On May 11, 2001, during the Boston US Attorneys Office's investigation into lupron's fraudulent marketing scheme, the below draft document (researched and written by Lynne Millican) was presented during a scheduled meeting between US Attorney Michael Loucks and Lynne Millican. This draft document had been an ongoing attempt on my part to make some semblance out of the lupron chaos, and it was no where near final form when this meeting arose (but it was presented anyway). This document was subsequently provided by the US Attorney's Office to the FDA's Office of Criminal Investigation, and ultimately nothing developed from either Offices review of this information. The bibliography to this document was not available in 2001, but I am attaching it now fyi.

REQUEST and RATIONALE FOR THE U.S. ATTORNEYS' INVESTIGATION [INTO LUPRON'S FRAUDULENT MARKETING SCHEME] TO ALSO INVESTIGATE THE FRAUDULENT SCIENCE AND HUMAN RIGHTS VIOLATIONS INVOLVED WITH LUPRON - INCLUDING SUPPORTIVE DATA JUSTIFYING PURSUIT OF REMUNERATION FOR 100% OF ALL COSTS OF ALL LUPRON.

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INTRODUCTION

As a result of the U.S. Attorney's Offices' investigation into the fraudulent billing scheme involving Lupron (leuprolide acetate), Takeda Abbott Pharmaceutical (TAP), and urologists, recent newspaper reports state that TAP 'may pay upwards of $800 million in fines'. The U.S. Attorneys' investigation appears not to have examined the much larger and, albeit, more complex issues involving lupron: for example, (1) the fraudulent schemes, misrepresentations, and marketing of the drug/agent, (2) the suppressed hazards of lupron, (3) the ab/use of lupron via industry-sponsored off-label gynecological promotion, (4) the mystifyingly rapid approvals of poorly controlled studies (during and FDA era of 'lengthy and tardy approvals'), (5) the chronic health sequelae post-lupron in *thousands* of women (as well as men and children), (6) the lack of medico-legal advocacy for lupron victims, and (7) the conflicts of interest found imbedded throughout.

While the U.S. Attorneys' investigation has resulted in fines related to the billing of free samples and the fraudulent overbilling of the allowable expense – in fact, the investigation should examine the fraudulent science and marketing which *created* the "allowable" expense; and determine whether Medicare and private insurers (and subjects) should be reimbursed for ***all of the cost*** of lupron. **This** is the stuff that demands prosecutorial action and should command remuneration ***in the many billions of dollars.*** The following incomplete tally of lupron annual sales for just six (6) of its sixteen (16) years on the market illustrates the magnitude of money involved: year 2000 sales "approximate 800 million dollars (Genta, 2000), 1998 sales of ">500 million" (Mosby, 1998), 1995 worldwide sales of 395 million (D'Amico, 1996), 1996 "forecasted revenues" were for 215 million (Anonymous, 1996), 1994 revenue "up from 18th to number 5 in closed-wall HMO's" (Anonymous, 1995) with sales of 270 million (Green & Cookson, 1995), and 1993 "Clinic Dollar Volume of 110 million in 1993" (Anonymous, 1995). These partial, lowball figures result in a sum of over 2.29 billion dollars alone.

Former U.S. Attorney Breckinridge Willcox championed for review and prosecution of scientific fraud with 'an eye toward prosecution', noting in the early 1990's that "at least 20 individual medical personnel – virtually all physicians – have been prosecuted for felony violations involving the preparation or dissemination of false data … during the clinical trials of investigational new drugs. Of the 20, 16 were found guilty. (Accountability in Research, 1992). More recently, headlines have focused on the multiple abuses of human subjects at the hands of vested researchers (Wilson & Health, 2001), which has prompted increased scrutiny (Duff, 2001) and proposed fines (LaSalandra, 2000), and focused some attention on the prevalence and perils of conflicts of interests.

What is lupron (leuprolide acetate)? Lupron is variously identified in the scientific literature as: a gonadotrophin-releasing hormone (GnRH) analog or agonist (GnRHa); a peptide; a synthetic version of the GnRH produced in the pig's brain but with two substitutions, one of which is an *un*natural amino acid; a chemotherapy

and an antineoplastic hormone; as well as used as a "probe" and "experimental model". Is lupron associated with fraudulent data and fraudulent representations – the results of which were influenced by corporate coercion and/or reward? Have TAP, investigators, physicians, and the FDA knowingly harmed babies, as well as men, women, and children? Did TAP, investigators, physicians, and the FDA withhold information concerning the risks of lupron? Have c/overt monies by TAP to gynecologists and reproductive endocrinologists (RE), and "patient support groups" (and urologists) caused the prescription of lupron? Do all of these situations continue to operate today?

As will be discussed below, the medical, pharmaceutical, and governmental literature pertaining to lupron contains ample evidence of problematic data for which the further scrutiny of subpoena power is warranted. With all due respect, if the U.S. Attorneys' Office received information that $3 worth of cheap toxic herbicides were combined by an evil schiester and sold as a 'curative tonic' for $400 to the unwitting public, who suffered bodily harm and death – would a multi-state investigation focus on the cost, the financial damange, the pecuniary harm, the profiteering, and the inflationary scheme of 'a curative tonic'?

One prominent physician has already admitted to falsifying and fabricating data related to lupron (Federal Register). There are numerous medical malpractice and product liability lawsuits resulting from serious adverse advents following the use of lupron (i.e. strokes, seizures [i.e., Kuha]), yet there are no published case reports in the medical literature describing these adverse events. As a leading gynecologist has stated: "Inclusion of patients with a poor response to GnRH-a therapy has not always occurred in outcome analysis in the published literature." (Redwine, 1994). The failure to report accurate data and/or negative results, failure to report adverse events, failure to publish negative results and adverse events, and the suppression of observations, case reports, and study findings are all forms of scientific misconduct and are individually as egregious as falsification and fabrication of data.

Since all subsequent lupron approvals were predicated on the initial 1985 approval of the daily lupron injections for the indication of *palliative treatment* of prostate cancer [management only of symptoms and not curative], an understanding of lupron's initial approval for daily administration is necessary. Highlights of the methodological flaws and investigator biases revealed within both the initial lupron prostate cancer studies as well as the initial studies for lupron's approval in females, for the indication of endometriosis, will be discussed below.

Briefly, the original patent that was filed for lupron was for ovulation induction (Patent # 4,005,063), but no FDA approval has ever been gained for the indication of ovulation induction or fertility treatment. The first indication for which FDA approval was granted, palliative treatment for prostate cancer, occurred in 1985. Promoted and rapidly approved as an "important" drug for older men terminally ill with cancer who had few alternatives, lupron gained lightning-speed FDA approval despite, among others, identified biases amongst investigators and unacceptable

bioavailability studies; and through granting of deferral of bioavailability studies and the withholding of tabulated adverse events. With this approval, the use of lupron in women quickly exponentiated and lupron became broadly applied to health young women for a variety of benign gynecological indications. Lupron gained extremely quick approval for '**pain** management' in women with endometriosis in 1990, following problematic studies (with identified investigator biases and study flaws) in less than 200 women who were **allowed to use narcotics while taking lupron.** Was lupron approved because it demonstrated safety and efficacy?

I.

II. WAS LUPRON'S INITIAL FDA APPROVAL BASED UPON SAFETY AND EFFICACY?

A – MALES: Initial Approval for Indication of Palliative Treatment of Prostate Cancer

1) Clinical trials involved a comparison of lupron to diethylstilbesterol (DES), and TAP claimed and marketed lupron as having **less** side-effects than DES – specifically less cardiovascular adverse events. Yet, in the 1984 FDA reviews leading to lupron's initial approval, the cardiovascular profile of lupron and DES patients was identified as not comparable, since 25% of the DES patients had pre-existing cardiovascular problems verses 15% of the lupron patients. And more serious imbalance is noted in the FDA's June 25, 1984 and October 5, 1984 FDA 'Statistical Review and Evaluation' of the trial data, wherein the FDA reviewer identifies "the willingness of investigators to switch DES patients to lupron" rather than vice versa.

The claim that lupron provided less side effects and a safer cardiovascular profile in comparison to DES were major identified selling points of lupron, and identified as such in Abbott's Annual Report of 1984. In these 1984 FDA statistical reviews, the "Conclusions to be Conveyed to the Sponsor" were that the early DES dropouts "could be due to adverse reactions ***and/or*** physicians' *willingness* to let DES patients crossover or drop out sooner than necessary", identifying that "[t]his practice could also *affect the conclusion* …" (emphasis added). The reviewer noted that **33 of the 36** lupron patients that crossed over to DES did so because of disease **progression** *versus 14 of the 28* DES patients that crossed over to lupron due to disease progression. "Most of the other half of the crossovers in the DES group did so because of adverse reactions. The willingness of the investigators to switch DES patients to lupron in the early stage of the treatment apparently influenced this result." (NDA, 1985)

Was lupron shown to have less cardiovascular side effects than DES, a claim that was critical to its approval? The Acting Group Leader of Oncology Drugs provided a Medical Officer Consultation on lupron's New Drug Application (NDA) in July 1984, and commented on the "biase[d] outcome in favor of L[euprolide]" and the "soft efficacy parameters" used, "particularly as measured in this NDA". Of note is the following statement within this Leader's review:

"Since DES has not been shown to improve survival, the rationale for its use is relief of symptoms. If Leuprolide [L] is worse in this regard, this is important. It appears L may be safer regarding cardiovascular adverse events, but L causes an initial temporary flare up of tumor and tumor related symptoms in perhaps 10% of patients. Exact percentage of tumor flare can not be determined from the submitted reports because some patients may have had ***more than one category*** of flare-up. This safety data can not be factored into the approval decision until the efficacy is adequately defined. In cancer drug NDA's review of the case report forms often shows the ***reported results are incorrect or not reliable.*** Unfortunately I can not use the micro fiche. We should request applicant to submit the case report forms (or at least some of them) in hard copy. Recommendations: 1) This NDA is ***not approvable because it lacks well controlled studies*** demonstrating substantial evidence of efficacy. … 6) The application mentions "isolated cases of short term worsening" soon after start of Leuprolide. The case report form number for each of these patients should be identified. 7) hard copy of case report forms should be submitted." (Johnson; NDA 1985). [emphasis added]

On December 24, 1984 Abbott/TAP presented to the FDA Medical Reviewer's office TAP/Abbott's "present label" Clinical Safety Update (clinical trial data updates, i.e., adverse reactions) along with a request by TAP/Abbott to the FDA to withhold the updated adverse reactions from lupron's initial label. The Medical Officer providing this review of lupron, Dr. Schaffenburg, concluded in favor of TAP: "The sponsor's proposal not to change these [updated adverse reactions] figures for the present label are acceptable." It is noted in this review that changing these numbers to *include* these *up*dated numbers "mak[es] them, of course, larger" yet these changes are claimed as "not significantly chang[ing] the differences between the *Lur*pon [sic] and DES groups." (emphasis added) This Medical Officer concludes that Drug Experience Reports "(1639s) … will be tabulated at a later date to save time", and recommends to "Approve label and promotional materials."

Lupron's initial label identified that "less than "3%" of pts (3 subjects) reported cardiac arrythmias and myocardial infarction. However, subsequent labels identify that "ECG changes/ischemia" were reported for 19% of the lupron patients (19 subjects) versus 21% of DES patients (21 subjects) – representing ***a nearly identical cardiovascular risk.*** In addition, the initial label revealed **no reports** of the adverse events cardiac murmur or high blood pressure, and reported just one (1) report of pulmonary emboli. However, subsequent labels identify that **there were reports** identifying that 3% of lupron patients experienced cardiac murmurs (vs. 8% DES), and 8% of lupron patients developed high blood pressure (vs. 5% DES), and that "less than 5%" of lupron patients developed pulmonary emboli. Is it "acceptable" to grant TAP's request to withhold the adverse events that were reported to have occurred in the lupron clinical trials from disclosure in the initial approval label – figures which, when tabulated, cast serious doubt upon lupron's alleged "improved cardiovascular risk profile in comparison to DES"?

In the April 1, 1985 Review of Final Printed Label by FDA Medical Officer, Dr. C.A. Schaffenburg, it is stated:

"As fully discussed with the Oncology Advisory Committee … the following possible modifications [were proposed]: 1) Indications and Usages: After the last sentence, add 'Present findings indicate that DES may present advantages for the treatment of pain due to bone metastases'. … Bioavailability Requirements: I don't know what the deficiencies are in this area, but it would seem to me that evidence of a full castration effect should be enough to prove the drug's bioavailability.

Recommendations: The label should be approved as is with the addition only of the sentence as above under Indications and Usage." (Schaffenburg, 1985).

Of note is the fact that this Medical Officer co-authored a book a year *prior* to lupron's approval, wherein the collaboration between industry, academia, and the FDA is identified, and it is stated "The FDA was privileged to have been involved early in the developmental process of this class of drugs [GnRHa's]" (Gueriguian, 1984). In another book written on GnRH analogs in 1981, Dr. Schaffenburg wrote a chapter and was a discussant on "Safety and Secondary Pharmacologic Studies of LHRH [GnRH] Analogs". In this chapter, Dr. Schaffenburg discusses "concerns about [GnRHa's] persistent effects after withdrawal", noting "unfortunately, a paucity of information … particularly in humans", and identifies "our ignorance of the pulsing LH rhythm in [the brain of] normally menstruating women." The suggestion for "investigators to undertake studies' is concluded with the following statement: "The safety of these substances, after long-range and wide application, remains a problem to be solved gradually and with caution. (Schaffenburg, 1981).

The following 2 quotes illustrate the concerns raised by lupron's cardiovascular and cerebrovascular effects following its approval:

"… Ischemia [cellular death due to lack of blood supply] resulting from vascular changes may also contribute to the degenerative changes in leiomyomas [fibroids]. … The florid and rapid development of vascular inflammation, fibrinoid deposits, and thrombosis after leuprolide acetate therapy suggest an immune-mediated process. Acute vascular changes are rarely seen in non-leuprolide-treated leiomyomas, even in those showing degenerative changes such as an infarction, suggesting a much more protracted course. Whatever the exact mechanism, ***these observations are significant and worrisome if such changes affect other organs.*** Acute myocardial infarction has been reported in a 43 year old woman who received one dose of leuprolide acetate depot … leuprolide acetate has also been linked to other vascular effects, including intraocular venous occlusions and hemorrhage." (Mesia, Gahr, 1997) (emphasis added)

"… Transcient cerebral ischemia (TCI) is one possibility that may explain the symptoms of numbness, headache, paresthesia and paresis [during GnRHa use in IVF]. … This could explain the various neurological symptoms occurring by means of vasospasm of intracerebral blood vessels. Furthermore, a direct effect of potent GnRH-analog on the central nervous system resulting in neurological effects independent of the hypothalamic-pituitary-gonadal axis is possible … it is quite possible that mild cases have escaped notice; thus, the occurrence of this type of complication may be far more common than we realize." (Ashkenazi, 1990)

TAP/Abbott claimed to the FDA (and continues to reiterate today through physicians and in its product literature) that certain adverse events are "physiological responses to lupron", yet it is known that "[s]imply classifying a response as expected pharmacology does not satisfy the safety evaluation obligation of the toxicologist". (Enna, 1998)

2) During the FDA reviews of the initial clinical trials of lupron, a bioavailability study was submitted by Keith G. Tolman, M.D., University of Utah. Keith G. Tolman M.D. is listed at the University of Utah's website as a consultant for TAP and Abbott, and the University's Center for Clinical Studies has conducted studies sponsored by Takeda. The FDA found this bioavailability study to be "unacceptable". It is not clear from the documents released by the FDA whether TAP subsequently requested a deferral for bioavailability study, however FDA memos identify that "deferral of the bioavailability requirements is recommended

under CFR 320.22(5)(e) because leuprolide is an *important* oncologic drug" (Skelly, 1984) (emphasis added). A December 1984 FDA Pharmacokinetics Evaluation Branch memo states that "after a discussion with [FDA's] Dr. Sobel … [t]his deferral is granted on the basis of CFR 320.22e because Leuprolide is classified as a 1A drug and it represent [sic] a significant contribution to the area of Oncology." (Frank, 1984 11/2).

However, inexplicably, lupron is NOT classified by the FDA as a Type "1A" drug, but rather lupron is classified by the FDA as a Type "1B" drug (FDC Reports, 2/23/87), and the *important* distinction will be addressed below. The Code of Federal Regulations (320.22) state that the FDA may defer bioavailability requirements if:

(5): The drug product contains the same active drug ingredient or therapeutic moiety and is in the same strength and dosage form as a drug product that is the subject of an approved full or abbreviated new drug application, and both drug products meet an appropriate in vitro test that has been approved by the Food and Drug Administration.

(e): The Food and Drug Administration, for good cause, may defer or waive a requirement for the submission of evidence of in vivo bioavailability if deferral or waiver is compatible with the protection of the public health.

Therefore, it is baffling how the FDA could proffer or accept this criteria in light of (1) the thousands of lupron victims within the National Lupron Victims Network alone, and (2) the FDA's own classification of lupron as being a Type "1B" category 'drug' (FDC Reports, May 27, 1985). The following are the pertinent FDA's definition for the FDA's drug classification system:

"Type 1: ***New*** molecular entity: An active ingredient that has **never** been marketed in this country. … A drug for which the active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) has **not been *previously* approved** or marketed in the United States for use in a drug product, either as a single ingredient or as part of a combination product or as part of a mixture of stereoisomers."

"Type B: Modest therapeutic gain, i.e., drug has a modest, but real, potential advantage over other available marketed drugs, for example, greater patient convienence, elimination of an annoying but not dangerous adverse reaction, potential for large cost reduction, less frequent dosage schedule, useful in specific subpopulation of those with disease (e.g., those allergic to other available drugs), etc." (FDA Consumer, 1988) [emphasis added]

Note that while lupron is described as an "important" oncologic drug in the FDA memo favoring a deferral of bioavailability studies, Type B drugs *actually* provide only a "modest" gain. Type "A" drugs, however, are designated by the FDA as those drugs that provide an "important" therapeutic gain. Why do FDA memos explain away the need for *minimal* testing prior to FDA approval based upon lupron being a Type "1A" drug – when, in fact, the FDA's classification of and for lupron is in a lesser, 'not so important', "modest gain" category? Moreover, lupron was a '***new*** molecular entity', and therefore *was*, in fact, **new;** and when approved by the FDA in 1985, lupron became the ***first*** GnRH analog to be approved in the United States. Therefore, how did lupron come to qualify for a deferral based upon CFR 320.22(5)(e)?

Two years after lupron's approval, in the 1987 Proceedings of Conference, entitled 'Biotechnologically Derived Medical Agents: The Scientific Basis of Their Regulation', Dr. Sobel and others from the FDA discussed proteins with a "chemically modified N-terminus" (i.e. lupron) and wrote in regards to the purity of the final product that:

" … impurities are derived from or structurally related to the active drug substance. … These contaminants often have reduced biological activity, and may be antigenic. Eliminating all of these impurities to ppm level is costly and impractical. It is common for a purified drug to contain up to 3 – 5% of these impurities all together." (Chiu, 1987)

And in the same 1987 Proceedings, Alex Jordan, who provided the FDA toxicology review for lupron's initial approval in 1985, wrote:

"… As was stated above, certain synthetic peptides or their analogues may have untoward effects when injected systemically. Whenever one gives larger than physiological doses or introduces even a human peptide into an 'unnatural' body compartment, there is a chance that nonphysiological receptors may be activated." (Jordan, 1987, p. 57)

3) The simplest way to answer the question of whether lupron was approved based upon demonstration of safety is through citation of the 1998 'Current Protocols in Pharmacology':

"It must be recognized that rDNA [recombinant DNA] products containing amino acid sequences purposefully altered to increase potency, duration of action, solubility, etc., relative to the native protein will require a more comprehensive toxicology profile. This situation was apparent with the [1994] FDA recommendations for nonclinical safety studies with analogs of GnRH. … GnRH analogs had originally been developed for the treatment of prostate cancer, and were accordingly subjected to a less rigorous toxicology program than the standard. The current focus with these agents on less serious conditions such as fertility disorders, and the modifications in the structure of the native compound have made it necessary to examine them in a more traditional way (Table 10.3.11)". The latter table identifies the 'acute toxicology, subchronic and chronic toxicology, genetic toxicology, carcinogenicity, and special studies, including antigenicity studies' that were recommended by the FDA. (Enna, 1998)

These 1994 recommendations "only pertain to GnRH analogues and should not be considered as guidance for the testing of any other drug classes". The authors of these 1994 FDA recommendations also participated as FDA officers in either the review of lupron's data for the approvals of prostate cancer and/or endometriosis. In the 1994 FDA recommendations, in which it is acknowledged that "unpublished work" from TAP Pharmaceuticals was used, Alexander Jordan writes:

"At necropsy, special attention should be given to the anterior pituitary, adrenal, pancreas, testes, and ovaries, since an increased incidence of neoplasia in these organs has been associated with GnRH agonist treatment. … Following restoration of fertility after cessation of treatment, the possibility exists that some germ cells may have been permanently affected by drug treatment. It is therefore important to investigate the effects on fetal morphology (teratogenicity) and on postnatal development of the offspring." (Raheja, Jordan, 1994).

The studies on lupron's pharmacological and toxicological data reviewed by FDA's Alexander Jordan in March 1984 were studies that were "approved and submitted by J.W. Kesterson, Abbott Labs". James W. Kesterson is a co-inventor on several patents involving lupron (i.e., 4,851,211; 4,897,256), the first being filed the year after lupron's initial FDA approval. In the 1984 FDA documents detailing the toxicological review of these studies, Alexander Jordan writes:

"[Rat] testes showed various degrees of testicular degeneration which were detectable within 2 days. 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*** [emphasis added]. … There are other inconsistent effects of Leuprolide in the various toxicology studies but potentially the most serious effect of

Leuprolide, inmy view, is its effect on spinal column bone marrow. This increased fat deposition and subsequent hypocellularity was explained as a physiological response to the drug. The sponsor states that there was no alteration in the type or number of hematopoietic cells in the peripheral circulation. … The only other consistent adverse effect of Leuprolide was the increased erythrocyte, hematocrit and hemoglobin values in female rats. … Leuprolide administration produced a dose-related increase in pituitary adenomas in rats. There was approximately a two-fold increase in pituitary adenomas in both male and females at the low dose (600 ug/kg) with no no-effect dose demonstrated. The sponsor's explanation is that Leuprolide acts as a constant stimulator of gonadotroph function resulting in hyperplasia and ultimately, production of tumors. However, in the method and dose employed, Leuprolide does not stimulate but actually inhibits pituitary gonadotropin synthesis and secretion. Nevertheless, the possibility exists that Leuprolide at the same time may be acting as a stimulator of other cell functions which could result in pituitary adenomas. There is no obvious reason to suggest that the same process could not occur in humans. … Other tumors which were significantly increased by Lupron treatment included pancreatic islet-cell adenoma and testicular interstitial-cell adenoma. [end of discussion redacted]" (Jordan, March 1984)

4) In April 1984, another FDA reviewer performing a 'Statistical Review and Evaluation' of these studies noted that once treatment failed to curb disease progression or when adverse reactions developed, "[a]ccording to the sponsor, there were indications that the investigators were less reluctant to take a patient off treatment with DES than leuprolide." This FDA reviewer identified that "[i]t should be commented that Subjective Response did not always agree with the Objective Response in [the M81-017] study. In about 10% of the patients the Subjective Response rating was in the opposite direction from the Objective Response."

Documents released by the FDA of it's reviews of the 2 human studies involved with the prostatic cancer approvals (Study M81-107 and M80-036) clearly identify biases amongst the study investigators – investigator/physicians who were "supported in part by TAP Pharmaceuticals/Abbott Laboratories" - and at least two of these investigators have numerous patents related to lupron. The FDA reviews also clearly identify methodological weaknesses and statistical flaws, as well as clearly state that efficacy and safety had not been demonstrated. What is not clear is *why* lupron was approved in the first place.

5) After less than sixteen (16) months under FDA review (FDC, 1987), lupron was approved – not by the Division of Drugs, or by the Division of Oncologic Drugs – but by the FDA's Office of **Biologics**, on April 9, 1985. (Lupron's label did *not* contain, among others, the patient advisory that "DES may present advantages for the treatment of pain due to bone metastases".) This initial approval of the daily lupron injections, for the palliative treatment of terminal cancer, thus allowed the prescription of lupron for *any and all* indications, many of which remain unapproved by the FDA some 15 years later (i.e. ovulation induction, fertility treatment, breast cancer, contraception). It would be a solid decade after this initial lupron approval before changes in FDA policy were instituted to reduce the 'infamously tardy and protracted FDA dug-approval process'.

6) By the summer of 1989, prior to ***any*** approved female used for lupron, Senator Kennedy had written to Abbott/TAP asking about advertising, marketing and promotional activities, and their "possible effects on the prescribing practices of physicians", as well as requesting specific information on any gifts, reminder items, and

dispensed samples of products, including the number of dispensed product and the method of delivery (Conlan, 1990). Following congressional hearings on this industry-wide problem:

"Kennedy was angry that individual drug firms chose not to appear: "Less than a week after receiving a warning from FDA against symposia on unapproved uses for Lupron, why did Abbott sponsor an all-expenses-paid symposium at Disney World for doctors and spouses devoted entirely to unapproved uses?" Abbott did not respond specifically to the Lupron charge; in a statement issued after the hearing, it said marketing activities "are planned and executed to maintain the high ethical and scientific standards required to assist physicians with the practice of good medicine." (Anonymous, 1991)

It is clear that lupron was quickly facilitated through the approval process with minimal scrutiny, due to its professed 'importance' for terminally ill men – all the while an orchestrated and aggressive attempt was underway for the broad application in women. Before *any* female approval was granted, FDC Reports identified that "Lupron is 'already being popularized'" for gynecological indications (FDC, 10/30/89). But even though the earliest studies of lupron centered on ovulation induction, it was approval for prostate cancer that was gained – and then the pharmaceutical literature headlines proclaimed "Cancer drug reborn as fertility treatment" (Starr, 1988). Yet neither the daily nor depot lupron has ever been able to gain FDA approval for the indication of fertility treatment, while both continue to enjoy widespread use for this off-label use.

<u>B – FEMALES: Initial Approval for Indication of Pain Management of Endometriosis.</u>

1) Early studies of continued use of lupron on female animals universally documents atrophy of the ovaries – and one recent lupron rat study showed "a significant decrease in ovarian weight (74%) with the resulting decrease in the number of cells per ovary (1,050,000 versus 75,000) (Guerrero, Stein, Asch, 1993). And the *initial* use of lupron in women undergoing fertility treatment often results in ovarian enlargement – including sever ovarian hyperstimulation syndrome induced by the sole use of lupron alone (Barbieri, Yeh, Hampton). Yet, curiously, neither such association (adverse event) was found during the clinical trials of lupron for endometriosis. In these trials (M86-031 and M86-039), no MRI monitoring data of ovaries (or uterus) is reported. The two trials, respectively, concluded that:

- "there was no difference in the response of lupron treated and placebo treated patients as far as examination of left or right ovarian enlargement/decrease in size is concerned", and
- "there was no difference in the response of lupron treated and danazol treated patients as far as examination of left or right ovarian enlargement/decrease in size is concerned." (NDA).

Yet Florence Comite (an investigator in both of the lupron endometriosis [and the fibroid] TAP-sponsored clinical trials, as well as an NIH investigator for GnRHa's), co-authored a separate study which details lupron's "significant effects upon the ovary". This separate study was published in May 1990, a time when the FDA was still evaluating the data submitted for the M86-031 and M86-039 endometriosis clinical trials. In this separate study, it is reported that:

"significant changes were noted in the pelvis in women who were receiving the GnRH analog [lupron]. After 6 months of therapy, the identifiability of the ovaries [by MRI] was significantly poorer. … 21 of the 43 endometriomas [present before lupron treatment] were still present. Of these 21 lesions [] two remained unchanged, and three had increased in size by 9.1 – 66.7%. One new 2.0 cm endometrioma was

seen after treatment. … Of the 13 women with endometrosis visible at MR imagine, [] two worsened. … The effects of analog therapy on the normal uterus and the ovaries were statistically significant … the experienced radiologist should expect to be able to identify the ovaries on only 70% of images." (Zawin, 1990)

The data from this study do not appear to jibe with the data submitted to, and simultaneously under review by, the FDA.

2) There are reports of women who observed suppression of adverse events during the endometriosis clinical trials. To quote one woman: "I told my doctor 7 symptoms [adverse events], and he wrote down one." (personal communication)

3) There were no formal dose ranging studies performed to arrive at the dose administered to female subjects – the dosage of 3.75 mg was based, in part, on data submitted by Dr. Andrew Friedman relative to lupron's use in older women with fibroids.

4) According to FDA documents, TAP/Abbott submitted its application for lupron's use for treatment of endometriosis in August 1989 – and gained approval for lupron's use in pain management of endometriosis in October 1990. In record-defying speed, this approval took just 14 months; allowing lupron to become the second GnRHa 'drug' approved for this indication (the first being Nafarelin).

In 1989, an Abbott employee, Dr. Lumpkin (who had directed Abbott's international research until 1989) moved to the employ of the FDA. Dr. Lumpkin "captained the FDA's shift to accelerated [drug] approvals and less-adversarial relations with drug companies" (William, 2000), and he played a pivotal role in fast-tracking Rezulin and maintaining it on the market through suppression of the Rezulin associated deaths, liver failures, and internal data confirming risks. The FDA's Office of Criminal Investigation has been asked to examine what, if any, role Dr. Lumpkin may have played in fast-tracking lupron's rapid approval for the indication of endometriosis, especially in light of the clinical trials' problematic studies, results, and small number of subjects.

5) During the 1990 review of lupron for endometriosis, it is acknowledged that "[r]ecently, the relative benefit/risk ration of the two regimens [lupron and nafarelin] was discussed in a public forum by the agency" held in April 1989. Several transcript statements from this 1989 public forum are noteworthy; one being in a statement made describing the effectiveness of lupron upon the health of one woman (who is sick and "lies on a couch with constant pain, breakthrough bleeding and no other life"): the transcript states the woman is not doing "very sell" – a 'typo' that is indeed telling. (Fertility and Maternal Health Committee Hearing, 1989)

The plain language of testimony presented at this April 1989 forum by Dr. Ragavan, the "FDA physician in charge of the medical review of GnRH drugs for gynecology" is also revealing:

" … I would like to close with a few comments in the context of my experience in observing the course of GnRH analog research over the past year. Most of the studies that have been presented for analog research are presently being conducted in young women for benign indications. … The number of studies trying to use these drugs has ***by no means slowed down*** recently. Industrial ***sponsors have been quick to fund these studies*** on these drugs ***seeing a potential market***. … [The Committee] may wish to

consider the ethical issues of continued intellectual searches for the use of analogs and the possible **risks** associated with such studies in this study population. **We have always used with *extreme caution* in our abilities to render men hypogonadal** albeit for different reasons. And have ***reserved* this treatment *for life threatening conditions in the male,*** such as prostate cancer. Should we use the same caution in women, especially when we treat benign chronic non-life threatening conditions such as endometriosis? In fact, **I propose for you as *even more caution* in this population who *must live with the consequences* of treatment *for a very long time.*** Thank you." (Ragavan, 1989) (emphasis added)

6) In February 1990, Dr. Ragavan provided the FDA's Medical Officer Review for lupron's application for approval in endometriosis. This review of the data submitted from the two studies (M86-031 and M86-039) identifies serious problems. Dr. Ragavan reports in Study M86-031 (comparing the safety and efficacy of 6 months of lupron in 30 patients versus 30 placebo patients, conducted by 12 investigators at 12 centers sponsored by TAP), that the primary efficacy parameter is "change in pain level", yet "analgesic use will be recorded as: none, non-narcotic, mild narcotic (codeine), strong oral narcotic (e.g. Dilaudid) and parenteral narcotic." She also notes the following:

"The lack of adequate blinding may cause bias. … the differences in side effects may influence recording of subjective complaints by the patient and examination by investigators. … problems with record keeping of personal diaries and observation about symptoms can create a major bias .. "[P]roblems with the scoring of symptoms are many, since the symptoms are recorded by recall at the end of a month. Recall biases and problems can influence such data collection." (Ragavan, Feb. 1990)

Of important note, lupron is known to induce memory loss and this poor memory is categorized as being "commonly observed patient complaints" – one study showed 72% of young women undergoing IVF treatment with lupron experienced memory loss, and 11% of subjects continued to complain of the symptom 6 months beyond cessation of lupron (Varney, 1993). The endometriosis clinical trials, by using lupron which was known to cause memory loss, were designed to capitalize upon the subjects' difficulty in recollection of symptoms experienced over a prolonged period of time.

Dr. Ragavan, in her FDA review of these lupron studies, continues:

" … In terms of adverse events, lupron patients significantly experienced [next 2 sentences redacted] hot flashes and headaches … because of the high dropout rate, this study can only be viewed as a supportive study and not as a separate, controlled study. … It is interesting to note that there was no difference in the six month and three month evaluations of relief of pain. If so, it may be possible to administer the drug for only 3 months and not for 6 months. This idea needs to be explored further. … The question remains why so many placebo patients dropped out, in spite of the fact that many of them derived some benefit from placebo. … Positive lupron efficacy was found in all centers, even though some centers enrolled very few patients. … The number of patients [evaluated for bone mineral density changes] in each group is extremely small … by [spinal CT scan], there was a -11.8% decrease in bone mineral density [Table 20], but we have no post-treatment recovery values. … So far, the CT scan results of the present NDA shows the greatest loss on bone density in 6 months of study. The variability between all these studies are troublesome."

7) In Study M86-039, comparing the safety and efficacy of 134 patients taking 6 months of lupron depot versus 136 patients taking danazol (in 22 centers, with 22 investigators, and supported by TAP-Abbott), (Wheeler, Knittle, 1993) Dr. Ragavan notes "The primary efficacy parameter in this study was change in extent of disease as measured by pre and post study American Fertility Scores (AFS) measured during laparoscopy, and second efficacy parameter will be level of pain." Yet it is also noted that the "usefulness [of AFS scores] in terms of predicting long-term outcomes have not

been validated … there are definite problems with the use of this scoring system as a primary efficacy indicator. In particular, their relevance to long term clinical outcome is not clear. Results of this study showed significant improvement in AFS scoring …" And the review notes that the analgesic use ("none, non-narcotic, mild narcotic [codeine], strong oral narcotic [e.g. Dilaudid] and parenteral narcotic") will be recorded once a month, "mak[ing] it difficult to provide adequate information about symptoms." "[T]he lack of adequate blinding should cause bias when the study evaluates symptoms". Dr. Ragavan further notes that:

"According to the statistical review, there were no major variation by centers. In my review of this data, I do see some variation in response from center to center, especially baseline starting scores and changes after treatment." … "62% of patients improved in their scoring, but 35% did not and 4% showed worsening of the disease with lupron". … "Patients with severe disease were not as likely to respond well and only a handful of patients who had minimal disease showed improvement … and patients with mild disease do not appear to show any further improvement." The "**majority of patients in this study had mild, moderate or absent disease."** And in the patient evaluation of pelvic pain, it is noted that "the improvement in this symptom had stabilized by the second month, with not much further improvement in the rating". Similarily, "[s]tatistically significant decreases were noted in spine-dual photon, hip-femoral neck, calcaneus-single photon and spine CT scan" in the "extremely small" numbers of patients tested. "[T]he mild leucopenia is **again** noted and needs to be followed" and "there are abnormalities of liver tests [] with lupron treatment". (emphasis added)

This reviewer raised pertinent issues in her summary, such as lupron treatment is for 6 months only and endometriosis is a chronic condition – "How will 6 months of treatment affect the long-term outcome of the disease? We do not have good data for relapse rates in this NDA. It is simply a matter of time before the disease returns. ***How many*** courses of treatment will be needed?" (emphasis added)

8) The FDA documents show that Dr. Ragavan recommended approval for lupron in pain management of endometriosis in February 1990, conditioned upon the receipt of new labeling, information about relapse rates, and approval by scientific investigation.

In October 1990, lupron received FDA approval for the indication of "management of endometriosis, including pain relief …", and classified this indication's use in the "3C" category (FDC Reports, December 24, 1990). According to the FDA's classification system, Type "3" denotes a "new formulation", and the Type "C" is specified for drugs that have "Little or no therapeutic gain" (FDA Consumer Report, 1988).

III. HAVE TAP, INVESTIGATORS, AND PHYSICIANS REPORTED ACCURATE AND FULL DATA REGARDING LUPRON?

1) The purported mechanism(s) of action of lupron, the fraudulent science and fraudulent marketing that has been perpetrated upon the public needs intense scrutiny. TAP brochures, for the indication of endometriosis, state:

"GnRH, a hormone produced in the brain, acts on the pituitary gland to stimulate two other hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH). The presence of these two hormones then stimulates the normal menstruation and the production of estrogen by the ovaries. When LUPRON DEPOT is administered monthly, production of these hormones ***is reduced to the very low levels found after menopause".*** (TAP, 1992) (emphasis added)

This premise is scientifically **unsound**! Any medical textbook will reveal that menopause is when estrogen production falls below a critical value, and FSH and LH are "produced thereafter in *large and continuous quantities.*" (Guyton, 1981)

In the April 1990 Medical Officer's Review of Revised Labeling for the endometriosis application, it was noted that "[t]he most common adverse event was hot flashes, the majority of which occurred within 3 months after stop of study. 50% of [available] patients in the follow-up study reported hot flashes. … By the sixth month of follow-up [of available patients], all symptoms except hot flashes had improved." (Ragavan, 1990) Likewise, 6 months after lupron treatment for fibroids, 16.3% of available patients continued to experience hot flushes (Friedman, Hoffman, 1991), and in a recent study of prostate cancer patients, 11% complained of hot flushes "for at least 3 months after" stopping lupron (Schow, 1998).

Why are lupron-induced hot flashes still occurring many months after discontinuation of lupron? And why do lupron-induced hot flashes occur despite elevated estrogen levels and/or the addition of 'add-back' estrogen? In the endometriosis approval, the FDA reviewer noted "It is also difficult to understand why symptoms seem to decrease within two – four weeks of starting the drug, **prior** to even well-established hypogonadism and amenorrhea" (Ragavan, 2/15/90) (emphasis added).

While numerous medical journal articles do identify lupron as causing a "hypophysectomy" (i.e, Serafini, 1988), which, by definition, is "removal or destruction of the pituitary", this 'information' does not reach the patient: she is simply told she will enter a beneficial, temporary, menopausal state. Yet, other reports cite the destructive effects of such an hypophysectomy, and relate the symptom of hot flash from GnRHa's as non-hormonal – and indicative of ***altered brain function:***

" … results as well as clinical evidence indicate that sustained treatment with GnRH agonists most likely abolished pituitary function." (Bischof, 1988)

" … it is the interference with the pulsatile pattern of GnRH that causes flushes … Thus, dysregulation of the GnRH releasing clock center in the nucleus arcuatus in the mediobasal hypothalamus is associated with altered central a-receptor activity which results in lowering of the set point of the central thermostat and the circulatory changes. … hot flushes occur during GnRH agonist treatment despite normal levels of serum oestradiol … Core temperature is normal prior to the onset of the flush and the flush is triggered by a sudden downward setting of the central thermostat. As a result mechanisms for heat loss (vasodilation and sweating) are activated. …" (Van Leusden, 1994)

2) The issue of how long lupron remains in the system is a pertinent (and unanswered) question. In the published reports of the data in the bioavailability study submitted by Dr. Tolman, it was reported that "the mean calculated peak circulating level [of subcutaneous lupron] was 32.3 ng/mL, which was reached 0.6 h[ours] following administration." (Sennello, 1986) However, while a study of women prescribed subcutaneous lupron for fertility treatment reported similar serum concentration of lupron (32.4 ng/ml) – these concentrations were noted at "one to two hours after lupron administration" and *not* "0.6 hours". In addition, at a time that approximated 12 hours after lupron was stopped (and exactly 35 hours before egg retrieval), serum concentrations of lupron in this fertility study were calculated to be 44.6 ng/ml (+/- 5.6). The follicular fluid concentrations of lupron on the day of egg retrieval, "when corrected

for the flushing occurring at oocyte retrieval, corresponds to <7.3 ng/ml." The article concludes that "there is **probably** no deleterious effect of leuprolide on oocyte maturation and early embryo development". (Dodson, 1988) (emphasis added).

While the FDA documents, as well as the medical literature, identify lupron's half-life following subcutaneous administration as 3.6 hours – this was the mean half-life from *six* (6) individuals. From those 6 subjects, the range of half-lives was 2.7 to 6.8 hours – indicating that in 17% of subjects studied, lupron broke down nearly twice as slow as is claimed and reported. The alleged 'clearance rate' of both daily and depot lupron is a crucial issue in relation to use in fertility treatment: TAP's former Medical Director reported that "subclinical but detectable levels of leuprolide have been found in one third of subjects eleven weeks after injection". (Miller, 1990)

3) In the FDA's 1989 public forum discussion of nafarelin and lupron, findings from the nafarelin animal studies were compared to lupron animal studies. In discussing long-term mouse carcinogenicity studies, data from lupron treated mice was cited as follows:

> Lupron increased pituitary adenomas at the "mid dose", and "[t]here was no carcinoma in the male. In the female there was 2 percent in the low and high dose, but they were not significant." Liver tumors were found at a high incidence with lupron, with "some indication that the low dose had increased [the tumors] as well." And pancreatic islet-cell adenomas were "increased at the low dose level and then they were decreased as the dose was increased" (Fertility and Maternal Health Committee, 1989, p. 78).

Yet, in an apparent contradiction to this data, lupron's product labeling for its endometriosis approval describes "a significant but not dose-related increase of pancreatic islet-cell adenomas in females". The data for the only long-term mouse carcinogenicity study submitted to the FDA for lupron's initial approval (Study TD78-538) claims that "palpable masses" were found to have "no statistically significant positive trends in tumor incidence with dosage". The transcripts of this public forum's discussion do not identify whether the discussed lupron data is or is not the same lupron mouse data submitted to the FDA for lupron's initial approval. However, it is interesting to note that Abbott's conclusion of Study TD78-538 is that lupron "was not considered to be oncogenic *in this study"* (NDA prostate, Table 4) (emphasis added).

In studies separate from lupron's FDA approval, mice (with mammary tumor virus) were given 20 "[d]aily injections of TAP-144 [lupron] … [which] resulted in the increase in the rate of HAN [precancerous mammary hyperplastic alveolar nodule] formation" (1980). In another separate study (conducted by Takeda) with lupron in rats with mammary tumor virus, it was found that in one tumor there were *co-existing* areas of regression of tumor as well as areas of tumor growth and "only one ***or*** 2 new tumors appear[ed] during treatment" (emphasis added) … yet it is claimed "lupron effectively prevents the occurrence of new tumors" (Okada, 1983). In another separate 1976 study using lupron on rats, conducted by Abbott, a "rapid growth" of one nonresponsive tumor occurred, and 4 weeks after stopping lupron there was "regrowth of palpable tumors and appearance of new tumors" in rats that had been treated for 6 weeks (DeSombre, 1976). (What caused the growth of this writer's gallbladder tumor [adenoma], occurring within 6 months after cessation of 6+ months of lupron "treatment"? One treating physician stated the tumor was "from lupron", but now denies the statement.)

The U.S. product label and Physician's Desk Reference (PDR) for lupron identifies that "In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years." Yet, in the Australian equivalent of the PDR (where lupron is identified as a "Poison Schedule S4"), Abbott reiterates this latter claim, but then also identifies that "In short-term toxicity studies in mice treated for 3 months with 20 to 200 mg/kg, hypertrophic and castration cells were found in the anterior pituitary." (MIMS, 1995). While data from short term mouse studies does not appear in U.S. lupron product literature, a short-term mouse study (T77-509) was submitted by Abbott to the FDA for lupron's initial approval – in which "hypertrophic cells were observed in the pituitaries of all [200 mg/kg dose] female mice" (NDA, 19-010).

4) Moreover, in the initial teratology studies done in rabbits submitted to the FDA, it is stated that "although even low levels of ABBOTT-43818 [lupron] are likely to prove embryolethal, animal studies indicate that survivors are able to develop normally" (NDA 19-010) – yet, "personal communication" by TAP's Medical Director in 1992 revealed that "[t]he most frequently observed malformations in rabbits were vertebral anomalies and hydrocephalus." (Briggs, 1994)

5) In many of the early investigations of lupron (by Takeda, Abbott, TAP and others), the resultant published studies contain a significant number of statements which reference "unpublished data" (Fujino, 1973; DeSombre, 1976; Rippel, 1975, 1976; Rose, 1979).

6) The Office of Research Integrity has previously reached an agreement with one leading lupron investigator, Dr. Andrew Friedman (formerly of Brigham & Women's Hospital) who admitted to "falsified and fabricated data and patient records in several instances from 1992 – 1995" and "falsified and fabricated data" within 2 unpublished and 2 published lupron studies (Federal Register, 1996). Is there evidence of other fraudulent data regarding lupron? (Have other lupron articles by Friedman been investigated?) Have other investigators been investigated?

7) In a separate TAP sponsored study of the effects of lupron in 29 prostate cancer patients, published in 1984, one patient died of pancreatic cancer 10 weeks into the study, 11 had disease relapse, and "an additional five died of other causes. … One subject developed phlebitis in the lower extremity on therapy and there was worsening of preexisting heart failure in another. Neither of these complications was apparently related to leuprolide." (Vance, 1984) A critical read of the medical literature pertaining to lupron (in animals and humans) provides numerous instances of serious consequences (including death) that "are not related to lupron". Are these 'problems' truly "unrelated to lupron"?

8) Of note is the February 1990 FDA Medical Officer's Review of the data from the 2 endometriosis clinical trials, in which it is identified that "Lupron causes some irreversible decreases in bone mass" – yet, the final product label for lupron for

endometriosis does not clearly identify for the consumer that "**irreversible** bone loss" occurs. TAP's product label states the following:

"After six months of LUPRON DEPOT treatment, vertebral trabecular bone density measured by QCT decreased by an average of 13.5% compared to pretreatment levels. A **small number** of original patients were retested at 6 and 12 months after completion of treatment. … These results show that there was partial to complete recovery of bone density in the post-treatment period." (emphasis added)

Subsequently, bone biopsies were conducted, and in 1995 it was identified that after 6 months of GnRHa use in young women, bones showed "severe disruption of the cancellous microstructure" and "the results suggest that bone loss induced by GnRH analogs may be associated with adverse effects on cancellous microstructure which are unlikely to be reversed following cessation of therapy." (Compstone, 1995)

Of note is another separate study by Comite et al., which does not involve the lupron clinical trial. This article by Comite et al. purports an association of bone loss to the *disease* of endometriosis, claiming that "women with endometriosis had significantly decreased cortical and trabecular bone mass" (Comite, 1989). This proposition is made without any mention of the irreversible bone loss that occurs *from the treatment for* endometriosis (i.e., GnRHa's, lupron). In this study, Comite et al. states "we have seen a highly statistically significant difference of bone mass in relatively young women with endometriosis (10% of their cortical and over 15% of the trabecular bone)". Yet, in another unrelated study, in which women with previous exposure to GnRH agonists "were excluded", there was "**no evidence** of low bone density in women with **untreated** endometriosis" to be found, and "[o]ne explanation for the difference between the results of this study and those of Comite et al. is that ***they*** [Comite et al] ***included*** women who previously **had** been *treated* with GnRH agonists and these agonists are associated with bone loss." (Dochi, 1994) (emphasis added)

9) In the prostate cancer study M81-107, the incidence of impotence was reported to be extremely small – "2" patients according to a Urology article (publication of which was supported by TAP), and "4" patients according to the FDA review of this data. Yet, paradoxically, it is common knowledge that sexual desire, sexual interest and sexual intercourse following the use of lupron is "totally annulled" – one study noted that "significant changes in frequency, magnitude, duration and rigidity of noctural erections [were] observed in all patients" (Marumo, 1999). How is it that the early investigations reported such a small percentage of subjects experiencing what is recognized as a common adverse event? The Emperor of Japan just received a public apology from a German newspaper for the *intimation* of impotence (did the Empress use lupron for their test-tube baby conception?) (Parry, 2001) --- and what have ordinary American men and women received after taking this Japanese drug: ordinary humans who have suffered *actual* and *continued* impotence, loss of sexual desire, and *continued* suppression of fertility, and/or suffered tumors, chronic and acute medical illnesses, and medico-legal abuses beyond description, including death?

10) While Abbott investigators noted that "X-irradiation [to induce ovulation] is undoubtedly a more severe treatment" than lupron-induced ovulation (Rippel, 1975) – it is interesting to note that the American Red Cross policies state that anyone receiving

injections of radioactive material cannot donate blood for 8 weeks, while anyone receiving injections of lupron cannot donate blood for 4 months. And available FDA Enforcement Reports indicate that blood products (red blood cells, platelets, fresh frozen plasma, and recovered plasma) have been recalled in each of the last 5 years due to contamination with lupron (i.e., FDA Enforcement Reports).

11) It is inexplicable that the patients who self administer or receive lupron injections, as well as the nurses who administer lupron injections, are unaware of the following:

- The Material Safety Data Sheet (MSDS) issued for lupron, available to all hospitals and healthcare institutions, and available at the NIH's website for employees only, states that leuprolide acetate (lupron) is "hazardous per OSHA criteria", and identifies that "women of child bearing potential must be excluded from working directly with product."
- The National Institutes of Health and OSHA (see i.e., OSHA, 2001) list leuprolide as a "hazardous drug", and recommends that health care workers who handle lupron wear protective gear, including, but not limited to, *two* pairs of chemotherapy gloves, a mask, and a chemotherapy gown.
- The American Hospital Formulary System advises health care workers to abstain from handling lupron for at least 3 months prior to fathering or conceiving a child (AHFS, 1999).
- California's Proposition 65 lists leuprolide as a "developmental toxicant" and a "reproductive toxicant" (Scorecard, 2001).
- The FDA has labeled lupron a Pregnancy Category X drug (fetal harm outweighs benefit). Why is the consumer/subject who is injecting this hazardous drug into their bodies **not informed** that lupron is a **hazardous** drug?

IV. HAS TAP, INVESTIGATORS, AND PHYSICIANS KNOWINGLY HARMED BABIES CONCEIVED WITH LUPRON?

1) The daily lupron injections have only been approved for one indication only – palliative treatment of prostate cancer. Yet, it is the daily lupron injections which are mostly prescribed to young healthy women undergoing fertility treatment and young health egg donors and surrogates (each a big cottage industry in its 'own right'). While men with terminal prostate cancer receive 7.5 mg per month, healthy young women attempting to conceive use up to 1 mg *per day* up to as many as 39 days and more before *each* cycle.

By 1987, just two (2) years after lupron's approval for terminal prostatic cancer (and without **any** other approvals granted), lupron was being administered to **young, healthy, fertile women** who sought fertility treatment only due to the fact that their partner suffered from *male* factor infertility (Awadalla, 1987; Klingman, 1995): in one such 1987 lupron **experiment,** fifty per cent (50%) of the *study* population were healthy *fertile* women with no infertility but whose male partners were infertile (Awadalla, 1987). In 1989, before any FDA approval for female usage, lupron was being "routinely" administered to women undergoing their *first* IVF cycle (Meldrum, 1989).

Lupron has never gained approval by the FDA for treatment of infertility or in vitro fertilization – but those studies were conducted, year after year after year. What did the data from these studies reveal for which no subsequent FDA approval was ever bestowed? Why is lupron routinely used in and promoted for fertility treatment? And who is doing the promoting and why?

2) In the March 21, 1990 FDA Notice of Adverse Findings to TAP regarding lupron, it is stated that TAP has:

"undertaken a deliberate campaign to promote this product for a wide range of unapproved uses. … involv[ing] a large number of detail representative visits … [to offices] … not within the usual range of activities undertaken by OB/GYN specialists. However, the unapproved uses of Lupron previously promoted by your firm would be within the usual practice of OB/GYN specialists. …. **Your firm is not listed** as having funded printing of this [off-label and TAP detail disseminated] publication, **but we must assume that TAP funded this publication** on the basis of the journal's focus upon approved uses of GnRH agonists" and "TAP's 'REACH' program [] brochures do not acknowledge the potential for discovery of significant hazards of efficacy limitations as you continue to characterize Lupron's possible usefulness for these indications. They focus upon administration of Lupron for these unapproved uses to an excessive degree. … Your firm was involved in direct promotion of these unapproved uses to physicians at the time of our meeting, but elected not to inform us of such activities at that time. We have since been informed that your firm has continued to promote these unapproved uses to physicians on an ongoing basis …" (FDA Notice, 3/21/90) (FDC 4/2/90) (emphasis added).

3) In addition to a 1988 FDC Report quoting Abbott's chairman stating that "researchers are studying Lupron in connection with in vitro fertilization (FDC, December 5, 1988), numerous Abbott Annual Reports reiterate the presence of this 'research':

- 1987: "… researchers have found that Lupron may be useful in connection with in vitro fertilization programs. Clinical studies are being conducted to determine the effectiveness of Lupron in treating these conditions."
- 1989: "… a clinical study is also under way to determine the effectiveness of Lupron in in vitro fertilization programs."
- 1990: "Additional clinical studies are under way to determine Lupron's effectiveness for a variety of gynecological indications, including infertility …"
- 1992: "Studies are also under way to evaluate Lupron's effectiveness for the treatment of infertility …"

4) Lupron is a known teratogen, and a known developmental and reproductive toxicant; and lupron is categorized by the FDA as a pregnancy Category X drug (meaning "studies in animals or humans demonstrate fetal abnormalities or adverse reaction reports indicate evidence of fetal risk, and the risk of use in a pregnant woman clearly outweighs any possible benefit"). Any PDR, in describing lupron, states that "any woman who is or who may become pregnant" should not use lupron. TAP states in its brochures "A nonhormonal or barrier method of contraception should be continued until 2 months after therapy. Pregnancy should not be attempted before this time." (TAP Brochures, i.e., April 1994, February 1995). **WHY** is lupron promoted and prescribed for fertility treatment?

5) Healthcare professionals handling lupron (and/or any hazardous drug) who intend to conceive or father a child, are advised to ***avoid*** *handling* the hazardous drug (lupron) for a recommended 3 months *prior to conception* (AHFS, 1999). Yet healthy young fertility patients handle lupron and self-inject lupron *daily* into their bodies up to within days of conception and embryo implantation, uninformed of any of the latter information. And these healthy young women are injecting lupron at a dose that far *exceeds* that used in the palliative treatment of terminal prostate cancer: terminal older men with cancer use 7.5 mg/month … young healthy women use as much as 1 mg or more *per day*, for up to and beyond one *month*, for *each* fertility 'cycle'.

6) In a 1992 article, it was identified that "A literature search failed to find data for return of ovulation after serial doses of LA [leuprolide acetate] were used to achieve pituitary-ovarian suppression, but one study found a return of menses on average of 40.6 days after leuprolide acetate was discontinued. One could reasonably conclude that suppression of endogenous gonadotropin release is continued for another 12 days or so after cessation of leuprolide." (Corson, 1992) In depot lupron, recall that leuprolide was still detectable eleven weeks after the lupron depot injection. Depot lupron (long acting formulation) is also used in fertility treatment and IVF cycles, creating a developmental milieu for any embryo that could be influenced by the continued presence and/or effects of lupron. It has been established in human reproduction that there is the "presence of GnRH receptors in preimplantation embryos at different developmental stages". (Casan, 2000) And it was acknowledged, during the use of lupron in fertility treatment, that even a brief, 5-day course of lupron "appears to suppress endogenous GnRH activity for at least 1 week afterward; and the profound suppression of LH that follows cessation of [lupron] can be important clinically." (Sungurtekin, 1995) In a matter of 4 or so days after stopping lupron, embryo(s) are transplanted into the woman. The patient, should she inquire, is told that lupron will be out of her system by the time of embryo transfer … but is it?

7) Abbott's Annual Reports report the investigation of lupron's "efficacy" in IVF and infertility treatment – **not** lupron's "safety" in IVF and infertility treatment. Just how safe is lupron?

Published medical reports have noted the occurrence of abnormal pregnancy outcomes associated with the use of lupron – 43.5% in one 1996 study (Fertility and Sterility, Abstract P-34, Program Supplement, April 1996, p.A27). Another report, using the 'long lupron protocol' showed a 38% abortion rate (Shanis, 1995). "Fetal growth retardation was observed with increased frequency among the offspring of rats or rabbits treated during pregnancy with subcutaneous doses of leuprolide similar to those used in humans" (Friedman JM, 1994)

In 1999, the first study was conducted on the *long-term* follow-up of children born after inadvertent administration of GnRHa in early (undetected) pregnancy. In the six children studied, a major congenital malformation and four neurodevelopmental abnormalities, including epileptic disorder, attention deficit hyperactivity disorder, motor difficulties and speech difficulties, were seen. The conclusion was that "[t]his

observation of neurodevelopmental abnormalities in four of six children in the study group justifies the need for long-term follow-up of more children previously exposed to GnRHa." (Lahat, 1999) In addition, a follow-up letter published in response to this article stated that "[t]he need for long term follow-up possibly sponsored by GnRH-analogue producing pharmaceutical companies echoes the intuition of many clinicians." (Human Reproduction, 1999, 15(6):1421)

8) In a patent for embryo culture composition, it is noted that "culture of primate embryos in the presence of a GnRH agonist … unexpectedly dramatically reduces the rate of embryo attachment and cell differentiation." (Hearn, 2000) Using lupron in fertility cycles, "some retrieved oocytes exhibit incomplete nuclear and cytoplamsic maturation after the use of this agonist [lupron]" (Racowsky, 1997). In rabbits, lupron caused "increased oocyte degeneration rate (Zanagnolo, 1996). Growth retardation has been noted in young monkeys given lupron (Golub, 1997).

9) In a study of ovarian response in baboons given lupron, "the doses used were derived from preliminary human data". (Scott, 1993)

10) "The effects of GnRHa treatment on developed corpora lutea are unknown." (Goto, 1999) A 1992 study using lupron in an IVF program identified that "[n]o data are available on the effect of LH-RH-a [GnRHa] on human small follicles." (Parinaud, 1992)

11) In a 1990 study utilizing GnRHa's, one of the group of women who had developed severe ovarian hyperstimulation syndrome and liver function abnormalities had a liver biopsy performed (at the time of surgical removal of conceptus due to intrauterine death 2 months into pregnancy): this liver biopsy showed "a striking abnormality consisting of macrovesicular fatty infiltration around and linking the portal tracts. This appearance could not be classified into any well-recognized clinical entity." (Forman, 1990)

12) Women have been reporting, including publicly posting on the internet, of birth defects in babies born following the use of lupron that include immunologic problems, and skeletal and cardiac anomalies; as well as causing pregnancy loss, infertility, and permanent menopause.

V. HAVE STATE AND FEDERAL GOVERNMENT AGENCIES ACTED ON BEHALF OF CONSUMERS RELATIVE TO LUPRON?

1) In 1988, the Office of Technology Assessment (OTA) commissioned a report on infertility treatment, "assessing social, ethical, medical and public policy concerns surrounding infertility treatment technologies, focusing on medically and surgically assisted conception, basic research on reproductive technologies, and surrogate motherhood." (OTA Report, 1988) Two contractors each provided a working paper entitled "Risks of Infertility Diagnosis and Treatment": one was written by Anthony Scialli M.D. (who has received TAP support to study lupron (Scialli, 1995)), and the other written by Helen Bequaert Holmes Ph.D. (who has written elsewhere that "infertile women who seek IVF almost invariably end up as subjects in research … patients often

are financially supporting their physician's research projects." [Holmes; Birth, 1988]). Inherent in the production of these OTA working papers was the advisory "not to discuss GnRH analogs". (Holmes, personal communication, 1997) Elsewhere, in a separate publication, Holmes discussed the risks of GnRH agonists in fertility use, and identified the risks of ovarian cysts, ovarian cancer, disrupted subsequent menstrual cycles, and lack of medical follow-up post-treatment." (Holmes, 1988)

2) Numerous lupron studies take place at the NIH. A number of NIH lupron investigators have been asked whether their administration of lupron adheres to the NIH recommendations for lupron's administration (i.e., handle with two pairs of chemotherapy gloves, gown, mask). No substantive response has been forthcoming. (Personal communications) At least one NIH investigator who has studied lupron has a 'cottage-industry' patent that relates to the monitoring of adverse effects from lupron.

3) Numerous requests, by numerous individuals (such as myself), were made of the Department of Health and Human Services, as well as to other state and federal agencies, requesting an investigation of lupron, yet no apparent investigation has taken place.

4) Complaints were submitted to the former MA. Attorney General regarding fertility treatment at Boston IVF, as well as specific requests made for an investigation into the ab/use of lupron – all were apparently dismissed without apparent action. Of note is the 1996 ticket price range (up to $500) quoted in the Boston Herald, to "line up for a chance to schmooze with [former] Attorney General Scott Harshbarger in chi-chi Chilmark", hosted by one of Boston IVF fertility clinic's doctor (Raposa, 1996). The former Attorney General and this Boston IVF physician and their spouses were all smiles in a 1998 Boston Globe "Partylines" photo from an event described by those in attendance as a "love fest". This event hosted a reporter who has been public regarding his use of lupron for prostate cancer (Hatfield, 1998).

5) Massachusetts, like an increasing number of other states, has mandated insurance coverage of fertility treatments since 1987 – treatments that frequently include the use of lupron. Massachusetts legislators, like an increasing number of other states' legislators, have experienced heavy lobbying on behalf of these insurance coverage mandates by 'RESOLVE', the allegedly "grass roots" organization devoted to "educating, advocating, and supporting the infertile". In essence, through this insurance mandate, the Commonwealth of Massachusetts has sponsored and increased the *use* of lupron, while it simultaneously thwarts (from 1992 to present) the passage of legislation (House 3308) which would mandate informed consent of the risks of lupron, reproductive technologies, and other fertility drugs (see Millican, 11/13/99).

RESOLVE, according to available Financial Disclosure forms from the MA. Attorney General's Office, began receiving TAP funds at least as early as 1989 – yet shields this information from its members and the public. It should be noted that TAP was giving RESOLVE thousands of dollars (and RESOLVE was receiving thousands of dollars from TAP) at a time when lupron was only approved for palliative treatment of prostate cancer and before any female application approval. Lobbying by RESOLVE to enact legislation

for insurance coverage for fertility treatment has been successful in many states in the country.

RESOLVE has a history of deceitful representations to the public, as evidenced by their recent statement to the Boston TAB that RESOLVE "does not receive any funding from drug companies" (and "the organization supports the use of lupron for fertility treatment") (see Seiffert, 2000). RESOLVE has received hundreds of thousands of dollars in a single year from drug companies, according to its financial statements; and this is not the first time that RESOLVE has misled the public (Letters, 1992, 1994). Moreover, during the second year of the MA. Hearings on 'An Act Relative to the Treatment of Fertility', MA. House 2019 (which would mandate informed consent of the risks of lupron, among other provisions), RESOLVE presented its first testimony on this bill – opposing the measure. Then, some three months *after* its opposition, RESOLVE informed its members of the bill's existence via its newsletter and that it had opposed the legislation. Since RESOLVE could not have "spoken" for its members on the issue of mandated informed consent of the risks of lupron and reproductive technologies as it had neither informed nor polled its members of this bill … so just whose "voice" does RESOLVE speak to?

6) An email request to all U.S. Senators was made in March 1999, asking for a Congressional investigation into the health risks and off-label promotion of lupron (Millican, 3/3/99): the one Senator who responded (Senator McCain) forwarded the request to the Department of Health and Human Services. In historical fashion, the Department of Health and Human Services responded in double-speak. Prior to the close of the Congressional hearings on TAP's urological marketing scheme, a staffer stated that the committee "was unaware of any health problems associated with lupron" (personal communication).

VI. WHAT ROLE HAS CONFLICTS OF INTEREST PLAYED IN THE HUMAN EXPERIMENTATION, SUPPRESSION OF INFORMATION, AND LACK OF MEDICO-LEGAL ADVOCACY RELATIVE TO LUPRON?

In addition to all of the above, the below is a collection of a variety of apparent conflicts of interests concerning lupron:

1) The MA. Department of Public Health (which has most of the $380,000 worth of state contracts that Abbott has with the state [Cassidy, 2000]), along with other state departments, has received numerous complaints over numerous years (i.e., personal communications 1992 – present) to examine the lupron matter. No substantive response is given, and the public is shunted to two places: the Board of Registration in Medicine (which shuttles consumers to the FDA) and the FDA (which shuttles consumers to the Board of Registration in Medicine).

2) The Endometriosis Association (EA), which has received grants, funds, and other monies from TAP for many years, touts the role that the EA had in pushing for and gaining the FDA approval the use of GnRH analogs in the treatment of endometriosis.

3) In the case of Kuha v. Friedman and Brigham & Women's Hospital, Kuha had been enrolled in a lupron clinical trial at Brigham & Women's, and suffered subsequent and permanently disabling strokes and seizure disorder … yet the ***plaintiff's*** medical expert barely mentioned lupron, posited a magic clot theory, and opined that drugs *other than* lupron were the causative factors in Kuha's damage.

According to court documents, this retained expert who opines that drugs *other than lupron* caused this woman's damage, also identifies in court documents that he's a "Consultant for Abbott from 1987 – present", and also served on the Abbott Young Investigator Award Advisory Board for many years, and also was an invited lecturer at the "FDA/NIH Conference on Industrial Academic Interface in 1989", among others.

Platelet abnormalities, intracranial hypertension, cerebrovascular accidents, convulsion (including grand mal), pulmonary embolism, thromboses, thrombophlebitis, deep thrombophlebitis, and arterial thromboses, among others, are all listed as reported adverse reactions to lupron. Please also recall that published medical literature identified in 1990 that during GnRHa 'treatment' in young women attempting conception: "transient cerebral ischemia is one possibility that may explain the symptoms of numbness, headaches, paresthesia and paresis. … This could explain the various neurological symptoms occurring by means of **vasospasm of intracerebral blood vessels.**" (Ashkenazi, 1990) Kuha's medical records document both a left gaze preference and a right gaze preference – the gaze preference being a predictor of the involved side of brain. In this writer's professional opinion, a critical review of the available medical records in the Kuha case indicate a troubling and disturbing picture.

Although Kuha's tests were negative for finding any clots, the medical records conclude that this plaintiff's clot made its way to her brain by a shunting through a congenital hole in her heart ("right-to-left shunting", or – as also documented – "left to right shunting") and that she suffered from a hypercoaguable disorder. Of note: the medical records indicate that while the homocysteine level was "actually normal", it is stated that "[u]nfortunately, despite the other tests being listed as having been performed in the Brigham computer system, there is no notation of their values. [The doctor is] unable to find these." Kuha's expert statement identifies that the plaintiff has "an activated Protein C resistance, determined by blood tests."

4) A pilot survey was mailed to U.S. pharmacists in various hospitals, inquiring of their policy and procedure, if any, for the administration of lupron (Millican, personal communications, Jan-Feb 2000). Of the 25% who responded, 100% stated they had no policy or procedure on the administration of lupron.

5) In 1990, at the Brigham & Women's Hospital Fertility and Endocrinology Clinic (F&E), lupron was described in clinic brochures as "only used in certain diagnoses", yet less than one year later this brochure was changed to read "lupron is widely prescribed". The Director of the F&E Clinic was the aforementioned Dr. Andrew Friedman, who was

found guilty of "falsifying and fabricating approximately 80% of data" in 4 lupron studies. What caused lupron's use to exponentiate at Brigham & Women's Hospital?

More recently, on Brigham & Women's website, there was a page entitled 'Corporations and Foundations' which showed that Abbott and TAP Pharmaceuticals Inc. donated "$25,000 +" (www.partners.org – page appears to be no longer accessible). A patent, with the assignees of "President and Fellows of Harvard College, Brigham & Women's Hospital, Inc." (Patent #5,541,081) "relates to methods and compositions for assessing the quality of an oocyte or preimplantation embryo" as "[s]ignificant improvements in ovulation induction, oocyte retrieval, and in vitro culture techniques have resulted in an abundance of embryos per patient or experimental animal." (Assignee, 1996)

VII. HAVE THERE ALSO BEEN GYNECOLOGICAL AND REPRODUCTIVE SCHEMES BY TAP, INVESTIGATORS AND PHSYCIANS?

1) Women have been reporting (including posting publicly on the internet) throughout the 1990's that they were "bullied" and "tricked", "badgered" and "forced", "pushed" and "convinced" into taking lupron by their gynecologist or reproductive endocrinologist (RE). Several women have used the term "shoved down [their] throat" to describe the physician's approach in prescribing lupron. Complaints registered with the MA. Board of Registration in Medicine regarding this inappropriate and 'mandated' use of lupron date as early as the late 1980's. In illustration of these facts, the following testimony was presented to the MA. Health Care Committee in support of House 2019, An Act Relative to the Treatment of Infertility (which would, among others, mandate informed consent of lupron): "In October 1990, despite my objection to using lupron again, I was told by Dr. Hornstein [who has received TAP funds] "if you want IVF you must use lupron" (Millican, 1995). Testimony provided in 1992 states: "Women who have never cycled before as well as women who have had previous IVF babies without Lupron are told that if they desire to enter into an IVF cycle, they must take Lupron or they will not be allowed in the program." (Millican, 1992) And another woman testified on March 30, 1993: " … There was no reason to change the previous [IVF] drug protocol … We were TOLD to use lupron." (DeBenedictis, 1993)

These aggressive tactics continue unchecked, and are not limited to fertility treatment. The following are April 2001 quotes publicly posted on an internet newsgroup: "[the doctor] brings up the dreaded Lupron word. He wants me on it for 4 to 6 months then have surgery … He said that I can bleed to death" (post April 10, 2001); and another states "I once saw an RE who INSISTED that I take lupron a second time" (post April 11, 2001). Why were/are women bullied and tricked, badgered and forced, pushed and convinced into taking lupron – frequently with coercive threats of hysterectomy, refusal of fertility treatment, or death by exanguination? Since when do urologists need to be ***enticed and paid*** to prescribe a 'drug' that claims a positive benefit for patients? *What* was the inducement for the widespread gynecological application of lupron – a market base that was already well established *before* lupron received its first FDA approval for a female indication?

2) Without question, the schemes utilized in urological prescription of lupron could be easily reenacted within the fields of reproductive endocrinology and gynecology. Free samples could be billed to the women's insurance company. Kickbacks for switching patients from a rival GnRHa to lupron could occur for female indications as easily as it did with prostate cancer. For years, women (as well as nurses) have reported office visits arranged around the 'buddy system', wherein two women split one 7.5 mg vial. Have physicians billed for ½ vial for each of the 2 female patients or was one whole vial billed for each patient? The Endometriosis Association, which has received tens of thousands of dollars from TAP (i..e., see EA Financial Disclosure, 1993), stated in a 1991 newsletter "some U.S. physicians also 'twinned' women with endo – bringing two women into the office on the same day to split a vial of Lupron packaged at the higher dose." (EA, 1991)

The TAP urological scheme identified by the Commerce Committee showed how much profit could be made purchasing in bulk for prescription of 7.5 mg to each patient – in female applications, such purchasing would create two available doses for administration and billing. Doses of 1.88 mg are also used, creating four doses within one 7.5 mg vial of lupron. Have physicians billed for ¼ vial for each of the 4 female patients or was one whole vial billed for each patient? (And what purpose would one particular HMO pharmacy have in recording each one of 7 individual purchases of a single vial of daily lupron instead as "2" vials per purchase – thereby creating a pharmaceutical history report that erroneously catalogs "14 dispensed quantities [vials] of lupron" vs. the actual 7 vials received?) A number of women have retained their lupron lot numbers.

The dubious behaviors and devious machinations of TAP have been made evident through your investigation as well as by the company's history – which include, among many others, demands by the FDA (via warnings, 'Dear Doctor' letters, and/or Notice of Adverse Findings) related to inappropriate promotion of TAP/Abbott's anti-neoplastic drug (lupron), as well as similar demands by the FDA to Abbott related to inappropriate promotion of its anti-hypertensive drug (FDC Reports, 3/12/90) *and* anti-epileptic drug (Scrip, 7/15/98). Other noteworthy company highlights are Takeda's involvement in one of the largest anti-trust settlements ever reached, where it was charged Takeda had a "cartel" and "held secret annual meetings to divide world markets and fix prices of vitamins (Richwine, 2000). In addition, the FTC's charge against Abbott for "collusion and bid rigging" in the infant formula market (Montgomery, 1992) resulted in Abbott's settlement of price-fixing charges in 17 states (AP, 1996).

A cursory glance at TAP's marketing maneuvers and off-label promotional use of lupron within the arenas of gynecology and reproductive endocrinology reveal TAP's abject indifferent to regulatory compliance and FDA warnings, and mirrors the conduct and flagrance seen in the urological scheming. It is critical to remain acutely aware of the purpose of lupron's initial filing for patent – to induce ovulation (produce eggs [ova]); and to consider the current fervor of genetic experimentation and the increasing prevalence of embryo research (which demand a supply of ova).

By 1988, "hundreds of products are being developed or marketed now, the beginnings of which depend on the availability of human embryos." (Shearer, 1988) In the NIH's 1994 Human Embryo Research Panel Hearings, many potential b(*u*)y-products from ova and embryos resulting from 'reprotech' were identified - such as proteins, vaccines, hormones, gene therapy, cell lines, organogenesis, ectogenesis, parthenogenesis, stem cells, 'therapeutic agents', chimeras, patents (NIH, 1994). At that time, "eleven [NIH] panel members have been awarded, between 1987 and 1993 alone, $20 million in NIH grants." (Rini, 1994) One renowned NIH panel member, having received $4 million of these federal grants, hailed from the institution whose IVF Clinic provided misleading testimony (Hornstein, 1995) in opposition to MA. House 5050 (current House 3308) – and this testimony was delivered by a physician who has received considerable TAP funds.

In a fertility *trade* journal, a commentary entitled "Tools of the Trade" refers to a recombinant product made from human embryonal kidney cells (McDonough, 1995). Abbott's own product, urokinase, illustrates the market well: urokinase is a product manufactured with neonatal human kidney cells. (In November, 1998, the FDA ordered Abbott to suspent distribution of urokinase after inspections turned up "multiple problems", including lot contaminations with hepatitis B virus or mycoplasma, and failure to test 10 lots (Knox, 12/2/0/98)

3) In Britain's 'The Times', an article titled "Scientists 'pillaging foreign embryos'" reported "the stem cells are derived from an anonymous embryo in the United States, left over from an IVF procedure" (Hawkes, 2000); and the U.K. has made public calls for eggs – one article was entitled "Wanted: Women's eggs for research" (Browne, 2000). In America, the bid appears in near-daily 'egg-donor want ads' of newspapers. In a recent Australian report about creating nerve cells from stem cells (the stem cells being taken from days-old human "embryos that had been created during IVF treatment, but were not implanted into the woman"), it was noted that "[o]ne U.S. stem cell expert … said that he and others had done similar work but hadn't yet published it." (Saltus, 4/5/00)

One study referenced ninety-one (91) oocytes being aspirated at one time from one woman (citation lost); another quoted fifty-six (56) oocytes being aspirated at one time from one woman (Lim, 1995). A random count of human oocytes and embryos taken from a mere 20 pages in just *one* of the United State's numerous relevant medical journal publications (from just one supplement of this one journal, in just one month, from just one year), yielded a total of 7,845 human oocytes and 266 human embryos used in research – again, in just 20 pages of just one large volume from just one month. (Journal, 1995). This genetic 'research material' is described in the published medical literature as: "coming from the IVF program", "surplus", "left-over", "discarded", "extra", "spare", "clinic", "donated", "research", "abnormal", "fertilized", "unfertilized", "nontransferable", "suboptimal", "nonviable", "aspirated". The Washington Post reported in 1998:

"Experimenting with Eggs: No one was paying attention. … The research required many eggs to practice on, said Joe B. Massey, the clinic's director, so doctors there turned to women who were donating

eggs to infertile women and used some of the leftover eggs for their research. "We call it sharing with the lab", he said." (Weiss, 2/9/98)

Although the occurrence of fertilization is a concrete, visible event that is readily detected by an embryologist with a microscope, a 3-part series aired by Boston's Channel 7 (11 pm. News) in July 1989 ("Expecting a Miracle") revealed serious problems with this 'simple' event. This series featured a couple who had undergone treatment at Boston IVF, one of the nation's "highest *volume* clinics". Following the egg retrieval process, the couple received a much-awaited phone call from the clinic informing them that 3 of their eggs had fertilized so far, and they were given a specific time to return to the clinic for transfer of these 3 (and maybe more) embryos into the woman. However, upon arrival for this scheduled transfer, the couple was told "the eggs never fertilized, we made a mistake, I thought they had [fertilized], they almost did". The Director of this clinic, Dr. Oskowitz (who asserted in an unrelated article that "women do not need to know that Lupron is not FDA approved for fertility treatment" [Kong, 1996]), explained to Channel 7 News that the disappearance of these 3 embryos was "an error in communication".

4) The profoundly significant and despicable thefts ("conversion", "sharing") of women's ova and embryos by Drs. Ricardo Asch, Sergio Stone and Jose Balmaceda at the University of California at Irvine (Press, 1995; Regents, 2001) should be viewed as a serious warning and as irrefutable evidence of the utter (and anesthetized) ease with which such menacing maneuvers can be executed. These contemptible violations highlight the profitability of schemes to procure women's eggs and embryos for use in research and/or for covert 're-$ale', and attention should be directed to the drug protocol(s) used – medications were "**deliberately**" administered "so there would be a surplus of eggs" (Challender, 1995). (Dr. Asch has co-authored studies of lupron, "which was kindly provided by Abbott" [Guerrero, Stein, Asch, 1993]). Dr. Asch's audacity is further compounded by his brazen authoring of an article that lectures on a woman's need for a psychological evaluation prior to egg donation. Before public exposure of his wrong-doing, Dr. Asch (as well as Dr. Friedman) was considered renowned, and voted by peers as one of the 'Best Doctors of the Year'. Undoubtedly, these physicians would still be considered renowned had an investigation of their fraudulent actions never been undertaken. Since researchers, etc. were paying Asch and cohorts thousands of dollars ('stuffed daily in briefcases') for this genetic research material then … **who** are they paying now, and **where** are these research eggs and embryos now coming from?

5) Critical consideration should be given to what the research-material 'supply and demand' situation was in the 1980's towards (and ramifications upon) the 'value' of women's eggs. As a result of reproductive technologies as well as the "dwindling supply of chimpanzees for medical research" (Fox, 1984), and the "severe shortage of mice used by approximately 11,000 labs in medical research" (CQ, 1989), women's ova/ries were (and are) in supply and demand. In 'Egg Snatchers', an ob/gyn resident describes the routine:

"Sometimes the infertility specialist would appear right before hysterectomies were scheduled. He would ask the gynecologists if they planned to take the ovaries out along with the uterus. He needs some, he would explain. 'Don't take them out just on my account' he would say." This resident "subsequently learned that this infertility specialist had been involved at that time in an in vitro fertilization program, the existence of which had not been publicly announced." (Corea, 1984)

And while today the justification for the use of embryos centers on "curing" a multitude of diseases, the initial use of embryonic tissue was alleged to be for "commercial purposes" – as in cosmetics (Lipstick, 1985). A West German testifying in 1985 before the Council of Europe alleged an "international trade in embryos for 'commercial purposes'" and stated that in 1981 French customs seized "a consignment of embryos" enroute to California; and in 1982 "the California police seized another five hundred embryos intended for cosmetic production." The Parliamentary Assembly of the Council of Europe was asked for legislation banning "commercial and industrial uses of embryos", however, the legislation was reportedly "stalled in committee because lobbyists for scientists and the pharmaceutical industry inhibited any passage of such legislation." (Raymond, 1993)

Despite the fact that it was not until October 1990 that lupron acquired its first female application approval by the FDA (for endometriosis), ***by*** 1990, data from infertility clinics (already more than a billion dollar industry [Talan, 1990]) reveals that 97% of ovulation induction cycles were **prescribed** GnRHa. These results "indicate[d] an ***increase*** in the *use* [**prescription**] of gonadotropin-releasing hormone analogs" (MRI, 1992) (emphasis added). Many, many physicians, including Dr. Joe Massey, have promoted lupron as "the GnRHa in use in most United States based [infertility] programs." (Keenan, Cohen, Suzman, Wright, Kort, Massey, 1991) And please bear in mind one of the industry's aggressive mantras to the resistive "patient": "But Lupron results in more eggs … !"

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