

To: Senate Health, Education, Labor and Pensions Committee
From: Lynne Millican, R.N., B.S.N., Paralegal
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Re: Human Embryo Cloning and Superovulation of Women, and specifically that:

A Drug Frequently Prescribed To Superovulate Women To Produce Multiple Eggs Has Been Known To Iatrogenically CAUSE The Very Diseases That Are Being Claimed As Those Diseases That Necessitate Cloning Research (Which Involves Superovulation Of Women)

Although I am a registered nurse, I am here before you today because of my personal experiences as a patient undergoing Superovulation during in vitro fertilization (IVF) attempts at several Boston IVF clinics in 1989 - 1991, and because of what I've learned in the last dozen years. Specifically, I would like to focus on the drug Lupron, which medical literature reports to be the most commonly prescribed gonadotrophin-releasing hormone analog (GnRHa) used in fertility treatment for a variety of reasons, including to maximize number of eggs produced. Most importantly, women who have taken Lupron have DEVELOPED diabetes, parkinson-like disorders, memory loss, arthritis, osteoporosis, immune problems, etc. Doesn't it seem preposterous to hype cloning research (which involves Superovulation with drugs such as Lupron) as probable cures for diabetes, Parkinson disease, Alzhiemers, etc. - when women who've received Lupron have now iatrogenically developed these and other diseases?

GnRHa drugs, which is the name for the classification of drugs to which Lupron belongs, act on the brain and are identified in the medical literature as resulting in a "hypophysectomy" -which by definition is "excision or destruction of the pituitary". Lupron's original patent is for ovulation induction, and Lupron is used to increase the number of eggs produced. But despite the fact that Lupron has never gained PDA approval for use in ovulation induction, IVF, or fertility treatment, and despite its listing as a hazardous drug according to National Institutes of Health (NIH) and Occupational Safety and Health Administration (OSHA), and despite its listing as a reproductive toxicant and a developmental toxicant.... nevertheless, and inexplicably, Lupron began to enjoy widespread use throughout fertility clinics in this country by the late 1980's. By 1990 fertility industry figures, GnRHa's were utilized in 97% of assisted reproductive technology cycles; and again - Lupron is the most frequently prescribed GnRHa in this country.

Is there relevance to the fact that for nearly a decade there has been a National Lupron Victims Network (www.lupronvictims.com)? Is it pertinent to this matter that the first long-term study of babies born after accidental exposure to GnRHa's revealed that 4 out of 6 babies has severe neurodevelopmental abnormalities? The conclusion of this study was that "[t]his observation ... justifies the need for long-term follow-up of more children previously exposed to GnRHa" (Lahat, 1999: Human Reproduction, 15(6): 1421). When Lupron is used in fertility treatment, upwards of 1 mg/day can be used for upwards of one month and to within days of egg retrieval - contrast a dose of 30 mg/month for the healthy young woman undergoing superovulation to the older man with prostate cancer who is prescribed 7.5 mg/month of Lupron.

Lupron is made by Takeda-Abbott Pharmaceuticals (TAP). In March 1990, TAP was cited by the FDA for unlawful promotion of Lupron for unapproved indications, including such off-label promotions at American Fertility Society symposiums. TAP received several Notices of Adverse Findings from the FDA, and these documents indicate that despite the FDA's warnings to TAP to cease its unlawful promotional activities, TAP continued its behavior nonetheless. More recently,

TAP has been criminally indicted for conspiring with physicians in a kickback scheme involving the prescription of Lupron and Medicare fraud, and TAP just paid the highest fine in history - \$875 million for its criminal activities.

As you deliberate the merit of banning all reproductive and therapeutic cloning, I hope to leave you thinking about 2 interconnected issues, which can be summed up in 2 words: the facts and the myths.

THE FACTS

In order to obtain the eggs and embryos needed for cloning research, millions of eggs will be recruited and extracted from women superovulated with superovulatory drugs. The maximum number of eggs I have seen in the published literature have been 91 eggs taken from one woman, with another report identifying 71 eggs retrieved from another woman. The risks to women from superovulation are already in existence today - but they have been diminished, suppressed and ignored. The prevalence of the risks to women remain to be quantified and qualified, since there has been no real long-term follow-up of the exposed women. But judging by the thousands of Lupron victims on the internet and within the National Lupron Victims Network ... I would ask - 'do you think there is a problem here, and what is the solution?'

The information women need to give informed consent to donate eggs for cloning research is the same information that the Fertility Industry has withheld from women undergoing superovulation for egg donation and IVF over the last 15 years. This is aptly evidenced by a Boston Globe interview with the director of the nation's highest volume fertility clinic, in which this doctor was quoted as saying that "women do not need to know about the lack of FDA approval" for Lupron in fertility treatment (8/4/96, p. 1/34). Incidentally, this clinic just entered into a deal to provide leftover embryos to Harvard University for stem cell research: "The [Howard Hughes Medical] Institute will give Boston IVF \$180,000 over two years to cover the cost of providing the embryos. It was unclear yesterday how much Harvard is to receive for extracting and preserving the stem cells." (Boston Globe, 8/24/01, p.1)

It is appalling that this debate has not centered on the adverse health effects of superovulation upon the woman, and especially the reports of adverse pregnancy and birth outcomes associated with treatment. Abbott annual reports for 1987, 1989, 1990, and 1992 indicate that "clinical studies are being conducted to determine the effectiveness of Lupron in IVF programs" and "clinical studies are underway to determine Lupron's effectiveness in the treatment of infertility". Note that these annual reports do not identify that the clinical trials were to determine Lupron's * safety*. These clinical trials have since been discontinued, and it is proprietary information whether these studies were discontinued because of safety reasons, efficacy reasons, both reasons, or other reasons. Does anyone think it is important to take a look at that secret data and see why the Lupron/IVF and Lupron/infertility clinical trials were discontinued, before more and more Lupron is used to superovulate women to make more and more eggs and embryos?

The first long-term follow-up of children who were accidentally exposed to GnRHa's was published in 1999, and revealed that 4 out of the 6 children studied had severe neurodevelopmental abnormalities (including seizure disorder). If that figure holds up in larger subsequent follow-up of children ... I would ask - 'do you think there is a problem here ... and what is the solution?' Archives of Ophthalmology, 2001, carried an article with a telling title: 'Ocular Anomalies Seen in Children Born After IVF'. On March 7, 2002 a new study was released indicating that the former 2-3% rate of major birth defects from IVF - a percentage always classified as consistent with the general

population - was, in fact, in error. This study now found a 9% rate of major birth defects among IVF offspring. Will the percentage of birth defects from IVF continue to climb?

Consider this statement by Robert Lee Hotz, in his 'Designs on Life', published in 1991: "Scientists ... noticed 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." According to the 1998 text, 'Drugs in Pregnancy and Lactation' (Briggs, Freeman, Yaffee), TAP communicated in 1992 that it was "maintaining a registry of inadvertent human exposure during pregnancy to leuprolide [Lupron] and currently has more than 100 such cases. No cases of congenital defects attributable to the drug have been reported ...". Yet, there have been accounts by women, including on the internet, reporting birth defects in babies conceived on or after stopping Lupron. Letters in response to the publication of the 1999 first long-term study of babies exposed to GnRHa's noted that there was concern among clinicians which extended also to the routine (advertent) exposure to GnRHa's prior to egg retrieval, as well as concerns involving inadvertent fetal exposure to GnRHa. Does TAP's secret registry contain information on healthy babies? Does anyone think it's important to compel TAP to disclose the data in that registry and take a look-see into the health status of these babies? If, as women have been reporting, there are problems with these children, wouldn't it be critical to ascertain that fact before proposing to embark upon creating allegedly curative stem cell lines from potentially compromised embryos?

Does Lupron have lasting effects on eggs? GnRHa's were found to have direct effect upon the rabbit follicle. In the fertility clinic setting, doctors tell patients Lupron is out of their system before a fertilized egg would be implanted - however there is ample indication in the published medical literature that effects continue after Lupron is stopped. Even FDA documents from Lupron's initial FDA approval for palliative treatment of prostate cancer revealed that in 1984 studies on rats "the severity of the lesions were greater in testes of rats sacrificed 7 days after cessation of treatment indicating that the effects continued after drug withdrawal." One study involving Lupron in fertility cycles reported that "some retrieved oocytes [eggs] exhibit incomplete nuclear and cytoplasmic maturation after the use of this agonist [Lupron]" (Racowsky, 1997). In a 1994 study of chickens using Lupron, 1 out of 25 of the hens died, and at the end of the 30-day experiment, all egg shells had thinned (Burke, Attia; Poultry Science, 73:122).

Without proper long-term follow-up study of the reports of adverse health outcomes to the superovulated women and without proper long-term follow-up of the adverse pregnancy and adverse birth outcomes in the babies conceived and exposed to drugs such as Lupron, how can you propel recklessly forward to create a massive demand for more superovulation of women for research eggs?

With a minimum estimated need for 5-8 million human eggs per year (maybe the need will be 20 million eggs - who knows?), the health consequences of this forecasted demand are enormous. Since the drugs and procedures are touted as "safe", egg donors will easily be lured by the \$2000 - \$5000 payment offered per 'donation'. According to msnbc.com, the same researcher who recruited egg donors for Advanced Cell Technology's human embryo cloning endeavors has a mobile embryology lab - "a conventional-looking recreation vehicle with a connected trailer. Inside is nearly all the gear needed for in-vitro fertilization." [<http://www.msnbc.com/news/161044.asp>]. Currently this mobile embryology lab is utilized to serve HIV + clients who wish IVF, but it is noted that such a traveling lab "could potentially provide location-flexible ART [assisted reproductive technologies] for underserved populations." [<http://www.reproduction.org/foundation/development.html>]. In the matter presently before Congress, there is discussion that if therapeutic cloning were allowed, it should be removed from the fertility clinic setting. Are traveling embryology vans, pulling trailers

and driving throughout the streets of the country, the answer? With the value of human eggs as research material increasing, imagine the obscene profit that an unscrupulous scientist could envision with a mobile IVF unit traveling the country, trafficking in underground egg sales.

Since the 1990's, there has been a major increase in the recruitment of egg donors, mostly under the auspices of "helping the infertile couple realize their dream of having a baby". I've brought a collection of these egg donor ads found from just within my community over the span of several years ... there are hundreds and hundreds and hundreds and hundreds of these egg donor want ads. It is interesting to note that while the industry was pitching a shortage of egg donors necessitating the recruitment of women to donate their eggs, the medical journals tell a different story. I randomly picked one journal supplement off the library shelf (Journal of Assisted Reproduction and Genetics, Vol. 12(3): 123S) and counted the number of eggs and embryos listed in just 20 pages. I counted 7,845 eggs and 266 embryos used in research within these mere 20 pages - from just one supplement, in just one journal, from just one month, in just one year. These "extra" eggs were classified in the literature as "surplus", "left-over", "discarded", "spare", "fertilized", "unfertilized", "suboptimal", "nonviable", "aspirated", "abnormal", etc. - and, as one reproductive endocrinologist was quoted as saying, the use of women's eggs by researchers is considered "sharing with the lab".

THE MYTHS

The message of research and biotech has resulted in the impression of hope, promise, cure, and benefit. My personal experience can be summed up by the words hype, myth, research fraud, conflicts of interest, and harm ... and all without any medicolegal advocacy for the injured victim. It is a myth that public safety is being protected by the FDA, evidenced by the fact that some 20 million people have taken drugs that have been recalled - drugs that were initially deemed 'safe and effective during study', only to later learn that data identifying serious problems, including deaths, had been suppressed.

In June, 2001, the editor of Lancet, stated that it was a "comforting but erroneous myth" that research involving drugs and devices still serves medicine. Time magazine's 4/14/02 cover story depicts yet another research debacle in which data identifying adverse side effects was kept secret - and only revealed by a whistleblower. Time also noted that there were more than 60 institutions that "failed to protect human subjects adequately." Other recent articles have identified the dramatic disparity in research results and reporting, depending on who is paying for the research - some researchers sign contracts which allow the pharmaceutical companies control over disclosure of bad data. Furthermore, large sums of money in the form of grants, stock options, company ownership, patents, consulting agreements, scientific agreements, speaking engagements, symposiums, trips, gifts, etc. (which are disclosed in less than half of 1%), have created an environment conducive to suppressing bad data and inducing outright fabrication of data. It would be nice to think that ethical behavior is the norm, but a review of recent news compels one to notice the increasingly rampant unethical machinations of research medicine.

To date there have been at least 5 renowned reproductive physicians/surgeons who have been found to have fabricated data: Dr. Andrew J. Friedman, a lead investigator for Lupron and director of Brigham & Women's IVF Program (where this writer was mandated to use Lupron), was found to have falsified and fabricated approximately 80% of the data in 2 published, and one unpublished, Lupron journal articles (Federal Register, 5/1/96, Vol.61(85): 19295). During the time that Friedman was director of Brigham & Women's IVF Program, the criteria for the administration

of Lupron with IVF changed from "Lupron is only used in certain diagnoses" to "Lupron is widely prescribed". Where is the data to justify such widespread application of a reproductive and developmental toxicant and hazardous drug? There has also been the 3 Drs. Nezhath brothers who were just expelled from Stanford for fabricating research - and the story of Dr. Asche is well known: Asche was overdosing women in superovulation to steal their eggs, selling them to researchers and other unsuspecting women, and reportedly often left his office with a briefcase stuffed with tens of thousands of dollars in cash.

The consumer who has been victimized by the fertility industry has no recourse, and with consumer protections woefully lacking in the fertility research enterprises today - whatever makes you think that protections are in place for additional cloning research. Complaints to the FDA about Lupron and lack of informed consent promulgate the mantra that the FDA has no supervision over the practice of medicine, which falls to state Boards of Medicine. State Boards of Medicine state a doctor can prescribe any drug they want off-label, and drugs are under the purview of the FDA. The Department of Public Health has no jurisdiction over fertility clinics, so refers one to the Board of Registration in Medicine. The FTC round-robins the consumer to the FDA. And there you go, round and round ... no informed consent, no advocacy, no accountability, no protection. The consumer is left stranded, while profits and abuses exponentiate.

The value of eggs and embryos for research was clearly identified in the National Institutes of Health's 1994 Human Embryo Research Panel hearings, wherein the profit from vaccines, hormones, proteins, stem cells, gene therapy, cell lines, organogenesis, ectogenesis, parthenogenesis, chimeras, patents, etc. was amply highlighted. There were a few voices of caution: i.e. Dr. Van Blerkom stated "The [medical] literature is the quality of the science in the field, and without offending anybody who might have a vested interest, I think the quality of science in this field has been awful, in this country at least, from the very beginning, awful because there are reports that get into journals based on handfuls of patients." And C. A. Tauer stated "I think the fact that the research enterprise has gone on out there without peer review and without the appropriate safeguards is something very bad that has happened."

It is very bad, indeed, that reproductive experimentation has been conducted without informed consent, and with 'treatment' using hazardous agents propagandized as safe and as science - but is neither. The Health, Education, and Welfare Department, in 1979, advised that a global study be undertaken to establish the safety of IVF, and although no such undertaking was done, it was proclaimed at the 1994 Human Embryo Research Panel Hearings that former concerns about IVF's safety had been abated. The March 2002 study indicating a 9% rate of major birth defects from IVF represents a substantial increase from former reports. Dolly, the cloned sheep, is lame. And there are thousands of Lupron victims.

Medical literature reports that the use of GnRHa's in IVF has caused neurological symptoms - migraines, numbness and tingling, paresthesia and weaknesses and sensory ataxia - "Transient cerebral ischemia is one possibility that may explain the symptoms ... a direct effect of potent GnRHa on the central nervous system resulting in neurological effects independent of the hypothalamic-pituitary-gonadal axis is possible ... [and] it is quite possible that mild cases with minor symptoms have escaped notice; thus, the occurrence of this type of complication may be far more common than we realize." (Ashkenazi, et al, *Fertility and Sterility*, 53(4):738). To quote one investigator: "GnRH analogs are not like any other medication currently available for treatment of disease. As we continue to learn more about these analogs' mechanisms of action, it is increasingly apparent that they do not just affect the gonadal [sex] hormones, but are powerful modulators of

autonomic neural function." (Mathias, 1995)

What really is the safety of IVF procedures (such as co-culture of human embryos with animal sera - what about prions and viruses?) and the drugs, especially Lupron — and why have women been so exploited? Women have been reporting on the internet, and in written testimonies submitted to the MA. Health Care Committee, that they have been forced, manipulated, badgered, and threatened into using Lupron. This writer was told by a physician at Brigham & Women's that "if you want IVF, you must take Lupron". Years later it would be learned that this treating physician, a co-author in one of Friedman's retracted Lupron journal article, has (along with many, many, many other physicians) received TAP funds to study Lupron.

A current online investigation of Lupron (www.redflagsweekly.com), as well as the National Lupron Victims Network, and others, have challenged TAP to produce data and to answer questions — but there has been no response from TAP. For further information on the adverse effects experienced by women taking Lupron, please see AOL and Delphi Forum message boards, under 'Lupron'.

The nation's highest volume clinic participated in a 1988 study which attempted to look at the long-term health consequences of assisted reproductive technologies and drugs on the women and offspring, however the study made no mention of GnRHa's and concluded with inconclusive results and too few study subjects. Of note, this writer, who has developed multiple health problems, was a patient during this study but was never asked to participate in this study. Significantly, another patient who did participate in this study, was dropped from the study following her hospitalization for severe ovarian hyperstimulation syndrome during fertility treatment - in which she went into kidney failure and nearly died.

Falsified and suppressed data (which can set, alter, and impact standards of care), along with conflicts of interest and abuses of human subjects in research endeavors are poisoning medicine systemically. Shouldn't you begin to address the forces that result in profit via dictation of data and spin and to hell with 'first do no harm'? And should you really open the reproductive research doors wider to the inevitable abuses in human embryo cloning research? The criminal penalties of jail and fines of at least \$1 million that President Bush has asked for should be applied not just to the use or importation of cloning technology, but rather should be applied like a heavy wet blanket over every research discipline in medicine in attempts to quash this destructive slow burn.

It is noteworthy to add that in another hearing taking place today on "current safeguards concerning the protection of human subjects in research" (which has been twice postponed), no public official is slated to testify. To quote the Alliance for Human Research Protection's response. "Public trust in research will surely not be improved if public officials are believed to be hiding the facts and limiting their appearances within the fraternity circuits."

This writer became involved in drafting a bill in MA. (H 3308) which would mandate informed consent of the drugs and procedures, among other provisions, within the fertility clinic setting - and submitted oral and written testimony in support of its passage 1992-1999. Today the bill continues stalled, in study, and opposed yearly by vested interests. In 1987, MA. passed legislation that mandated insurance coverage of fertility treatment - effectively promoting and sponsoring further treatment (experimentation) with hazardous substances without informed consent. This legislation, along with similar legislation throughout the country, has been the result of effective lobbying from RESOLVE, Inc. (the astroturf organization that alleges to educate,

support, and advocate for the infertile). RESOLVE (which "supports the use of Lupron for fertility treatment"), according to its annual reports, has received thousands of dollars from TAP as well as from other fertility drug manufacturers - despite RESOLVE'S statement to the contrary in the Boston TAB (3/3/00) alleging that RESOLVE "does not receive any funding from drug companies". (For further examples of pharmaceutical puppet groups, see New York Times 'Drug Industry Has Ties to Groups With Many Different Voices', 10/5/00)

When legislation does not protect consumers, and Institutional Review Boards (IRB's) are "serv[ing] an exemplary role as a universal vehicle to develop technology" - who protects the consumer? Please note in the 1989 101st Congressional hearings prompted by Rep. Wyden (as a result of false and misleading advertising of fertility clinic IVF success rates) that of the 100+ clinics who reported data, practically none of those clinics utilized an IRB (see Publication Serial No. 101-5). A significant number of these reporting fertility clinics identified that they had "switched" and/or "began to use" Lupron in their superovulation regimes - without IRB review. (One reporting clinic provided testimony identifying Lupron as "a costly, experimental medicine ..."). In this writer's situation, the healthcare providers simply changed definitions: they state that IRB review was unnecessary because Lupron was not being used in "research", but rather was being used in a "therapeutic" manner.

In closing, for the above stated reasons, I would urge the Committee to ban reproductive and therapeutic cloning, as well as to begin investigation into the prevalence of negative sequelae to women and children exposed to Lupron.

Respectfully submitted,

Lynne Millican