In terms of percentage of the basal value, LH increment was more in the pre-pubertal (54 fold) than seen in the adults (32 fold), whereas the FSH increment was just opposite, being 2.5 fold for the pre-pubertal and 4.2 fold for the mature animals. Prior treatment of the animals with sex steroids and gonadotropins upset the steroid-gonadotropin feedback mechanism, and great divurgence emerged between immature and mature animals when LH-RH was infused in them. The significance of this difference in the observed response during mammalian sexual maturation is discussed.

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Hypothalamic-Pituitary-Ovarian Feedback Mechanisms

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Feedback control involves regulation predominantly by circulating levels of hormones. There are stimulatory and inhibitory as well as internal and external forms of feedback. In the classic external feedback the controlling signals are the hormones produced by the peripheral target glands. The receptors which respond to changes in circulating steroid levels by initiating a change in the secretion of gonadotropins are located in the basal medial hypothalamus, anterior hypothalamus and preoptic area as well as the anterior pituitary. The stimulatory effects of gonadal steroids which are thought to bring about ovulation in the normal animal are presumably mediated in the suprachiasmatic region and preoptic area. It is postulated that a noradrenergic synapse mediates the stimulatory effects of estrogen and progesterone on the ovulatory release of gonadotropins (cyclic release center). The arcuate nucleus-median eminence dopaminergic tract may be involved in the so-called tonic discharge of gonadotropins and in the negative feedback action of gonadal steroids.

Sex steroids also affect the response to natural and synthetic LRH. Complex interaction of sex steroids both in the hypothalamus and pituitary may evoke differential release of LH and FSH thus indicating the possible existence of separate control mechanisms for LH and FSH.

There is recent evidence for short feedback loops, also referred to as auto or internal feedback. Short systems are involved in the regulation of LH and FSH secretion. LH *via* an effect on the basal median eminence seems to inhibit its on secretion.

Inhibitory as well as stimulatory short feedback mechanisms have been described for the control of FSH secretion. This positive short feedback appears to be peculiar for immature animals and may play a role at the time of puberty.

Finally, a third type described as ultrashort feedback has been found for the control of the gonadotropin releasing hormone on its own production. There are data indicating that hypothalamic LRH content is increased following small doses of chronically applied synthetic LRH in rodents under conditions which do not alter circulating gonadotropins or pituitary sensitivity to LRH.

Control systems concepts have become widespread among reproductive neuro-endocrinologists. No sufficiently reliable data exist today which could be used to successfully apply the systems analysis approach.

Identification and Measurement of LH-RH in Biological Fluids by Radioimmunoassay

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A radioimmunoassay for LH-RH has been developed using the following reagents: Synthetic LH-RH decapeptide (Hoechst) as standard; an antiserum raised in a rat to the des-glu^1, his^2-octapeptide of LH-RH conjugated to albumin; [^{125}I]labelled LH-RH decapeptide; ethanol precipitation is used to separate free and bound fractions.

The assay is highly specific for LH-RH and particularly for the C-terminus of the molecule; lack of the C-terminal amide group results in a complete loss of immunoreactivity. The sensitivity of the assay is 0.5 pg of LH-RH.

Assay of *hypothalamic extracts* after gel filtration, thin-layer chromatography and ion-exchange chromatography has shown that synthetic LH-RH and mammalian and avian LH-RH are immunochemically and chromatographically identical.

LH-RH can also be assayed in *urine*. 1 – 2 percent of an injected dose is excreted within 8 hours. Basal excretion rates in normal human subjects are 15 – 60 ng/day. Urine LH-RH is immunochemically identical but chromatographically (on ion-exchange columns) different and evidence sugests that it is the des-glu^1-nonapeptide or des-glu^1, his^2-octapeptide of LH-RH.

LH-RH has been detected and measured by radioimmunoassay in the *blood* of rats, rabbits, chickens, sheep and human subjects. In man the levels in peripheral blood range between <0.25 pg/ml and 3.5 pg/ml. Levels of up to 10,000 pg/ml can be detected in the jugular vein of the ewe during the oestrous cycle. Ion-exchange chromatography of serum extracts from various species followed by radioimmunoassay suggests that circulating immunoreactive LH-RH is heterogeneous and 4 distinct components have been identified.

LH-RH in Paediatrics

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Secretion of gonadotropins before puberty has been considered a dormant function until measurable levels in plasma and urine were reported in young children by means of radioimmunoassay techniques (Johanson *et al.* 1969, Raiti *et al.* 1969). More detailed studies and reports on feedback of sex hormones in prepuberal children (Burr *et al.* 1970, Kehl *et al.* 1973) supported the earlier concept of the gonadostat already functioning before puberty with decreasing sensitivity for circulating sex hormones. Even with expanding insight into the complicated dependency of CNS, pituitary, and end organ for the maturation of the reproductive system in man the mechanism of puberty onset remains obscure (Root 1973, Visser 1973).

The purification and synthesis of the hypothalamic gonadotropin releasing factor (LH-RH) (Schally *et al.* 1971, Monahan *et al.* 1971) provides a new tool for the evaluation of physiological and pathological relations between CNS and pituitary (Job *et al.* 1972, Grumbach *et al.* 1972). At present it is still uncertain whether the prepuberal pituitary can be stimulated to adult secretion of FSH and LH by LH-RH (Kastin *et al.* 1972). Dose responses of graded infusions of LH-RH in prepuberal boys and girls have not been reported so far. With a reliable RIA for FSH and LH in children (Joel *et al.* 1973) we found a distinct rise of the gonadotropins in prepuberal boys but no dose response after LH-RH (Hoe 471) in doses of $6.25 - 200\ \mu g/m^2$. In contrast prepuberal girls had a much higher rise of FSH with clear dose response while LH was comparable to boys. After puberty onset the starting levels of FSH were higher but were only moderately elevated after LH-RH with nearly no dose response. LH levels were less elevated at start but could be stimulated to a greater extent with more pronounced dose response. The interpretation of a sex dependent alteration in responsiveness and depletion of the pituitary during puberty will await more data on stimulation and feedback. Estrogens may play a role in prepuberal girls in triggering the more pronounced stimulation of FSH. The preponderance of LH after puberty onset may reflect the start of cyclic discharge and importance in adult females.

For the clinical evaluation of the CNS-pituitary axis in hypo- and hypergonadism in children first promising results have been published (Job *et al.* 1972, Roth *et al* 1972). The group of constitutional delay of maturation can be clearly distinguished. Results for organical gonadotropin deficiency are more difficult to interpret (Grumbach 1972). In precocious puberty the LH-RH test may be useful for the diagnosis of true or pseudoprecocity but for the treatment with competitive LH-RH analogs also (Vale *et al.* 1972). Routine treatment which still is not entirely satisfactory would be another field of this test in paediatrics. (Literature on request.)

LH-RH in Ovarian-Insufficiency *

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The use of synthetic LH-RH permits the assessment of pituitary responsiveness and helps to differentiate ovarian dysfunction originating in the pituitary from that originating in the hypothalamus and or in the central nervous system. In 100 patients with various types of ovarian insufficiency LH-RH-stimulation was done. The patients were classified according to their total gonadotrophin excretion: group 1: <2.4 IU II. IRP HMG/24 h, group 2:

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