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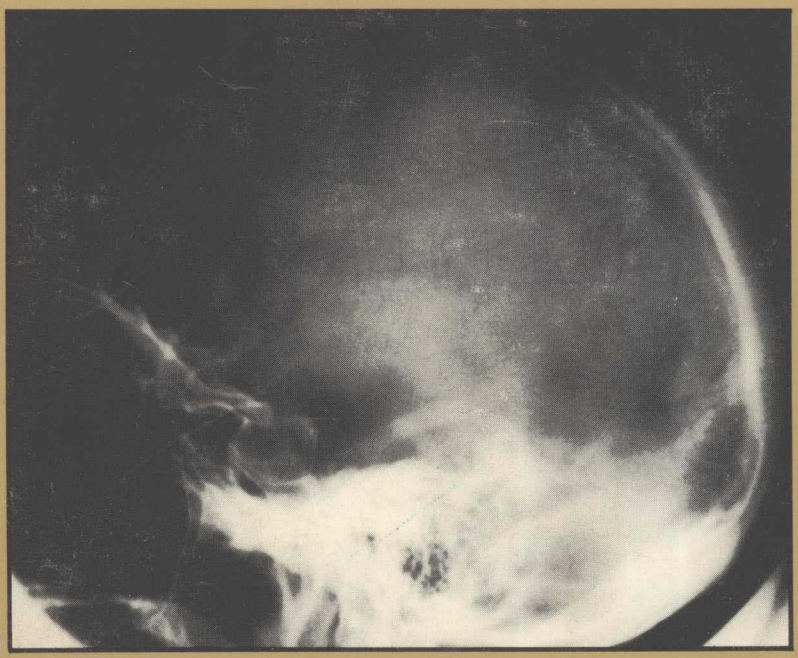
CLINICAL REPRODUCTIVE NEUROENDOCRINOLOGY

Edited by
Judith L. Vaitukaitis



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CLINICAL REPRODUCTIVE NEUROENDOCRINOLOGY

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FOREWORD

Although endocrinology textbooks satisfy a fundamental educational need and are routinely used as reference standards, an information gap often exists between the current state of the art and the published contents. Refinements in laboratory methods and assay techniques, the ever increasing awareness of metabolic and endocrine correlates that were once unapparent, and the dramatic discoveries in molecular biology and genetics make it extremely difficult to present an up-to-date volume at time of publication. The endocrinology textbook may effectively serve the academic community only for 3–5 years.

Despite the constant change in the state of the art, new discoveries defining relationships between endocrinology and molecular biology, physiology, genetics, biochemistry, biophysics, and immunology do not proceed at comparable rates. In fact, certain areas of endocrinology have been dormant for years.

In an attempt to offer timely reviews, a number of well-established authorities were offered the challenge of editing small editions that characterize the state-of-the-art in *specific* areas of endocrinology. This format relieves the editor (or editors) from the nearly impossible task of producing a "current textbook" of endocrinology and facilitates the pro-

cess of rapid and timely revision. Moreover, a specific endocrine discipline review can be revised if and when necessary without revising an entire textbook.

Endocrine Control of Growth, edited by W. Daughaday, was the first review in this series, *Current Endocrinology: Basic and Clinical Aspects.* This has been followed by individual texts on *Glucagon* and *Prolactin,* edited by R. Unger and L. Orci, and R. Jaffe, respectively. This series presents those current aspects of endocrinology of interest to the basic scientist, clinician, house officer, trainee, and medical student alike. These initial volumes will be followed by others on *Thyroid, Posterior Pituitary, Prostaglandins, Clinical Reproductive Neuroendocrinology, Androgens-Hirsutism, Biochemical Action of Steroid Hormones, The Adrenal, Hormonal Control of Skeletal Remodeling, Gastrointestinal Hormones,* and *Endocrine Aspects of Aging.* We are confident that this complete series and its revised editions, when appropriate, will serve the academic community well.

Louis V. Avioli, M.D.

PREFACE

Over the past several years hypothalamic peptides, biogenic amines, and several drugs have become available to serve as probes for the better understanding of the neuroendocrine secretory control of gonadotropins and prolactin. Moreover, availability of sensitive assays for measuring biogenic amines, releasing factors, and hormones combined with more sensitive diagnostic techniques have provided the tools necessary for better defining the pathophysiology of a variety of disorders of the hypothalamic-pituitary axis affecting reproduction. As a result, an exceedingly large volume of literature describing reproductive clinical disorders has accumulated over the past few years. A distillate of that vast body of information will be discussed.

The following chapters will provide a background of normal reproductive events throughout the life span. The background will serve as a basis for understanding and defining the pathophysiology of several endocrinologic disorders of reproduction affecting hypothalamic-pituitary secretion of gonadotropin and prolactin. Guidelines for diagnostic evaluation and therapeutic intervention will also be discussed.

The material presented by several experts in the endocrinology of reproduction is intended not only for the physician-in-training but also for the gynecologist, urologist, pediatrician, and internist who undoubtedly encounter many of the clinical disorders described herein.

Judith L. Vaitukaitis, M.D.

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GRIFF T. ROSS, M.D., Ph.D

CORRELATES OF GONADOTROPINS WITH OVARIAN MORPHOLOGY AND FUNCTION THROUGHOUT LIFE

INTRODUCTION

Gonadotropins and sex steroid hormones are both required for and are markers of normal ovarian function from the time that follicles appear in fetal ovaries until they disappear from postmenopausal ovaries. Indeed, the relationship of these hormones to ovarian function is sufficiently well established that given knowledge of the one, reliable inferences can be drawn about the other at any time in life. Consequently, the changes in gonadotropin secretion and the follicular responses elicited throughout life are of special interest to those physicians who are called upon to diagnose and treat disorders of ovarian function.

HORMONAL REQUIREMENTS FOR FOLLICLE MATURATION

Hormonal requirements for normal progression of follicle maturation have been adduced from morphologic and functional results of manipulating the hormonal milieu in rats of all ages. Although there appear to be significant species differences, there is convincing evidence, albeit indirect in some instances, that conclusions drawn from studies in rats

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are relevant to hormonal requirements for follicle maturation in human ovaries. Events that occur sequentially during follicle maturation and the hormonal requirements for these events will be considered in the following summary, designed to either inform or remind the reader of current information on the relationships of hormones to follicle maturation.

The follicle, the basic structural unit in the primate ovary, consists of a complex of cells that are functionally interactive in producing gamete and sex steroid hormones. The cells are: (a) a primary oocyte in which the first meiotic division has been suspended in prophase; (b) granulosa cells, which not only surround the oocyte but also form junctional complexes with its plasma membrane; (c) a limiting membrane (basal lamina), which surrounds the oocyte and its attached granulosa cells; (d) blood and lymphatic vessels, which approximate but do not penetrate the basal lamina; (e) thecal cells, which surround the basal lamina proximally (theca interna cells) and distally (theca externa cells) and blend with a variety of cells that collectively are referred to as stromal cells [49,50].

The morphologic and functional properties of each of these components undergo characteristic changes as follicles mature, and these properties serve as the basis for classifying preovulatory follicles as primordial, preantral, or antral [49,50]. A variety of subclasses such as primary, secondary, tertiary, or other numeric systems have been used to classify maturing follicles in quantitative studies of ovarian morphology [40]. In addition to these classifications based upon stage of maturation, another classification is based upon the ultimate consequences of maturation. Thus, the terminal event is either atresia for most or ovulation for a few follicles undergoing maturation. Atresia may occur at any stage during preovulatory maturation, and while the oocyte dies in all cases, the morphologic changes in other cells of the follicle complex vary with the stage achieved prior to undergoing atresia [9]. On the other hand, ovulation is associated with progressive enlargement even after antrum formation. These sequential changes are shown diagrammatically in Figure 1.

Appearance of cuboidal granulosa cells and formation of a zona pellucida are morphologic indicators that follicle maturation has begun in mammalian ovaries. While the nature of the stimuli for initiating these changes in a small fraction of extant primordial follicles remains unknown, the changes do not appear to depend upon pituitary hormones [20]. Moreover, until these changes have occurred, follicles in rodent ovaries are refractory to gonadotropins. However, in the absence of a pituitary, proportions of follicles in earlier stages are increased relative to those in later stages of maturation [11]. Conversely, when a pituitary is present or when gonadotropins are given to hypophysectomized rats, proportions of these earlier stages are relatively reduced. Thus, although gonadotropins do not appear to stimulate dramatically initiation of follicle maturation, subsequent growth is stimulated by these hormones.

Once initiated, subsequent preovulatory follicle growth results initially from granulosa cell proliferation alone and, subsequently, from antrum

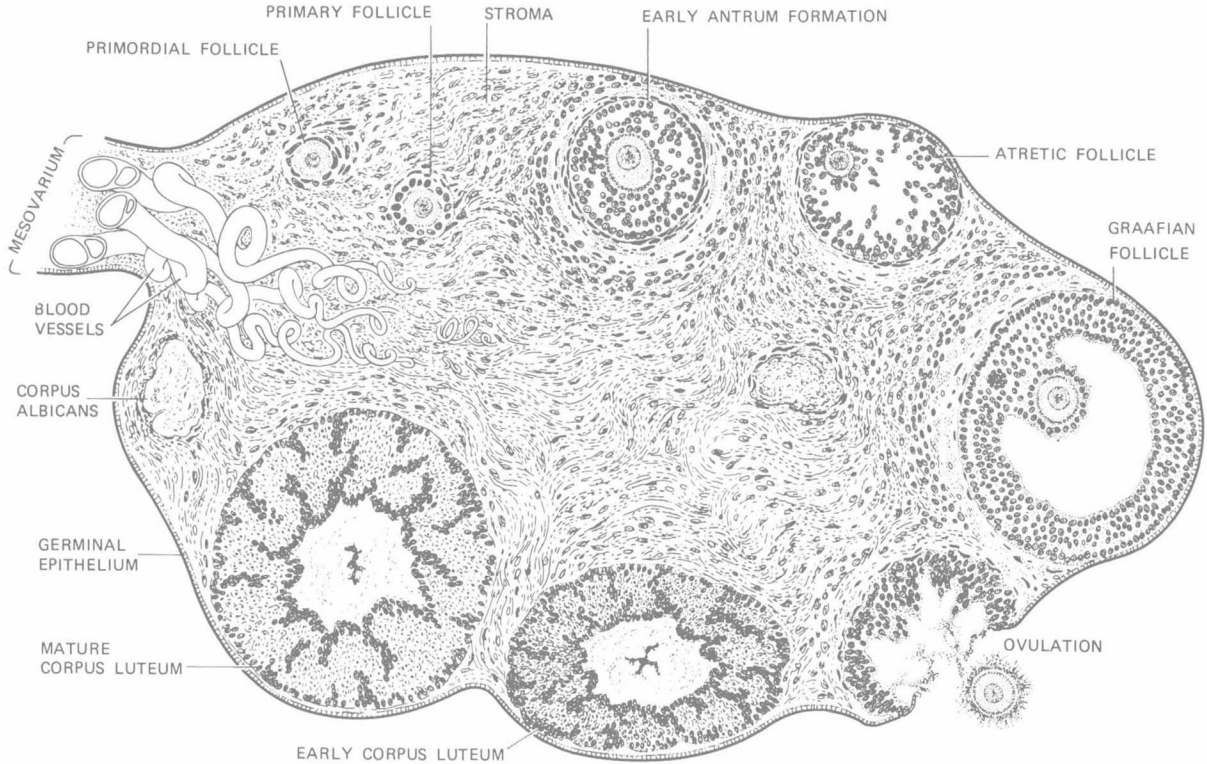

FIGURE 1. Schematic representation of ovarian histology, showing changes in components of follicular complex occurring during atresia and ovulation. *(Reproduced with permission of the publishers of Reproductive Endocrinology, Ch. 3, p. 64.)*

formation and enlargement in addition. Hormonal control of these phenomena has been studied extensively in hypophysectomized immature female rats. Hypophysectomy results not only in atresia of extant follicles, but also, as noted above, in a marked reduction in the number of follicles progressing to advanced stages of maturation [56]. Both processes are reversed by giving mixtures of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) or human chorionic gonadotropin (hCG) to these animals [47,48]. For endogenous estrogen synthesis, both FSH and LH are required [29], and quantities of either may be rate limiting [5]. While FSH induces aromatase activity in granulosa cells, LH stimulates interstitial cells to synthesize androgens, necessary precursors for estrogen synthesis [2,30].

Concomitant administration of gonadotropins and inhibitors of the biologic action of estrogens reduces the stimulatory effects of FSH and LH on preantral follicle growth and increases proportions of preantral follicles undergoing atresia in hypophysectomized immature female rats [19]. Conversely, when FSH and LH are given concomitantly with inhibitors of the biologic action of androgens, follicle growth is stimulated and the proportion of atretic follicles is reduced [30,65]. When estrogens are given alone, preantral follicle growth is enhanced. When androgens are given with estrogens, preantral follicle growth is inhibited and atresia is stimulated [21]. It is clear that estrogens and androgens produced by the ovaries act locally to mediate the effects of gonadotropins on preantral follicle growth and on atresia.

While estrogens alone adequately stimulate preantral follicle growth, FSH is required for both antrum formation and postantral follicle growth [13]. Coincident with antrum formation, FSH stimulates granulosa cell secretion of mucopolysaccharides, which accumulate in antral fluid [4,34]. In the presence of estrogens, FSH induces LH [12,42,66] and prolactin receptors in granulosa cell membranes [42].

Subsequently, LH stimulates ovulation by mechanisms that have not been elucidated completely. Among other events that occur in the periovulatory period, LH stimulates prostaglandin synthesis by granulosa cells [1,3]. In turn, prostaglandins are required for ovulation to occur, since administration of inhibitors of prostaglandin synthesis inhibits ovulatory responses to LH or hCG [1,59].

After ovulation, granulosa cells that remain in the collapsed follicle combine with thecal cells from the same follicle complex to form a corpus luteum. These cells have membrane receptors for LH and prolactin induced prior to ovulation, and occupancy of these receptors stimulates secretion of estrogens and progestogens [42,46].

HORMONES AND FOLLICLE MATURATION IN FETAL OVARIES

The role, if any, of hormones in gonadal differentiation during fetal life has not been examined definitively. However, once primordial follicles appear in fetal primate ovaries, pituitary hormones are required not only for maintenance of these "resting" follicles, but also for normal pro-