

Editorial

LESSONS FROM THE HISTORY OF HORMONE REPLACEMENT THERAPY

“Murderer!” he said suddenly in a quiet but clear and distinct voice. Raskolnikov went on walking beside him. His legs felt suddenly weak, a cold shiver ran down his spine, and his heart seemed to stand still for a moment, then suddenly began throbbing as though it were set free. So they walked for about a hundred paces, side by side in silence. The man did not look at him. “What do you mean... what is... Who is a murderer?” muttered Raskolnikov hardly audibly. “You are a murderer,” the man answered still more articulately and emphatically, with a smile of triumphant hatred, and again he looked straight into Raskolnikov’s pale face and stricken eyes.

Crime and Punishment (Fyodor Dostoevsky, 1866)

Rodion Romanovich Raskolnikov in Dostoevsky’s classic novel *Crime and Punishment* formulates and executes a plan to kill a rich lady for her money and justifies it by the doctrine that murder is permissible in pursuit of a higher purpose. In Russian language ‘raskolnik’ means ‘schism’, that is ‘the offense of attempting to produce a formal breach of union’. The history of rise and fall of hormone replacement therapy indeed reflects such a ‘raskolnik’ science at display, making mockery to the spirit of credible science and humanist ethical science.

‘Hormone replacement therapy’ (HRT) has been prescribed to women at menopause since 1960s. It can refer to the use of estrogen alone or to a combination of estrogen and a progestogen or a combination of estrogen and an androgen. The word ‘replacement’ in it is wrong, because the treatment never raised postmenopausal women’s hormones to premenopausal levels. Also, hormone treatment after menopause will not replace the function that gonadal steroids play in the body before menopause.

Also, the word ‘therapy’ is misnomer. The term ‘therapy’ is used in medicine when there is some form of pathognomy; menopausal transition, on the contrary, is a normal physiological process with age in women.

Although estrogen has been used since 1930s to treat various physical

changes that women experience at menopause, mid-1960 onward the idea that every woman alive today had the option to remain *feminine forever* was catching up, courtesy aggressive selling tactics of pharmaceutical companies. It is now evident that the entire concept of hormone replacement therapy was more of a clever marketing idea and was never supported by good science. During post world war II, many big pharmaceutical companies sensed an easily sellable commodity in the form of 'estrogen' and identified a huge mass of consumer in the form of 'menopausal women', based on a few reports available in this area; they cleverly infused the market with a few *myths*, as if derived from research, innovation and science. Some of these myths are:

1. Menopause is a relatively new phenomenon emerged because of extended life period.
2. Menopause is a disorder.
3. Menopause is a deficiency condition, especially of estrogen.
4. Menopause is bad socially and individually.
5. Menopause can be cured by estrogen.

All of these claims ranged from unsubstantiated suggestions to glaring lies. Furthermore, it was claimed by the sellers that estrogen not only protects women from hot flashes, vasomotor and cardiovascular problems, and osteoporosis associated with menopause, it prevents broad range of ailments associated with aging in women, from general aches and pains to Alzheimer's

disease, depression, and heart attack. There was however very rudimentary science behind it to support all the tall claims. At the best, it appeared that estrogen along with exercise and enrichment of life process might provide to-some-extent an improvement in the quality of life to a subpopulation of aging women.

On the other hand, there was clear indication in evidence-based interpretation since 1940s that estrogen treatment might actually be harmful to women's health. Some of the red warnings were raised by the scientists who were directly involved in estrogen research, like Edgar Allen and his associates (who initiated research on estrogen in females since 1923), and Charles Dodds (who discovered diethyl stilbestrol, DES in 1938). There was evidence to suggest that estrogen might precipitate cancer in females. In the mid-1970s, several studies linked estrogen treatment to endometrial cancer and breast cancer in women in consonance with Dr. Allen's prediction. But it was claimed that adding a progestin to estrogen may reduce this risk. After that, doctors all around began prescribing combined hormone treatment to women who still had a uterus and thus were at risk of endometrial cancer, while women who had undergone hysterectomy continued to take estrogen alone despite seemingly conflicting data available in the literature with some research suggesting benefits and other studies indicating perils.

The observation that estrogen treatment might be detrimental to cardiovascular

physiology has been documented repeatedly; however, these reports were brushed aside in one pretext or other. In 1993, a study on 3000 women with heart disease who volunteered for four years in randomized manner to take either estrogen-progesterone combined pill or placebo in the Heart and Estrogen/Progestin Study (HERS). HERS reports challenged the theory that hormone treatment was indeed beneficial for heart disease in women. It was published in 1998 indicating that women with heart disease who used hormone treatment had worse outcomes than those who did not take hormones. Again HERS results were discounted by the argument that the observation did not hold good for healthy women. Thus, the use of hormone therapy continued unabated.

The Women's Health Initiative (WHI) instituted a large-scale research study in 1991 on benefits and risks of combination HRT involving a total of 161,808 women participants. In the course of the study, in May 2002, it was observed that there were an increase in cases of breast cancer, heart attacks, strokes and blood clots with fewer hip and other fractures and cases of colorectal cancer with no additional risk of endometrial cancer after an average of 5.2 years of use. The impact of the results was so significant that the study was stopped on July 8, 2002 although it was supposed to be continued till 2005. Million Women Study in England reported in 2003 also observed unequivocally higher chances of breast and uterine cancers in women following long term hormone treatment.

An interesting observation of the WHI study is that participants were asked to guess whether they have been taking a HRT or a placebo, about half of those on placebos thought that they were taking active medicine. According to one calculation from the WHI study results reveals that if 6 million women are taking combination HRT, it would result in an extra 4800 cases of breast cancer every year and if all the women took it for 5 years it would mean an extra 24,000 cases of breast cancer. One may therefore conclude that pharmaceutical companies that have been pushing such unsafe medicine into women's body who are otherwise healthy were indeed 'Murderer'!

The underlying agonizing history of hormone replacement therapy however reveals a few important lessons for everybody. It is imperative that generalized social thinking should be based on objective, concrete and scientific knowledge, be it hormone treatment for menopausal women, or validity of HIV-AIDS linkage in the term of Koch's postulation, or safety of GM seeds. Of course, science and scientific research may be practiced towards practical necessity of humankind, but with due sanctity and optimized methodologies for obtaining robust interpretation. The conclusion it derives must not be nested upon any vested interest. Finally, the investors and sellers should acknowledge that inflicting healthy body with unsubstantiated biological strategy is a serious immorality to the humanist arm of science and to humanity. So, it should be avoided at any rate. Even if all these sound UTOPIAN!

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