

AN INTRODUCTORY HORMONE TALE

Ready, Fire, then Aim

Once upon a time, the pharmaceutical giants Searle, Upjohn and Wyeth-Ayerst hired a fellow named Robert A. Wilson MD to write a book extolling the virtues of estrogen supplementation for women after menopause. The take-home message from Dr. Wilson's book was basically this: if women didn't take estrogen after menopause, they were doomed to become unattractive hags and die prematurely. Women didn't take kindly to the thought that they would shrivel up and die without estrogen, and their physicians didn't want to be responsible for letting that happen either. The net result was that sales of prescription, patented oral estrogen began to climb, and didn't look back. Unfortunately, Dr. Wilson neglected to mention one detail: there really wasn't much research supporting the benefits of oral estrogen, especially estrogens from another species (pregnant mare's urine being the most common source). Pharmaceutical companies led the charge for hormone replacement in the 1960's and physicians willingly followed: a classic case of Ready, Fire – *then Aim*.

After a few years of giving women fairly high oral doses of non-human estrogens, we discovered that this approach led to an increased risk of cancer of the uterine endometrium or lining of the uterus. We had a chance at that point, to step back and reassess what we were doing.

We could have added progesterone, the natural hormone produced by the ovaries every month, to oppose the stimulating effect of the horse estrogen. We could have questioned our use of horse estrogen in human beings. We could have questioned the wisdom of *swallowing* hormones, which normally trickle directly into the blood from the ovaries. Instead, we kept the horse estrogen, and added oral medroxyprogesterone acetate (MPA), a synthetic, patentable molecule similar, but not identical; to the body's own progesterone. To be sure, MPA effectively suppressed the development of endometrial cancer, but in retrospect it was probably the worst possible partner for the horse estrogen, as we will discuss.

Time went on and sales continued to grow. Premarin[®] (conjugated estrogens from pregnant mare's urine) became the number one selling prescription drug in the United States, and hormone replacement therapy (HRT) became a billion dollar industry. In the research world, clouds were appearing on the horizon, but few physicians were watching the weather. Studies were accumulating that showed oral estrogen was associated with a small but definite increase in breast cancer, and that addition of MPA to the mix increased the risk. Studies on primates showed that even though estrogens exerted positive effects on the cardiovascular system, MPA opposed those benefits if the two were given together. Studies also showed that MPA given alone as a contraceptive had adverse effects on bone density. The clouds on the horizon were gathering for a storm!

THE WOMEN'S HEALTH INITIATIVE STUDY (WHIS) Key Points

Premarin® and Provera® arm

THE STUDY

- 16,608 postmenopausal women aged 50-79 years with an intact uterus.
- Women received either Premarin® 0.625mg and Provera® 2.5mg daily (8506 women) or placebo (8102 women).
- Outcomes measured included heart disease, invasive breast cancer, colorectal cancer, hip fracture, endometrial cancer, stroke and blood clots in lungs
- A global index summarizing the balance of risks versus benefits was also used.

RESULTS

- The study was stopped early because the global index indicated that on balance, the harm from using Premarin®/Provera® was greater than the benefit.
- Compared to placebo, Premarin®/Provera® had:
 - A 41% increase in strokes
 - A 29% increase in heart attacks
 - A doubling of rates of blood clots
 - A 22% increase in total heart disease
 - A 26% increase in breast cancer
 - A 37% *reduction* in colorectal cancer
 - A 1/3 *reduction* in hip fracture rates
 - A 24% *reduction* in total fractures

The WHI proved that oral dosing with non-human and synthetic hormones in the form of Premarin® and Provera® is more harmful to women than giving them no hormones.

By the end of the 1980's numerous studies had been done looking at the effects of hormones in animals, human cells and humans. The papers written on the subject could

easily fill a room. Despite mounting evidence of increased breast cancer and cardiovascular risks, there was still enough data to suggest that estrogens *should* be good for the heart and *were* good for the bones, the brain, the urogenital system and the skin. No one was too worried.

Eventually, in an attempt to resolve some of the apparent contradictions, various large trials of HRT were launched, studying thousands of women, looking at multiple outcomes to determine whether the benefits outweighed the risks. In the summer of 2002, the storm finally broke. The Women's Health Initiative examined combined HRT in over 16,000 women and found that the risks of combined horse estrogen and MPA outweighed the benefits. An anti-HRT backlash, whose effects will be felt by women for decades, was unleashed.

Therein lies the purpose of this book. The backlash against HRT is causing needless suffering for many women in menopause. Our aim is to clear up the confusion around hormone replacement, offer 3 simple strategies to determine whether a woman would benefit from hormone replacement *and* look at the best options for HRT in light of recent research findings. We are ready: we have a clear target: let's fire away!