Introduction

Sea sponges, jellyfish and worms all share the same steroid hormones as humans, making this very efficient system of endocrine communication at least five hundred million years old. Though the word ‘hormone’ was not used until 1905 (by the British physiologist Ernest Starling), the concept of using hormones as medical therapy is much older than that. In 1025 CE, Chinese physicians were distilling hormonal elixirs from the urine of young men and women in the hope of preserving youth and vigour in their older patients.

Early Oestrogens

A similar approach was taken by the pharmaceutical company Merck in the late nineteenth century, although they sourced their hormonal material from pulverised cow ovaries and restricted its use to women. Their product, ‘Ovariin,’ was marketed across Europe as a treatment for both menopausal symptoms and menstrual problems. In the 1920s, scientists isolated a hormone they called ‘folliculin’ (actually oestrone) from the urine of pregnant women, and the modern era of hormone therapy really began. By 1930,
two pharmaceutical companies, Schering (in Germany), and Ayerst (in Canada), were both marketing oral oestrone to alleviate menopausal symptoms and to ‘preserve youth’.

However, the extraction of hormonal compounds from human urine was logistically difficult and the final product was very expensive. It wasn’t long before researchers began to look for a cheaper and more reliable source from which they could manufacture steroid hormones. By the mid-1930s, German scientists found this source in the cholesterol harvested from the animal brains and spinal cords that were readily available from the local slaughter houses. The Canadian company Ayerst took a different approach when, in 1941, it realised that biologically active oestrogens could be just as readily obtained from the urine of pregnant mares as from pregnant humans. The availability of Premarin® (Pregnant mares’ urine) greatly increased the use of menopausal oestrogen therapy in the United States and Canada, since it was significantly less expensive than the earlier oestrogen therapies.

**Early Progestogens**

The early twentieth century also saw scientists attempting to develop an effective hormonal contraceptive. Most researchers realised that the answer to this was likely to be found in the hormones produced by the corpus luteum. In 1934, the American gynaecologist Professor Willard Allen finally succeeded in isolating a pure form of the hormone we now call ‘progesterone’, and used it to successfully inhibit ovulation in a number of experimental animals. Allen’s luteal hormone was, however, extremely expensive. It required the corpora lutea of fifty thousand sows to produce 1mg of what is now called ‘progesterone’. This was equivalent to a cost today of around US $14,000.00/gram.

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Proluton® combined cyclically to induce menses in a woman with previous amenorrhoea, in the hope that such treatment might reverse infertility. Ironically, the effect of this combination was almost certainly contraceptive. In the quest for an orally-absorbed oestrogen, scientists modified the side-chains of the basic progesterone structure, attempting to produce a synthetic analogue with progesterone-like effects. The first orally active synthetic progestogen, ethisterone, was developed by Schering in 1939 and was given the trade name Proluton-C®. However, this product was not only expensive, but had limited appeal due to the high incidence of androgenic side-effects.

**Enter Russell Marker**

By the early 1940s, the American biochemist Russell Marker had developed a relatively simple five-step process for converting various plant steroids into active progesterone. He found a likely source for commercial production in the massive tubers of the Mexican wild yam and proceeded to smuggle several bags of these back to the United States. Marker approached several large pharmaceutical companies to back the project, but was unable to reach a suitable financial agreement with any of them and decided to continue the development himself. Within a month, he had produced about three kilograms of progesterone in a borrowed laboratory, worth in 1942 the equivalent of US $3.5 million today! The impact of Marker’s work was such that, by 1955, 80% to 90% of all steroid hormone synthesis began with the Mexican yam.

**Steroid Hormones for Menopause Management and Contraception**

In the 1950s, both oestrogens and testosterone were widely promoted, particularly in the United States, as the panacea for a wide range of menopausal symptoms (both physical and psychological). The author suggests that it is most enlightening to explore these uses at [https://www.youtube.com/watch?v=HxgxsT5zLU](https://www.youtube.com/watch?v=HxgxsT5zLU). It would, however, be some years before the dangers were understood of using unopposed oestrogens in women who still had a uterus. The search for an effective hormonal contraceptive also continued, and this saw the development of several more orally active synthetic progesterone-like compounds. It also saw the beginning of a rift in terminology. While the rest of the world refers to both progestrone and its synthetic analogues as ‘progestogens’, the United States called these new synthetic steroids ‘progestins.’

**The Development of the Oral Contraceptive Pill**

The original oral contraceptive pill trials were designed to test a variety of progestogen-only preparations for efficacy and side-effects. It became obvious early in the piece, however, that a flaw in the production process meant that one of the manufactured progestogens had been contaminated by a small amount of the synthetic oestrogen mestranol. Subsequent efforts to eliminate the mestranol led to significantly more irregular bleeding in the trial subjects than had been seen in the subjects taking the
contaminated product. Mestranol was added in combination with the progestogens and thus, through sheer serendipity, the combined oral contraceptive pill was created.

Progestogens in Menopausal Hormone Therapy and Contraception

In the mid-1970s, the link between unopposed oestrogen used in menopausal hormone therapy and an increased risk of endometrial cancer was discovered. At this point, the synthetic progestogens used in contraceptive preparations were tentatively added to the menopausal therapy for women with an intact uterus. In the United States, the progestogen used was most commonly medroxyprogesterone acetate, or to lesser extent, norethisterone or levonorgestrel. However, there was a problem in that the addition of a progestogen increased the potential for side-effects in women using combined therapy. European clinicians had in fact adopted combined menopausal hormone therapy several years earlier, but preferred different synthetic progestogens (mainly norethisterone acetate, cyproterone acetate, dydrogesterone, nomegestrol acetate and promegestone). It had become possible by the 1980s to micronise progesterone itself, to the point where oral or vaginal absorption became significantly more reliable. This compound, identical to that produced by the corpus luteum, became the preferred progestogen for use in menopausal hormone therapy in much of Europe, and particularly in France. Since, for many women, progesterone is associated with fewer side-effects than synthetic progestogens, the use of micronised progesterone, (marketed as ‘Prometrium®’ in Australia), in combination menopausal hormone therapy is now increasing across the world.

Summary

The ability to manufacture ovarian hormones has revolutionised both contraception and menopause management over the last century. We now have a wide range of steroid hormones, both synthetic and body-identical, which allow clinicians to individualise such therapy.

Declaration

Dr Terri Foran was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author. The advertiser does not necessarily endorse or support the views expressed in this article.

The author’s competing interests statement can be viewed at www.healthed.com.au/monographs.

Further Reading


References


