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PRINCIPLES AND MANAGEMENT OF HUMAN REPRODUCTION

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Preface

In keeping with concepts put forth in Reid's *Textbook of Obstetrics* (Saunders, 1962), its transformation into *Principles and Management of Human Reproduction* has occurred in a setting of burgeoning knowledge in this field, stimulated to a large extent by societal concern about the quantity and quality of human life.

Advances have occurred in our understanding of many aspects of reproductive processes which have altered the approach to the care of patients. As a consequence of endocrine and reproduction research, one can measure steroid and protein hormones with precision in minute amounts of blood throughout the cycle and pregnancy. Human follicle-stimulating and luteinizing hormones are available for induction of ovulation, and the isolation and structural identity of hypothalamic releasing hormones have been achieved. Details of the dynamics of the feto-placental unit during human pregnancy are more completely defined.

Genetic assessment of the fetus in utero, of the newborn, and of prospective parents has contributed materially to a rational approach in management of and counseling in hereditary diseases, including mental retardation and congenital defects. Monitoring of the fetus in utero by electronic and chemical means assures a more adequate surveillance of the infant's health prior to birth, even to the point of predicting respiratory competence in the newborn period. Treatment and prevention of the hitherto disastrous consequences of diseases such as choriocarcinoma and Rh isoimmunization are dramatic examples of progress made in recent years.

Principles and Management of Human Reproduction has been divided into sections covering: endocrine and neuroendocrine control, physiology, pathology, clinical obstetrics, neonatology, and public health aspects of reproduction.

This arrangement was designed to aid readers of varying backgrounds and interest, the "student of medicine," whether he be in medical school, internship-residency training, or the clinical practice of obstetrics and gynecology.

It is the hope that principles have been emphasized, controversy identified, and the minutiae of a specialty avoided. Thus, it has been the authors' objective to relate the process of human reproduction to the general framework of medicine and biology. Emphasis has been placed on the interaction of medical and surgical diseases in pregnancy and on the disciplines fundamental to the understanding of reproductive processes. The concern here has been to see obstetrics and the physiology of human reproduction in a meaningful relationship. Furthermore, the ultimate aim of medical science is the prevention of disease, and the first step must be related to life at its inception.

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Acknowledgments

As stated in the Preface, if obstetrics and related areas of gynecology are to be soundly practiced and patients optimally served, it is imperative that the more basic aspects of human reproduction be emphasized. To attain this objective, two former associates and authorities in reproductive biology, Drs. Kenneth J. Ryan and Kurt Benirschke, kindly accepted my request to assume joint authorship.

In Part I Dr. Ryan presents a unified concept of endocrinology, particularly as it relates to the development and growth of the new individual and the overall process of reproduction. Dr. Benirschke is responsible for much of Parts II and III, particularly genetics, immunology, the biology of multiple pregnancy, and the role of infection in the outcome of the fetus and newborn.

I am indebted to Drs. Fred H. Allen, Jr., and Irving Umansky for the chapter on Erythroblastosis Fetalis. Also, Dr. Jerold F. Lucey contributed immeasurably to the chapters on the evaluation and examination of, and conditions and diseases in, the newborn. Each has brought to his writing the background of a rich clinical experience.

The remarks on psychiatric states most often encountered in women in the childbearing age reflect my long-time association with Dr. Mandel E. Cohen.

The manuscript has been under the supervision of Miss Ruth E. Brown. We are deeply grateful for her infinite patience and efforts and her meticulous concern for each chapter.

Finally, the assistance and patience of the W. B. Saunders Company was again in evidence. The authors are especially obligated to Miss Elizabeth Taylor, and the expert advice and help of Mr. John L. Dusseau is again deeply appreciated.

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Contents

PART I

The Endocrine and Neuroendocrine Control of Reproduction

"Endocrines are nature's gift to man and beast, without them he can neither grow nor reproduce. They are the architects of love and marriage, the paramount basis of every social order."* These "endocrines" do not work alone, however; they depend upon a complex nervous system–endocrine interplay that regulates the fundamental processes of reproduction and homeostasis.

As animal life evolved from unicellular to multicellular organisms, from aquatic to terrestrial forms, from asexual to sexual reproduction, from monoecious (hermaphrodites) to dioecius (separate sexes) individuals, the endocrine glands and their neurologic control mechanisms continually developed and adapted to the needs imposed by these changes in life style and means of replication. Endocrine and neurologic processes have been the facilitating bases for the evolution of reproduction, and it is supposedly not the hormones themselves that have evolved and varied so much as the diverse roles that they play in different species. Hence one finds the same hormones—estrogens, progestins, oxytocins—in a broad spectrum of animal life (fish, birds, reptiles, and mammals) but the hormonal function in any given animal seems to depend upon an evolutionary need.

*Greep, R. O.: The Presidential Address of the Endocrine Society. Endocrinology: orphan and Cinderella science. Endocrinology, 79:823, 1966.

EVOLUTION OF REPRODUCTION

The general forms of evolutionary reproductive processes from those in simple animal life to the eutherian mammals and man include:

1. *Reduction of the number of ova shed for fertilization at any given time, from the extremes of millions in fish to one in the human.* This reduction in number of ova released to one a month in man created a requirement for careful control of ovulatory timing and the need for a high success rate for fertilization and fetal development via internal fertilization and viviparity, all subject to evolving neuroendocrine control.

2. *Internal fertilization.* This means of fertilization is characteristic of all land forms of animal life (as well as of some fish) and was accomplished by changes in socialization and the cues for sexual receptivity,

such as the estrus phenomenon, which are under endocrine direction.

3. *Retention of the embryo and fetus within the mother and birth of live young by ovoviviparity or viviparity.* This process is seen not only in mammals but also in insects, cartilaginous and bony fish, amphibia, and reptiles. Viviparity, at least in man and most mammals, imposed the requirement for development of immune tolerance by the mother for the infant maintained within her. Requirements were also generated for physical accommodation of the conceptus, for life support by exchange of nutrients and wastes, and finally for a mechanism of parturition, all of which are largely endocrine-regulated.

4. *Development of new organs for exchange in the form of extraembryonic membranes and placenta.* These organs fulfill the needs imposed by viviparity as already noted.

5. *Acquisition by the placenta of endocrine function and provision for postpartum nutrition by lactation.* Placental endocrine function seems to be an accommodation to a lengthening of the gestational period and insures hormonal support of pregnancy for prolonged periods. Postpartum lactation and maternal behavior provide a degree of nutritional and physical security for the newborn that is especially critical for terrestrial animals with a limited number of offspring.

REPRODUCTIVE ENDOCRINOLOGY IN MAN

The status of reproduction in man at this point in evolution consists of: monthly ovulation of a single ovum, internal fertilization, a long gestational period, viviparity, a hormonally active placenta, parturition through a pelvic girdle modified by the erect posture, and postpartum lactation. This is a far cry from the simplest forms of replication, division of a single cell in a unicellular organism, or the release of eggs by fish with external fertilization. Reduced to its fundamentals, however, reproduction in man and other mammals represents no more than a continuum of hereditary information passed on from one generation to the next by the germ cells. The entire body may be viewed as merely a repository, conveyer, and incubator for the gametes which are sequestered in the gonads awaiting release, fertilization, and development. This continuous and cyclic process is thus fundamentally simple in the concept of a germ cell continuum but extremely complex in the organizational control of the body in accomplishing the task.

For reproduction in all higher forms of animal life certain hormones such as estrogens and progestins are essential. A large part of the working of reproductive endocrinology depends on how and where such hormones are produced and how they influence gestation. To provide these hormones in proper association with gamete development and fertilization requires a highly complex interplay between the central nervous system, the hypothalamus, the gonadotropin-secreting adenohypophysis, the steroid- and gamete-producing gonads, and the reproductive tract. After implantation there is an interaction between the developing fetus, the placenta, and the maternal organism that supersedes much of the endocrine mechanism of the nonpregnant state. In the chapters that follow, the discussion of the reproductive process will be developed by consideration of: the hormones, the endocrine glands that produce them, and finally the integrative mechanisms that control the various aspects of the reproductive cycle.

HORMONES OF REPRODUCTION

The most proximate circulating effector substances now known for control and maintenance of gestation are hormones, of which six should be singled out for consideration in detail: estrogens, progesterone, human chorionic gonadotropin, human chorionic somato-mammotropin (placental lactogen), oxytocin, and pituitary prolactin. These six hormones figure extensively in the literature of obstetrics and reproduction because of their central role in various aspects of the pregnant state.

In addition to estrogens and progestins, the androgens and the pituitary gonadotropins are involved in the reproductive cycles of both male and female, and hormonal substances such as relaxin and catecholamines and the more recently discovered prostaglandins have as yet poorly understood roles in human reproduction.

The other major hormonal substances, namely growth hormone, insulin, adrenal corticoids, and thyroxin, generally con-

tribute homeostatic support for the pregnant state, which is essential but somewhat peripheral to the direct endocrine control of gestation. These latter hormones are essential for good health in general and for replication as just one of the normal bodily functions. Their absence can be immediately life-threatening to the human whether pregnant or not. On the other hand, absence of sex hormones and gonadotropins is not immediately life-threatening but their presence is more fundamentally essential for reproduction to take place.

These various substances will be discussed under the general classifications of steroid (Chapter 1) and protein or polypeptide hormones (Chapter 2) with emphasis on those most directly involved in the reproductive processes.

Chapter 1

Steroid Hormones and Prostaglandins

UNIFIED CONCEPT OF STEROID BIOSYNTHESIS AND METABOLISM

Steroids are a class of hormones with a common basic chemical structure related to the cholesterol backbone (Fig. 1).[3] These steroids have certain group characteristics in regard to biosynthesis and metabolism which simplify consideration of their biologic behavior. These characteristics may be catalogued as broad generalizations which follow:

1. Steroids are ultimately derived from the simple two-carbon substance acetate via cholesterol (or a cholesterol-like intermediate) and pregnenolone. The steroids can be synthesized de novo from acetate by any of the major steroid-producing endocrine organs: ovary, testis, or adrenal (Fig. 2). These pathways are similar for any of these endocrine tissues, and each of these organs can make any type of steroid hormone.[4] The adrenal can synthesize not only corticoids but progestins, androgens, and estrogens as well; the testis can synthesize androgens, progestins, estrogens, and corticoids, as can the ovary. Although the adrenal usually produces corticoids and adrenal androgens, the testis usually produces androgens, and the ovary usually produces estrogens and progestins, the potential for "aberrant steroid production" becomes manifest in disease states or after malignant change. Examples are estrogens from the adrenal in certain tumors, estrogens and androgens from the adrenal in the adrenogenital syndrome, and androgens from the ovary in polycystic ovary disease. These types of deviant steroid secretion become less mysterious when one realizes that in most endocrine tissues progestins are converted to androgens and androgens to estrogens in the usual course of events. The disease states can be associated with blocks or defects in the enzymatic steps that are most characteristic for a particular endocrine gland, or with acceleration of a minor pathway. Recognition of this is clinically important since such abnormalities are usually associated with defects in reproduction (Table 1).

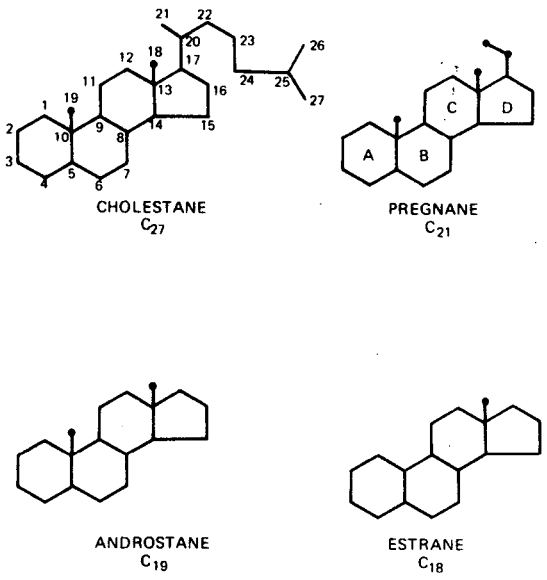

Figure 1. Common steroid skeleton. The intersections and apices of lines in these figures represent a carbon atom numbered as in the cholestane molecule. The four rings are designated according to letters as illustrated in the pregnane structure.

Active hormones and sterols occurring in nature have corresponding basic carbon structures—cholesterol (C-27), progesterone (C-21), testosterone (C-19), and estradiol (C-18)—but differ from the illustration in terms of ring and side-chain carbon substituents and unsaturated bonds in the A or B rings.

2. Not only the pathways for steroid hormone formation but also the location and types of enzymes involved are remarkably similar for each of these endocrine tissues. Only the control mechanisms, tropic hormones, and histology vary. As a conse-

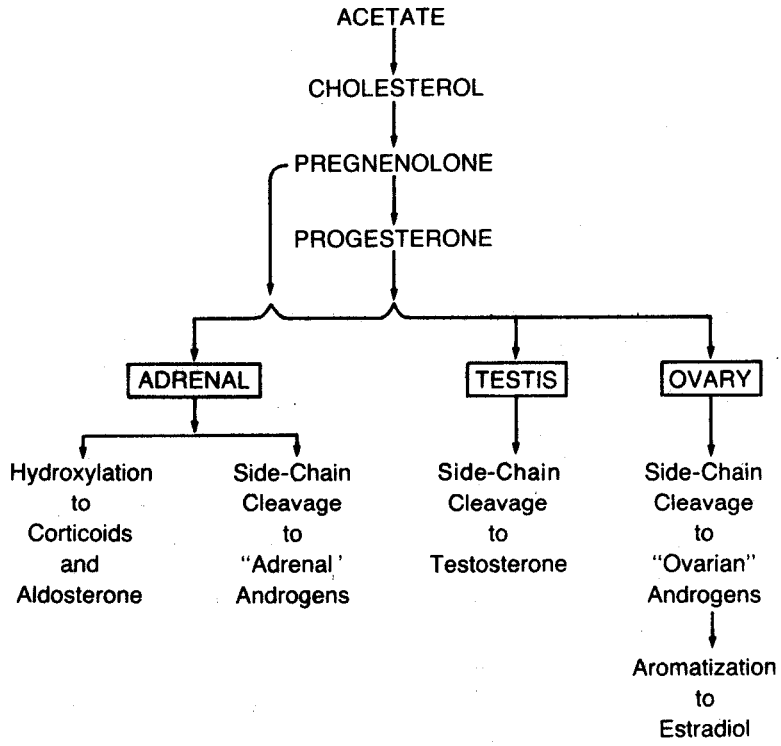

Figure 2. Unified concept of steroid formation.

TABLE 1. COMMON FEATURES OF STEROID-PRODUCING ENDOCRINE TISSUES

Steps in Steroid Biosynthesis	*Adrenal* Normal Activity	*Adrenal* Disease Defect	*Testis* Normal Activity	*Testis* Disease Defect	*Ovary* Normal Activity	*Ovary* Disease Defect	*Placenta* Normal Activity	*Placenta* Disease Defect
Acetate to cholesterol	+++		+++		+++		+	
Cholesterol to pregnenolone	+++		+++		+++		++++	
Pregnenolone to progesterone	+++	↓ Adreno-genital syndrome	+++		+++		++++	
Hydroxylation to corticoids and aldosterone	++++	Tumor Cushing's disease ↑ ↓ Adreno-genital syndrome	±	Rare in tumors ↑	–	Rare in tumors ↑	–	
Side-chain cleavage to androgens	+++	↑ Adreno-genital syndrome	++++		++	↑ Poly-cystic disease	–	
Aromatization to estrogens	±	↑ Tumors ↑ Adreno-genital syndrome	++	↑ Tumors	+++	↓ Poly-cystic disease	++++	↓ Sulfatase deficiency

Of special note: (1) The capacity of all tissues to convert acetate to cholesterol, but the relative deficiency of activity of the placenta. (2) The capacity of all tissues to convert cholesterol to pregnenolone and thence to progesterone. (3) Increased androgen production via side-chain cleavage in adrenogenital syndrome and polycystic ovary disease and absence of such production in the placenta. (4) Aromatization of androgens to estrogens in essentially all tissues, but in the case of the placenta the androgen substrate is delivered via the blood stream as a conjugate which must be cleaved prior to further metabolism.

TABLE 2. PREHORMONES IN ENDOCRINOLOGY

Prehormones	*Active Hormone Product*
Pregnenolone sulfate	Progesterone
Dehydroepiandrosterone sulfate	Estradiol
Androstenedione	Estrone; testosterone
16-Hydroxydehydroepiandrosterone sulfate	Estriol

quence, the pathways for each of the hormones to be listed are equally applicable to any of the steroid-producing endocrine tissues.

3. Steroids can also be synthesized from intermediate blood-borne precursors such as cholesterol, pregnenolone, testosterone, androstenedione, or dehydroepiandrosterone by "incomplete" endocrine organs, such as the liver or placenta, that form steroids from acetate poorly or not at all. Some of these intermediate precursors such as dehydroepiandrosterone or androstenedione have little direct hormonal action themselves but can in this manner be converted to potent hormones, i.e., estradiol or testosterone.[1] These precursors have thus been designated as "prehormones" (Table 2).

4. Metabolism of steroids following secretion occurs in many tissues of the body but the liver's central location, abundant blood flow, and repertory of enzymes allow it to play the major role. In general, steroids are metabolized and usually made less biologically active by reduction of double bonds; cleavage of side chains; addition, reduction, or oxidation of hydroxyl groups (Fig. 3); and conjugation with the acidic moieties sulfate or glucuronate.[2] Note that with prehormones in the blood, the liver or other tissues could convert a steroid into either a more or a less biologically active substance. The factors that regulate this balance in steroid metabolism are as yet not fully understood, but clearly important. In the male, for instance, too much estrogen can be produced by peripheral conversion of androstenedione to estrone, rather than its usual conversion and excretion by way of the androgen metabolites, 17-ketosteroids.

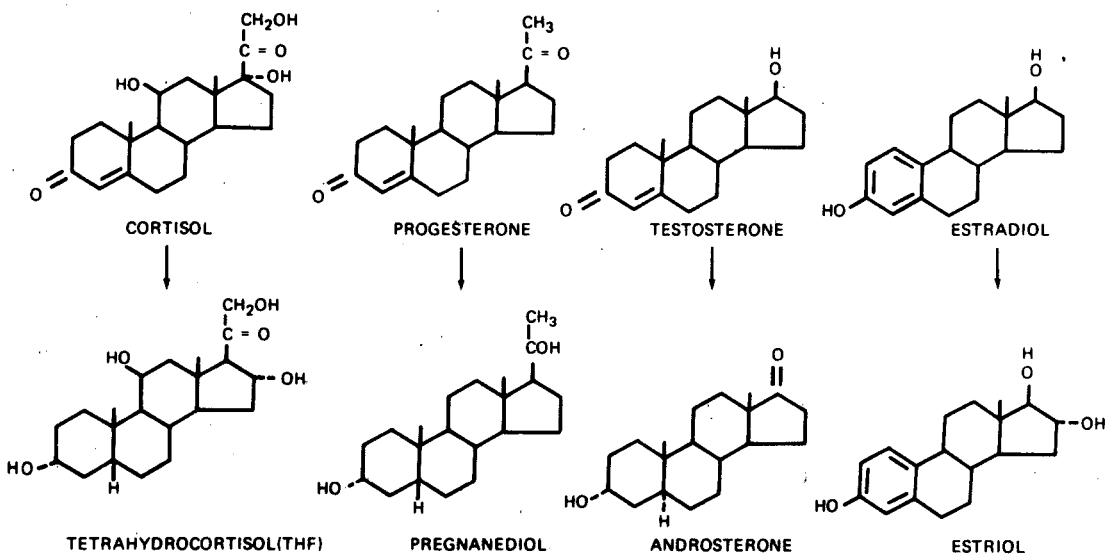

Figure 3. Examples of common steps in steroid catabolism. 1. Ring A double-bond reduction in all steroids except estrogens. 2. Reduction of the ketonic oxygen at position C-3. 3. Opportunity for stereoisomerism at positions C-3 (hydroxyl in α position on THF, androsterone, and pregnanediol), C-5 (hydrogen in β position in THF and pregnanediol and α position in androsterone), C-20, C-16, and any other asymmetric carbon substitution. 4. Steroid hydroxylation (at C-16 in estriol) possible at essentially any carbon position, but most frequent at positions C-2, C-6, C-16, and C-17.

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ESTROGENS

Estrogens may be defined as hormones that produce characteristic biologic effects such as cornification of the vaginal mucosa, growth of the uterus, estrus behavior in animals, and development of a proliferative endometrium in a gonadectomized subject.[7] More simply stated, estrogens are the hormones of femininity and as such are the major determinants of the development and functional maintenance of the female secondary sex characteristics, the breasts, the feminine body type, and metabolism. It should be stressed that estrogen effects are ultimately the result of the degree of responsiveness of the end-organ to the estrogen and also of a complex interplay of this hormone with any other steroids present, such as androgens or progestins.

Men and women have both estrogens and androgens circulating in their blood at the same time and yet masculinity in the male and femininity in the female are usually readily apparent. It is not the absolute amount of estrogen available that determines its effect but the relative amount of competing androgen present that can interfere with estrogen expression. For example, in the syndrome of testicular feminization the relative amounts of hormone present are appropriate but the tissues do not respond normally to androgens and a genotypic male resembles a phenotypic female.[5]

These variables (end-organ response and the presence of other hormones) are undoubtedly the determinants of the wide spectrum of bodily habitus, breast development, hair growth, and reproductive activity observed in different women. Although the word estrogen is derived from its capacity to induce sexual receptivity, estrus behavior or heat in animals, human sexuality is so steeped in overlying social custom and culture that no consistent direct effects of estrogen on sexual behavior in the human have been verified. (It is interesting that only the androgens when used in large doses, as for palliation of breast cancer, have resulted in increased libido in the human female.)

CHEMISTRY

The first natural estrogens to be described were estradiol, estrone, and estriol, which bear the metabolic relationships indicated in Figure 4. Estradiol is the most active or parent compound, and is secreted by the

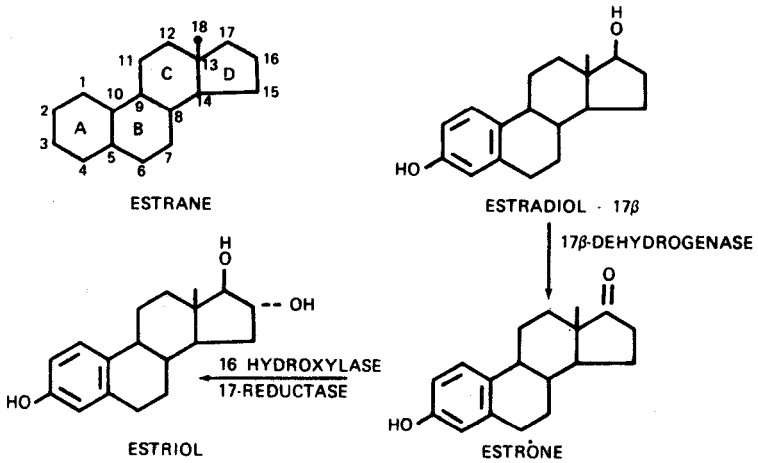

Figure 4. Major natural estrogens.