DATA: Hormone Therapy with Pellet Implants

Hormone replacement therapy by pellet implantation has been used with great success in the United States, Europe and Australia since 1938 and found to be superior to other methods of hormone delivery (Greenblatt 49, Mishnell 41, Stanczyk 88). It is **not** experimental. Pellets deliver **consistent**, physiologic levels of hormones and avoid the fluctuations of hormone levels seen with other methods of delivery (Greenblatt 49, Thom 81, Stanczyk 88). Estrogen delivered by subcutaneous implants maintains the normal ratio of estradiol to estrone (Thom 81, Stanczyk 88, Owen 92, Cravioto 01).

Hormones delivered by the subcutaneous implants bypass the liver, do not affect clotting factors and do not increase the risk of thrombosis (Notelovitz 87, Seed 00). Bioidentical testosterone delivered subcutaneously by pellets is cardiac protective, unlike oral, synthetic testosterone (Sands 97, Worboys 00).

Testosterone and estradiol delivered by pellet implantation, does not adversely affect blood pressure, lipid levels, glucose or liver functions (Burger 84, Barlow 86, Notelovitz 84, Stanczyk 88, Davis 95, 00, Sands 97, Seed 00, Cravioto 01).

Pellets are **superior** to oral and topical hormone therapy with respect to relief of menopausal symptoms (Staland 78, Cardoza 84). Estradiol and testosterone implants have consistently been shown to improve insomnia, sex drive, libido, hot flashes, palpitations, headaches, irritability, depression, aches, pains, and vaginal dryness (Staland 78, Thom 81, Brincat 84, Davis 95, 00, Cravioto 01).

Hormone replacement therapy with estradiol and testosterone implants is **superior** to oral and topical (both the patch and gel) hormone replacement therapy for **bone density** (Savvas 88, 92, Davis 95, Anderson 97). The pellets not only prevent bone loss but also actually **increase** bone density (Savvas 88, Studd 90, Garnett 91, Savvas 92, Naessen 93, Holland 94, Studd 94, Davis 95, Anderson 97, Seed 00, Panay 00).

Testosterone implants in women have been shown to improve lethargy, depression, loss of libido, and hot flashes without attenuating the beneficial affects of estradiol on cardiac and lipid profiles (Sands 97, Seed 00). Testosterone delivered by subcutaneous implants does not increase the risk of breast cancer (Dimitrakakis 04, Tutera 06 under publication, Natrajan 02) as does oral, synthetic methyl-testosterone (Tamimi 06).

Pellets do not have the same risk of breast cancer as the synthetic progestins or synthetic Methy-testosterone. In fact, studies show a **reduction** in the incidence of breast cancer with the implantation of **testosterone** pellets, with or without estradiol pellets (Dimitrakakis 04, Tutera 06). Hormone replacement therapy with a 20 mg estradiol pellet has been shown to have a lower risk of breast cancer than patients without hormone replacement therapy (Davelaar 91). Even after over 20 years of therapy with hormone implants, the risk of breast cancer is not increased (Gambrel 06). In breast cancer survivors, hormone replacement therapy with pellet implantation does **not** increase the risk of cancer recurrence or death (Natrajan 02) as does estrogen in combination with the synthetic progestins (Habits Trial 04).

Hormone replacement therapy with pellet implantation has an extremely low incidence of side effects (Cardoza 84, Barlow 86, Ganger 89, Pirwany 02)) and high compliance rate (Gambrell 06). It has been shown to be extremely effective in the treatment of migraine headaches (Magos 83).

Testosterone replacement therapy in men with subcutaneous implants (pellets) has been show to be extremely effective, convenient and safe (Handelsman 90, 92, 97, Kelleher 01, 04, Conway 88, Jockenhoval 96, Zacharin 03, Schubert 03, Dunning 04).

The testosterone implant is the only licensed form of testosterone in England for women. The 75 mg testosterone implant is FDA approved in the US (July 13,1972, male patients). Other doses need to be compounded by trained pharmacists.

This sterile product is cylindrically shaped and weighs approximately 77mg (75mg testosterone). The inactive ingredients include 0.2mg stearic acid USP and 2mg polyvinylpyrroidone USP. Other pellets may be up to 100% active ingredient.

The routine doses of testosterone delivered by pellet implantation in recent studies are between 750 and 1200 mg in men. The pharmacokinetics and pharmacodynamics are well established showing that these doses deliver reproducible physiologic levels of testosterone for 4-6 months. The studies show that pellets have a zero order release rate. Although individuals vary, the 75 mg testosterone pellet has a consistent release rate approximately 0.5 mg of testosterone per day for a total of approximately 6 mg per day for 12 pellets. A 6-9 mg daily production of testosterone is a 'physiologic' level produced by the testicles.

Testosterone implants have a near linear release rate. Peak serum testosterone levels with the implants are usually seen at month one. Therapeutic testosterone levels at month one, are expected at the upper limits of normal for healthy young males (800-1100 ng/dL). By month 4 to 5 testosterone levels drop to below 500-600 ng/dL at which time symptoms return and the pellets are reinserted. Each individual has their own reproducible levels where symptoms return.

Testosterone implants have been used in women. Doses used in studies are as low as 50 mg and up to 225 mg. In the United States, common doses are 75, 100, 110 mg, 125 and 150 mg. There are minimal side effects at these doses (slight increase in facial hair 20% and mild acne 5%), which may be reduced by lowering the dose, if the patient chooses. If measured, serum treatment levels are elevated above non-treatment levels at month one (Burger 84, Gambrel 06l, Thom 81, Glaser unpublished 2008). Urine and saliva levels remain normal. There are no signs of androgen excess at these treatment levels. Symptoms return when testosterone levels reach the upper end of endogenous ranges (Burger 84, Glaser). End organ response to testosterone remains optimal (i.e., relief of depression, increase in bone density, relief from insomnia, relief from aches and pains, lessened anxiety, improved memory and concentration, increased energy, etc.). Testosterone implants last between 2.5 and 5 months in female patients. Individual treatment doses and treatment ranges are established and are reproducible.

In a paper published in the journal 'Menopause' in 2004, '*Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy'* women were referred for testosterone supplementation for the following indications:

- Complaints of emotional lability
- Fatigue and loss of stamina
- Impaired concentration and memory
- Breast tenderness
- Loss of libido
- Sleep disturbance
- Muscle weakness

Patients received testosterone implant containing 50-150 mg of testosterone every 5 months in addition to conventional estrogen or estrogen/progestin therapy. The testosterone dose was titrated to alleviate symptoms (listed above), **improve bone mineral density** and minimize adverse affects (slight increase in facial hair and acne). The most common dose was 100 mg.

The addition of testosterone, delivered by pellet implant, was shown to reduce the incidence of breast cancer in women treated with conventional hormone therapy. In women, not on synthetic progestin therapy (which is known to increase the incidence of breast cancer RR 1.69-2.00), the incidence of breast cancer was lower than 'no hormone therapy'.