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January 18, 1980.

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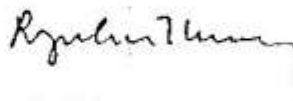
Dear Dr. Castro:

Thank you for your good letter of September 11, 1979, and the accompanying reprints of your earlier papers! These were, I must say, unknown to me. There is indeed no doubt that you had come to a conclusion identical to ours; we will most certainly quote your reference in future notes by us.

You may be interested in the latest development in the field, in our laboratory; we have shown that aqueous extracts of ovarian tissue, as well as the culture medium of the rat granulosa cells, contain a peptide with LRF-like activity (see a note in late November or December, C.R. (Acad. Sci. - Paris). This molecule is probably different from the decapeptide LRF.

With thanks and best wishes,

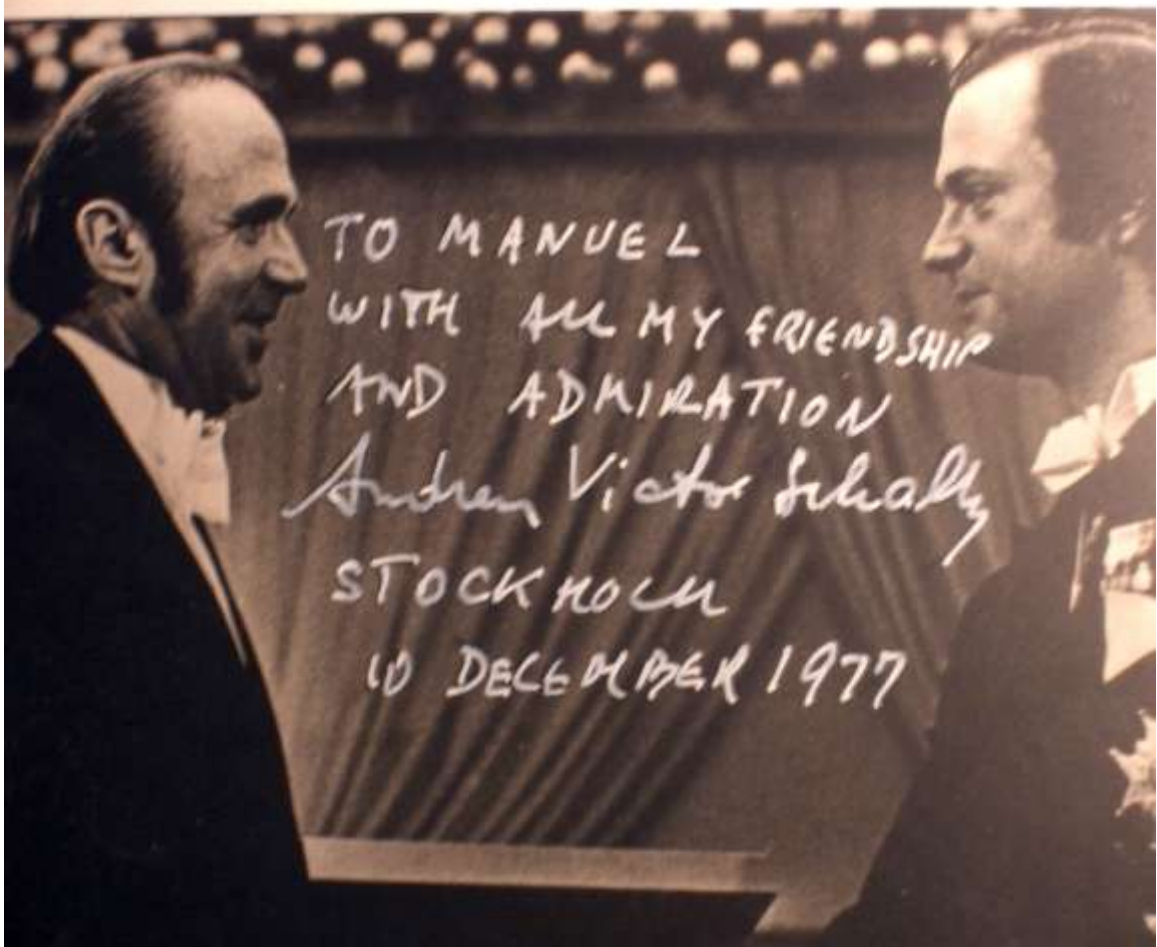
Yours sincerely,



Roger Guillemin.

RG/aww

NOBEL LAUREATE



TO MANUEL
WITH ALL MY FRIENDSHIP
AND ADMIRATION
Andreu Victor Schally
STOCKHOLM
10 DECEMBER 1977

NOBEL LAUREATE 8535
(1901-1972)

VIAMINS AND HORMONES VOL. 18
VITAMINS AND HORMONES

Recent Approaches to Fertility Control Based on
Derivatives of LH-RH*

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This chapter is dedicated to the memory of Emanuel (Manya) M. Bogdanov, Professor of Physiology, Medical College of Virginia, colleague, collaborator, and friend, who contributed much to the concepts of regulation of pituitary gonadotropin secretion and whose untimely passing is a great loss to all endocrinologists.

decrease in the number of viable pups delivered (Corbin *et al.*, 1978a). Chronic precoital injections of LH-RH (100 μ g) for 7 days also caused a contraceptive effect and inhibited pregnancy (Beattie and Corbin, 1977).

The mechanism of this action was studied by various investigators. The possibility of a direct effect of LH-RH on the ovary was first suggested by Neves-e-Castro *et al.* (1974) and Neves-e-Castro and Reis-Valle (1975). Rippel and Johnson (1976b) were the first to observe that hypophysectomy did not alter the inhibitory effect of LH-RH on the ovarian weight gain caused by hCG (see also next section). Concomitant treatment of hypophysectomized female rats with FSH and D-Leu⁶, (N⁶-Me)Leu⁷-LH-RH or D-Trp⁶-LH-RH EA suppressed the FSH-induced increase in ovarian weight and in ovarian aromatase. Granulosa cells harvested from hypophysectomized rats treated with LH-RH analogs produced a significantly smaller amount of estrogen than did the cells from rats treated with FSH alone (Hensch and

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from 16% premenopausally to 25% in the last group, with an over-all incidence of 20%. Of 16 instances of cortical thecomatosis, 13 (81%) occurred in association with cortical stroma hyperplasia. Cortical granulomas (53%) and cortical stroma fibrosis (59%) showed less significant association.

► [Neves Castro (*Gaz. méd. port.* 11:49, 1958) says that pseudopregnancy in the uterus produced by the persistence of the corpus luteum is due to direct hormonal action on the traumatized endometrium by the ovaries rather than stimulation of luteal activity through the pituitary gland. He observed a trophic action of rabbits' deciduoma grafts on the genital tract of young female mice. The same author (*Arq. pat.* 30:129, 1958) performed experiments to show that the uterus has an endocrine action. He found fluorescence in the endometrium of the rabbit on microscopic examination and determined that the fluorescence and traumatic deciduomas are identical. He believes that the problem of the hormones and their relation to the uterine mucosa can be solved not by electrophoresis but by immunoelectrophoresis.—Ed.]

Ovarian Function After Menopause was investigated by Clyde L. Randall, Paul K. Birteh and John L. Harkins³ (Univ. of Buffalo) in 1,768 smears from women who had not menstruated for over a year and had received no estrogen therapy for 6 months or more. In 661 (44.8%), a deficiency of estrogen effect was noted, which persisted in 812 (55.2%). Of women whose vaginal smears were evaluated 1-2 years after spontaneous cessation of periods, 17.7% had a moderate to marked estrogen deficiency and 8.2% had a slight deficiency. In 24.8% of this group, moderate to marked estrogen effect persisted and the other 50% showed only slight estrogen effect.

Of those whose vaginal smears were evaluated 2-5 years after spontaneous cessation of menses, 30.1% showed a marked to moderate and 6% a slight deficiency. Smears of 16.8% of this group indicated persistence of a moderate to marked estrogen effect, whereas 46.9% indicated only slight effect. In those evaluated 5-10 years after spontaneous menopause, estrogen deficiency was marked to moderate in 36.9% and slight in 7.9%. Estrogen effect was moderate to marked in 16.5% and slight in 38.6%. Estrogen deficiency was marked to moderate in 53.5% 10-15 years after spontaneous menopause and slight in 5%. Moderate to marked estrogen effect persisted in 13%. Vaginal smears 15 or more years after spontaneous cessation of menstruation showed marked to moderate deficiency in 50.7%, but 16% retained a

(3) *Am. J. Obst. & Gynec.* 74:719-732, October, 1957.

adrenal
adreny - arrey - plasmu (12)
virilism - adren - test. - viril.
hyperandrogenism - ovary - adrenal - hyperf.

Chapter 50

The Clinical Usefulness of Testosterone Measurements in Virilizing Syndromes in Women

C. WAYNE BARDIN, M.D. and MARVIN A. KIRSCHNER, M.D.

INTRODUCTION

There is considerable biologic evidence indicating that testosterone is the most important androgen secreted in man, and when production rates have been measured they were increased in almost every virilized patient studied. Since virilization is a normal manifestation of sexual development in man, this review will consider only the usefulness of androgen measurements in women where signs of hyperandrogenicity are distinctly abnormal. Although there are potent androgens other than testosterone (androst-5en-3 β ,17 β -diol, 17 β -hydroxy-5 α -androstan-3-one, 5 α -androstan-3 α , 17 β -diol) that may be implicated in some cases of virilism, their potential importance remains to be determined. We will, therefore, confine our remarks to testosterone.

Testosterone was first quantified in plasma in 1961 (Einkelstein *et al.*) and in urine in 1963 (Camacho and Migeon). Subsequent development of double isotope derivative techniques for the estimation of testosterone in biological fluids allowed the precise study of androgen physiology in normal and viril-

ized subject. Double isotope procedures, however, were difficult and time consuming, and only with the more recent development of noncompetitive protein binding and the gas chromatographic assays have testosterone analyses been widely available to the clinician. It is, therefore, pertinent to review the pathophysiology of testosterone metabolism in order to assess the usefulness and limitations of testosterone measurements in various biological fluids. However, since plasma testosterone analysis is particularly convenient, we will emphasize the importance of this measurement.

PLASMA TESTOSTERONE

Origin of Testosterone in Women: The origin of testosterone in the plasma is illustrated in Figure 1. There is considerable evidence to indicate that this androgen is secreted by both the adrenals and ovaries. For obvious reasons, however, there are few data on the levels of testosterone in these endocrine glands.

Ovarian venous testosterone levels have been estimated by several groups of investigators in a few women (Riva-

to test plasma of test. adren
1961

Cushing's Hyperplasia: Although hirsutism is not a manifestation of cortisol excess *per se*, it is frequently associated with increased ACTH secretion and hyperadrenocorticalism. A detailed study of testosterone production in Cushing's hyperplasia has not been reported. However, androstenedione production increased in normal women during ACTH treatment (Rivavola *et al.*, 1966). It follows, therefore, that plasma androstenedione could be the precursor of increased testosterone in adrenal cortical hyperplasia.

Adrenal Tumors: Virilization is a well established manifestation of many adrenal neoplasms. Androgen secretion by these tumors was demonstrated by finding higher levels in the tumor venous effluent than in the peripheral circulation (Wieland *et al.*, 1963; Saez *et al.*, 1967; Gandy and Peterson, 1968). In a recent study of 5 women with metastatic adrenal carcinoma, testosterone production rates ranged from high normal to above the range for men. In two of these women, approximately one half of plasma testosterone was derived from plasma androstenedione, and in two others, testosterone was either secreted or produced from some other plasma steroid precursor (Bardin *et al.*, 1968b).

For all three abnormalities of the adrenal cortex mentioned above, there are well established diagnostic tests: for virilizing congenital hyperplasia—demonstration of increased 17-hydroxyprogesterone or 11-deoxycortisol production; for Cushing's hyperplasia—demonstration of increased cortisol production; for adrenal tumors—demonstration of an adrenal mass. Although androgen levels in adrenal venous blood may localize adrenal tumors, it is important to note that the use of testosterone mea-

surements are usually not required for the diagnosis or management of adrenal virilism.

OVARIAN VIRILISM

Stromal Hyperthecosis: Ovarian stromal hyperthecosis (thecomatosis, thecosis or diffuse luteinization of ovarian stroma) is a condition of undetermined etiology characterized clinically by virilization and pathologically by diffuse hyperplasia and luteinization of ovarian stroma. The studies of Neves e Castro *et al.* (1963) demonstrated an elevated plasma testosterone level in a patient with this condition. In another study, the testosterone production rate was increased in a woman with stromal hyperthecosis, and 95% of the plasma testosterone was secreted by the ovaries with a relatively small quantity from peripheral synthesis (Bardin *et al.*, 1967). The origin of plasma testosterone in this and several other patients with ovarian disorders are compared in Table III.

Leydig (Hilar) Cell Hyperplasia: Ovarian Leydig cell hyperplasia and virilization has been reported in women with ovarian cysts and dysgenetic gonads. Although this association has been recognized for many years, the testosterone secretion and production in this syndrome was studied only recently. The patient was a 33-year-old woman with primary gonadal dysgenesis, hirsutism, clitoral enlargement and diffuse nodular Leydig cell hyperplasia of both gonads. Despite their striking morphologic abnormalities, the gonads secreted only 30% of the plasma testosterone. An additional 30% was from androstenedione and 40% was of adrenal origin or from some other plasma precursor which did not enter the androstenedione pool (Bardin *et al.*, 1969). These findings

Church plan on families

FROM OUR CORRESPONDENT

LISBON, OCT. 23

The Portuguese Government and Church have approved the organization of a family planning association, promoted by a group of progressive Roman Catholics and including priests among its members, but open to people of all creeds.

Its founder, Dr. Manuel Neves e Castro, expresses the aims of the association as "to enlighten, and to free from the shackles of ignorance".

A "moral consultation centre" will operate side by side with medical services to solve marriage problems, and the inaugural meeting of the association tomorrow, will include the first of a series of lectures by Dr. C. P. Sporken, the Dutch theologian.

Times 22-4-67