and telling.

Even armed with all the data, how would a fertility patient know that the Director of Fertility and Endocrinology at her clinic was a lead investigator and paid lecturer for the pharmaceutical manufacturer of lupron - as was the case in my experience at Brigham & Women's? But physicians and drug companies aren't the only gate keepers of information. The media withholds much information from the public as well.

Again, take for example Dr. Friedman, former Director of Brigham & Women's IVF Clinic: On May 1, 1996, the Federal Register published notification of Findings of Scientific Misconduct against Andrew Friedman, M.D. by the Department of Health and Human Services for some of his published, peer-reviewed, research using lupron. When a Boston fertility doctor has committed such egregious act, and admits to "alter(ing) and fabricat(ing) information in permanent patient medical records and notes by changing dates, changing and adding text, and fabricating notes for clinical visits that did not occur... admitt(ing) that he had falsified and fabricated approximately 80 percent of the data in research reports published" (Federal Register, p.19295) ... the women who have been given this drug in and around Boston and beyond have a right to know this information. Yet this information has not been publicized outside of the Federal Register and the NLVN.

A Boston paper did quote one local fertility clinic director as saying "women do not need to know about the lack of FDA approval for lupron's use in fertility treatment" (Kong, 1996) - which is a clarion call for regulating mandated informed consent right there. This same doctor's clinic generously provided lupron for a student biology dissertation on the effects of lupron on mouse oocyte maturation. Apparently, you give lupron away free if you study/experiment with it on mouse eggs - but when you study/experiment with lupron on women and human eggs, you charge exorbitant costs and intentionally withhold the information that it is not approved by the FDA.

Any attempts at internal quality assurance or self-regulation by this industry should be met with a critical eye. Scientific misconduct is no longer considered rare, with abundant instances that could be cited. The NIH recently charged a leading reproductive biologist with breaching the government ban on federal funding for human embryo research. Simply put, this industry has consistently displayed its untrustworthiness. Examples of conflicts of interests within this industry are ample. External regulation is clearly warranted. And with predictions that the populations of infertile women requiring fertility treatment will not rise, the industry is already established and poised for research in the area of genetic engineering.

The existence of human experimentation, in any and all of its forms within reprotech, has been promoted under the guise of science... yet scientific data on safety and efficacy

remains pending. Numerous experts, as detailed in my 1995 written testimony, have stated "clinical work goes on out there without peer review, based upon a few studies, based upon exchanges of information at meetings, without appropriate safeguards" (Human Embryo Research Panel, 1994). Procedures have been given the stamp of ethical approval by the industry and subsequently promoted as such by the media, without any public discourse, yet "there are remaining questions about how to assure that it is done in an ethically sound manner" (National Advisory Board on Ethics in Reproduction, 1996). In the meantime, patients take drugs that are not approved by the FDA for fertility treatment, procedures are sliced, diced, and tossed about like a salad; while patents for designer sperm, human embryo proteins, and artificial uteruses, etc., are pursued.

Procedures such as cloning by blastomy or separation, preimplantation genetic diagnosis, intracytoplasmic sperm injection (ICSI), sex selection, and posthumous reproduction are issues that society and legislators need to address. The historical propensity of man to pursue fame, power, and profit, logically implies that human cloning by nuclear transplantation of embryonic or adult cells is inevitable. Given it's likelihood, it can really only be said with certainty that no *report* of human cloning has yet to occur. Today, as reproductive endocrinologists advocate that a women with no ovaries has 'the right to procreate' using donor egg - will the call of the future be for a similar woman's 'right to replicate'?

The rate of twin births is up 30% since 1980, and likewise the rate of triplets has also increased; it is now estimated that between 60 to 80% of all neonatal intensive care units are due to fertility treatment - at a great financial cost to insurers and subsequently the public. The financial, social, and psychological burdens from the impaired function of these children is a serious problem that should be addressed. The daily procedures done at fertility clinics are well recognized as being research efforts, but this research is taking place is a nonresearch setting - and the consent process is therefore less structured.

The American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry (SART) will point to their annual collection and publication of data for ART procedures in the U.S. And they will state that in order for a clinic to be a member of SART, that clinic must participate in the data collection or they cannot maintain membership. But the 1994 results show this not to be the case. The number of participating clinics reporting data declined - thereby reflecting an inaccurate number of procedures performed by member clinics. Yet these nonreporting clinics continue to be members, excused this year due to this being the first year of a centralized collection of the database program.

Alteration of computerized data has been shown numerous times to take place, and take place with relative ease, therefore external collection of this data is indicated. Of interest is SART's acknowledgment that their new (experimental) data program has 'kinks' which need(s) refining -but what of the whirlwind of experimental procedures that women and oocytes and embryos are exposed to? These new 'procedures' are never debated in light of difficulties, but summarily promoted as the latest 'miracle treatment' ... despite the lack of safety and efficacy data.

According to the 1989 and 1990 Annual Reports of Abbott Labs, which manufactures lupron, "clinical trials for lupron's use in in vitro fertilization and fertility treatment are underway". The FDA will not provide consumers information, citing proprietary protection, and Abbott Labs will not provide consumers with any information on these trials. However, an internal letter from Abbott states "clinical studies for Lupron's use in treating infertility have been discontinued" (Abbott Labs, personal correspondence, 1995). Were these trials discontinued because of lack of safety, lack of efficacy, or both? Who is protecting the consumer?

Pergonal and Metrodin, introduced some thirty years ago, today remain with "methodologically sound research still lacking" on the long term effects on the health of the women and offspring (St. Clair, 1991). Although Serono, the manufacturer of Pergonal and Metrodin, intended to genetically engineer these drugs by 1996, historically they have been obtained from the urine of 100,000 donor women whose "health must be monitored closely" (Adelson, 1995). Yet the recipient or offspring of these drugs has no health monitoring. Clomid has been associated with testicular cancer, ectopic pregnancy, and ovarian cancer (Leikin, 1996) to name a few - and is chemically similar to DES [which has been associated with autoimmune diseases to name just one (Turiel, et al., 1988)].

In short, I believe that a moratorium on and an investigation of the use of lupron needs to be instituted immediately, and a registry developed for each and every prospective and retrospective consumer of fertility drugs and ART. The International Federation of Fertility Societies (IFFS) stated during the 1995 International Consensus on Assisted Procreation: "Doctors... must inform the patients [regarding the risk of ovarian cancer] and keep detailed files for further retrospective studies." In the United States, neither the government, research institutions, or drug companies have conducted long term studies on the effects of fertility drugs on the women or their offspring (Herman, 1994), and the long term health impacts of reprotech are unknown (Napolie, 1994). None of the current studies that are underway include *all* women undergoing ART at that designated study fertility clinic (Kaufman, personal communication, 1996), but rather selects (randomly ?) subjects - thereby creating potential bias.

Some form of external accountability of this industry is necessary, and House 2863 is a start. Without boundaries on these procedures, drugs/agents, and technologies, and the promise of profits - the potential for dangers with unthinkable proportions looms for the future. Issues such as the use of cadaveric oocytes and 'neo-mort' (brain dead) gestations need to be discussed. Research involving genetic engineering, use of sperm as gene delivery systems, parthenogenesis, organogenesis, chimeras, and cloning, to name just a few, will continue unabated. It is no longer the consumer that needs protection - it is society as well. While the world sang 'Hello Dolly', a more fitting name might have been 'Human Folly'.

There is much, much more information that I would be happy to share with the Committee. I have submitted written testimony each year since 1992 in support of this

bill, and I would urge Committee members to refer to this detailed information. Further information, further references and/or a complete bibliography can be provided upon request.

Respectfully submitted,

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