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SCIENZA E... NON SOLO  
L'ISTITUTO LOMBARDO PER LUCIANO MARTINI

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# A WALK THROUGH LUCIANO'S ROLE IN INTERNATIONAL MEETINGS AND THE ROAD TO A NOVEL UNDERSTANDING OF SEX STEROID PHYSIOLOGY

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SUNTO. – Luciano Martini è stato un endocrinologo di fama internazionale e un ambasciatore dell'endocrinologia italiana in tutto il mondo. Ha portato importanti contributi sperimentali a sostegno della nuova scienza dell'intracrinologia. Dopo la menopausa, la secrezione degli estrogeni viene a cessare mentre i livelli di DHEA raggiungono valori minimi. Estrogeni e androgeni vengono prodotti all'interno delle cellule a partire dalle piccole quantità residue di DHEA. Questi steroidi sessuali svolgono una azione intracellulare e vengono escreti solo dopo inattivazione, evitando così una stimolazione dell'endometrio e possibili azioni in altri tessuti. In tre studi clinici prospettici, randomizzati, in doppio cieco e controllati con placebo, della durata di 12 settimane, è stato dimostrato come la somministrazione intravaginale di DHEA (prasterone) sia in grado di migliorare i sintomi più disturbanti della menopausa quali secchezza della mucosa vaginale e dispareunia. Di particolare importanza, i livelli sierici degli steroidi sessuali sono rimasti entro i limiti di norma, spiegando così l'assenza di effetti sistemici. In conclusione, la causa principale dei sintomi della menopausa non risiede nella mancanza di estrogeni ma in quella di DHEA e questa nozione deve essere alla base della strategia terapeutica.

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ABSTRACT. – Luciano Martini has been an internationally renowned endocrinologist and a remarkable ambassador of Italian endocrinology through the world. He brought important experimental contributions in support of the new science of intracrinology. After the menopause, the secretion of estrogens stops while serum DHEA attains its lowest values. Estrogens and androgens are produced intra cellularly from the small residual amounts of DHEA. They act within the cells and are released only after inactivation, thus avoiding stimulation of the endometrium and possible actions in other tissues. In three independent 12-week prospective, randomized, double-blind and placebo-controlled clinical studies, it was shown that intravaginal administration of DHEA

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(prasterone) improves the severity score of the most bothersome symptom of the menopause such as vaginal dryness and dyspareunia. Most importantly, all serum sex steroids remained within normal values, thus explaining the absence of systemic effects. In conclusion, the lack of DHEA availability, not the lack of estrogens, is the main cause of the symptoms of menopause and this notion should guide the therapeutic strategy.

Luciano Martini has been a remarkable ambassador of Italian endocrinology through the world and has been, especially through the organisation of international meetings, a major promoter of science, including his support for the new science of intracrinology. Following demonstration of the essential role of intracrinology in prostate cancer in 1982 by the development in Quebec City of combined androgen blockade, the most efficacious treatment of prostate cancer recognized worldwide as most efficacious androgen blockade, intracrinology has now been found to be the exclusive mechanism of sex steroid formation after menopause.

At menopause, the secretion of estrogens stops while the secretion of dehydroepiandrosterone (DHEA), which started decreasing earlier at the age of 30 years, is already decreased, on average, by 60% and continues to decrease thereafter. Accordingly, after menopause, DHEA becomes the exclusive source of both estrogens and androgens made intracellularly in each peripheral tissue. Since sex steroids are inactivated inside the cells, intracrinology maintains the circulating levels of estrogens at very low and biologically inactive concentrations, thus avoiding stimulation of the endometrium and a possible action in other tissues.

In three independent 12-week prospective, randomized, double-blind, and placebo-controlled clinical studies, the effect of daily intravaginal 0.50% (6.5 mg) prasterone was examined on the four co-primary objectives required by the US FDA in women having moderate to severe (MS) pain at sexual activity (dyspareunia), a main symptom of vulvovaginal atrophy (VVA) due to menopause. In 436 women treated with prasterone and 260 women who received placebo, an average 35.1% decrease over placebo in the percentage of parabasal cells ( $P < 0.0001$ ), an average 7.7% increase in the percentage of superficial cells ( $P < 0.0001$ ), and a mean 0.72 pH unit decrease in vaginal pH ( $P < 0.0001$ ) were observed. The severity score of the most bothersome symptom dyspareunia was decreased by 0.46 unit (49%)

( $P < 0.0001$  over placebo), whereas the severity score of MS vaginal dryness decreased by 0.31 unit ( $P < 0.0001$  over placebo). A very positive evaluation was obtained on the acceptability of the technique of administration of the insert, whereas the male partners reported a very positive evaluation of the changes observed in their sexual partner. Most importantly, all serum sex steroids remained within normal values, thus explaining the absence of systemic effects. Intrarosa® has been approved by both the US FDA and EMA for all European Union countries.

## CONCLUSIONS

In order to correct VVA/genitourinary syndrome of menopause (GSM), the logical objective of therapy should simply be to remove the cause of the problem. The lack of DHEA availability, not the lack of estrogens, is the main cause of the symptoms of menopause. Such a strategy is essentially based upon the physiology of sex steroids in women or intracrinology and corrects the symptoms of VVA/GSM with no systemic safety different from normal.