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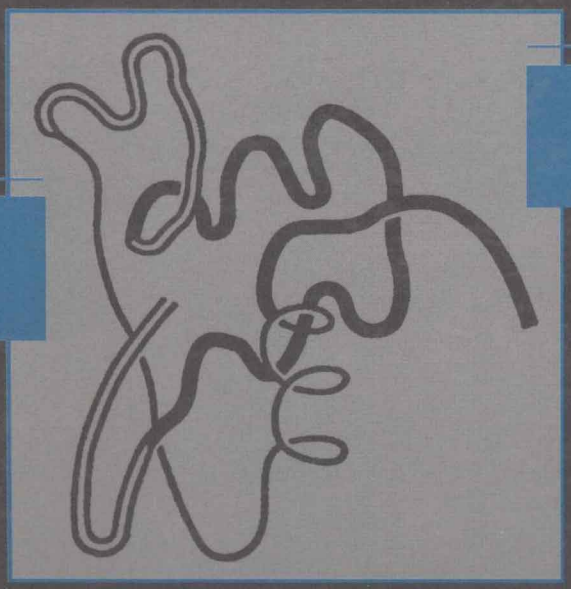
Yen ■ Jaffe ■ Barbieri

生殖内分泌学

Reproductive Endocrinology

Physiology, Pathophysiology, and Clinical Management



4th Edition

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第 4 版 ● Fourth Edition

Samuel S. C. Yen, MD, D. Sci
Robert B. Jaffe, MD
Robert L. Barbieri, MD

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Reproductive Endocrinology

Physiology, Pathophysiology, and Clinical Management

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This book is dedicated to our families
and to all those investigators and clinicians
who have contributed to the advances
in the understanding of reproductive processes and disorders.

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Preface to the Fourth Edition

It has been over twenty years since the first edition of Reproductive Endocrinology appeared. Since that time, the face of the discipline has changed remarkably. We have attempted to keep pace with these advances with each edition. In this fourth edition, we have incorporated recent developments in the molecular, genetic, cellular and clinical aspects of the endocrinology and neuroendocrinology of reproduction in a comprehensive, lucid, and readable manner, without becoming encyclopedic. The fourth edition continues the tradition of having world-recognized experts present the most up-to-date overviews of the areas of their expertise in a comprehensive yet comprehensible manner.

There have been a number of significant changes to the fourth edition which we feel will make it more attractive and useful to our readers. New chapters and authors have been added, in part reflecting new areas of major interest in reproductive endocrinology. Additionally, the format has changed in several respects for ease of reading and comprehension. For example, each chapter is introduced by a series of Key Points to highlight the major areas addressed. This will allow the reader to keep in focus the major themes of each chapter. In addition, the typeface and illustrations have been improved over the previous editions. When review articles are available, they have been referenced to allow the reader to seek further detail in a particular area.

We have not shied away from controversy. When there are differing views concerning a particular topic, these have been included, rather than presenting a dogmatic, unifocused perspective. If we have provided our readers with a useful, readable, encompassing perspective of this dynamic, rapidly changing, and exciting field, we will have achieved our objective.

With this fourth edition, we welcome Robert L. Barbieri as a co-editor. Dr. Barbieri is a well known investigator in reproductive endocrinology and an effective communicator. He has contributed some of the key chapters in the present edition. Our task as editors was greatly facilitated by the help and cooperation of the contributing authors. We also wish to express our appreciation to Deidre Dolan (R. Barbieri), Lee Hillman (R. Jaffe), and Dawn Nye/ Gail Laughlin (S. Yen) for the excellent assistance and dedication. Finally, we extend our thanks to Janice Gaillard, Lisette Bralow, and the staff at W.B. Saunders Company, whose capable assistance helped overcome some of the trying problems we met.

Samuel S.C. Yen
Robert B. Jaffe
Robert L. Barbieri

Preface to the First Edition

Among those biomedical fields in which a virtual explosion of new knowledge and understanding has occurred over the past decade, the physiology and pathophysiology of reproductive processes are prime examples. The neural and endocrine regulation of reproduction has been explored with new and sophisticated methods and with increasing comprehension of the important factors involved in the control of this important function. By extrapolation from animal models, as well as by direct investigation involving humans, new light has been shed on the operation of the human reproductive system in both health and disease.

The planning of a book embodying these advances began in July, 1976, when the author-editors were Visiting Scholars at the Villa Serbelloni, an elegant conference and study center operated under the auspices of the Rockefeller Foundation in the picturesque environment of Lake Como, Italy. An outline of this book was completed there, contributing authors were identified, and the writing of several chapters was begun.

Our overall purpose is to provide contemporary factual information and new understanding of human reproductive processes. We attempted to keep in mind the needs of students and investigators in reproductive endocrinology and biology, as well as the needs of clinicians who face the problem of diagnosing and treating reproductive dysfunction. To accomplish these purposes, our authors' expert knowledge ranges from the clinical and systemic to the cellular and molecular. Thus, whenever possible, cellular or molecular mechanisms for normal or disturbed function are presented.

The elements of the reproductive system with which we deal most extensively are various parts of the brain, the pituitary gland, and the gonads. Each of these obviously is a separate and distinguishable component of the system. However, not only are they intimately associated to form an integrated system for periodically releasing germ cells and hormones but, in addition, they have a number of common mechanistic features. We hope that these similarities and integrated modes of action will impress the reader as they have impressed us, and that some readers will be provoked into continued, deeper study of this intriguing field.

The contributing authors were chosen for recognized authority in their respective areas and for their ability to transmit information in a manner we think is lucid and interesting. The lists of references are not intended to be exhaustive but do include key articles and reviews.

Our task as editors was greatly facilitated by the help and cooperation of the contributing authors. We also wish to express our appreciation to Marcia Finkle, Leslie Muga, Alana Schilling, and Rae Feinstein, our secretaries, whose capable assistance helped overcome the few trying problems we met. My (S.Y.) special thanks to Dr. Allen Lein for his critical review of and suggestions for several of my chapters. The editors are grateful to the staff of the W.B. Saunders Company, particularly John Hanley for his confidence, encouragement, and courtesies, which made the preparation of this book a satisfying experience.

The information in this book is at the cutting edge of contemporary reproductive endocrinology. If the book assists the clinician, excites and teaches the student and investigator, and lends deeper understanding of the control of reproductive processes, it will have served its purpose.

S. S. C. Yen
R. B. Jaffe

NOTICE

Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy become necessary or appropriate. Readers are advised to check the product information currently provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the responsibility of the treating physician, relying on experience and knowledge of the patient, to determine dosages and the best treatment for the patient. Neither the publisher nor the editors assume any responsibility for any injury and/or damage to persons or property.

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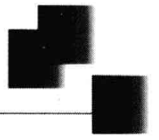

Part I

Endocrine Regulation of the Reproductive System

Chapter 1

MOLECULAR BIOLOGY AND THE REPRODUCTIVE SCIENCES

Paul G. McDonough

CHAPTER OUTLINE

KEY POINTS

- The numbers of mutations in genes that affect reproductive disorders and the technology to identify them are expanding greatly. This windfall has been spearheaded by conceptual and experimental advances made possible by the polymerase chain reaction.
- The multiple uses of this technique to amplify DNA, RNA, and the whole genome are clarified. Many of the other techniques described in this chapter for disease diagnosis are increasingly important in identification of molecular mutation in humans.
- The use of transgenic animals as in vivo analytical models of human reproductive disorders is a prime example of the innovative power of this new and ever-changing technology. All these promising advances are being tested in many laboratories and within the Human Genome Project.
- These new, evolving techniques help us to understand the biochemical basis for disease, the etiology of fundamental developmental aberrations, and individual genomic variation.

MOLECULAR GENETICS

In the several years since the previous edition of this book, direct examination of a patient's deoxyribonucleic acid (DNA) has emerged as a definitive means of establishing the presence of specific genetic changes that cause disease. The analysis of human genomic DNA (nucleated cells in blood or other nucleated cells) for disease-associated mutations has become an increasingly important part of clinical reproductive medicine. One can anticipate that all monogenic disorders related to reproductive endocrinology will have molecular determinants by the year 2000. The identification of these molecular determinants for monogenic disorders and the development of further insights into polygenic diseases will radically alter the approach to clinical diagnosis in humans. The ambiguity of clinical criteria for disease, phenotypic similarities between different disorders, and the latent period for disease onset can be largely avoided by molecular diagnosis. In addition, the high specificity of molecular diagnosis makes it possible with some diseases to screen populations for the carrier state. The precise structural alteration in DNA will be the final arbitrator of phenotypic and biochemical variations of

the same disease in different subjects. A knowledge of the precise pathologic process at the molecular level has provided important insights into the biochemical basis for many diseases of humans. It is apparent that a firm knowledge of the DNA alterations in disease will also provide more directed therapeutic strategies to modify or limit the expression of these mutant nucleotides.

The remarkable advances in DNA diagnostics have been expedited by development of the polymerase chain reaction (PCR) and the ability to isolate DNA from many different sources such as blood, saliva, hair roots, microscopic slides, paraffin-embedded tissue sections, clinical swabs, and even cancellous bone. These technical advances have been bolstered by the development of an increasing number of effective screening techniques to scan genomic DNA for unknown point mutations. At the same time, unique sequence DNA probes and probes for simple sequence repeat polymorphisms are being generated at an exponential rate. In late 1995, the first physical map of the human genome based on 15,000 specific sequence markers distributed over all the human chromosomes was completed.[1] These human genome markers consist of short sequences of 200 to 500 base pairs (bp) approximately 200 kilobases (kb) apart. These markers, referred to as sequence-tagged sites, do not need to be stored as DNA. Given the sequence of the marker DNAs, one can simply use this information to design the appropriate primers to amplify the intervening segment of DNA with PCR. The amplification product will give the investigator a stretch of DNA that comes from a specific location in the genome. One of the objectives of the Human Genome Project is to provide DNA markers that cover the human genome at approximately 50- to 100-kb intervals. These closely spaced markers are important, but the ultimate target of the project is to sequence the entire genome. The continued development of technology for this purpose will ultimately result in automated DNA diagnosis for the practicing clinician.

This chapter is designed to acquaint the reader with recent concepts of DNA structure, current techniques of testing at the DNA level, prototype mutations in the reproductive sciences, new concepts in the molecular mechanisms of disease, and several important transgenic models of disorders of human reproduction. Finally, the most vital use of this new science, understanding the biochemical basis for disease, is outlined along with the broader applications of recombinant technology. Understanding the physical and biochemical properties of nucleic acids is crucial to the development and implementation of clinical assays that test for diseases at the gene level.

Biochemistry of the DNA Molecule

Genetic information is carried in DNA, the helix or "spiral staircase" molecule described by Watson and Crick[2] in 1953. In its natural state, DNA consists of two linear strands that are wound helically around each other. The backbone of the strands or staircase is made of simple sugar and phosphate molecules. The rungs consist of four bases or nucleotides: adenine (A), guanine (G), cytosine (C), and thymine (T). The molecule is held together by hydrogen bonds between the four specific nucleotide bases on each of the rungs or strands. The single strands are complementary, meaning that thymine is always linked with adenine (A–T) and guanine with cytosine (G–C). As a result, the two strands are mirror images of each other and will not fit together in any other way. The use of DNA probes centers on the process of molecular hybridization, which depends on the mutual attraction of the paired bases. Individual strands of double-stranded DNA can be artificially separated by heating or by the addition of chemical agents to produce a single-stranded DNA. This process is referred to as denaturation. Under controlled conditions, cooling will force the single strands to reassociate or reanneal but only with complementary sequences. The constrained requirement for complementary pairing is the reason for the great specificity of DNA probe assays. This specificity is put to use in a wide spectrum of techniques used to identify different forms of human mutations that alter the function of the resulting protein. Similar techniques are used for detecting the presence of pathogenic bacteria, fungi, parasites, or viruses.

Basic Structure of Human Genes

Genes encode information that specifies functional products, either ribonucleic acid (RNA) molecules or proteins that are used for various cellular functions. A gene itself is a defined unit of DNA that determines the structure of a string of amino acids that form the building blocks of all enzymes and proteins. Each naturally occurring amino acid is coded for by a trio of bases called a codon or triplet. Because there are 64 possible ways to arrange four bases in unique sets of three, there is a degeneracy in the genetic code, that is, there is more than one way of coding for a particular amino acid. Genes, with their regulatory machinery, ensure that their products are synthesized in cells in precisely the right amounts in the appropriate tissues and at the correct time during development. Each cell contains the genetic information to make an entire human being. Certain genes encoding proteins that are vital to every cell in the organism are called "housekeeping genes." Other genes encode proteins that have tissue-specific or temporal-specific patterns of expression.

A structural gene consists of several regions, referred to as exons, that encode proteins. These exons are separated by DNA sequences, referred to as intervening sequences or introns, that do not encode proteins. Figure 1–1 is a theoretical mammalian gene that encodes a structural protein with 200 amino acids for which these features can be demonstrated. This gene has three coding regions, now termed exons, and two intervening sequences or introns. Even though only 600 nucleotides are necessary to encode the protein (three nucleotides per amino acid), because of introns the gene contains roughly 1000 nucleotides.[3] The polarity of a DNA strand is conventionally marked according to the phosphodiester bond from the fifth carbon atom on a deoxyribose subunit to the third carbon atom on the adjacent deoxyribose. In a double helix (or duplex) of DNA, one strand runs in the 5′ to 3′ direction, whereas the complementary strand runs in the 3′ to 5′ direction (i.e., the two strands are antiparallel). At the 5′ end of the gene, there is a specific triplet (ATG) that determines the initiation of protein synthesis on messenger RNA (mRNA);

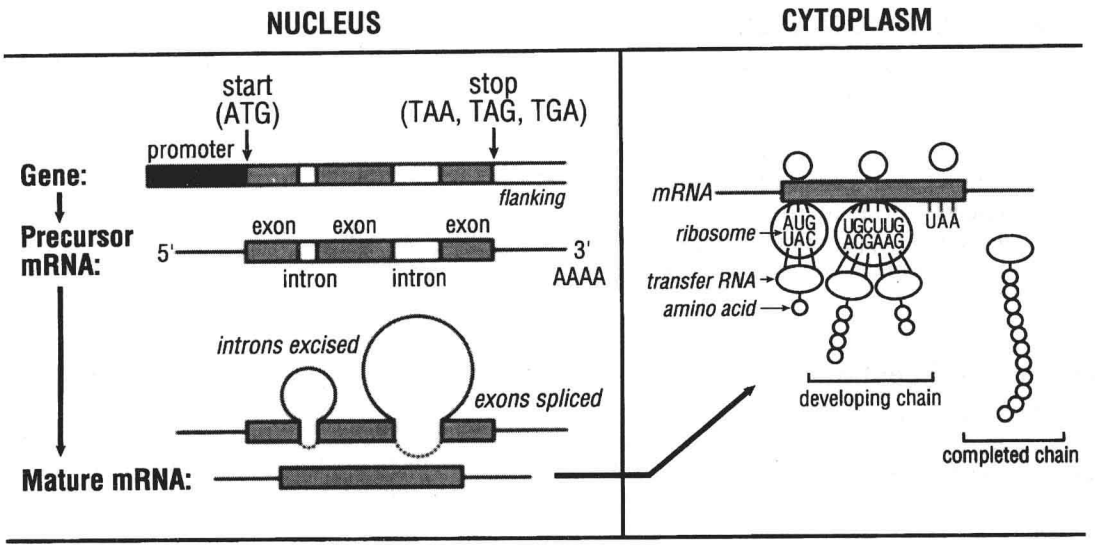

Figure 1–1 ■ Depiction of a typical mammalian gene and mechanism of gene expression. Messenger RNA (mRNA) is synthesized on its DNA template in a 5′ → 3′ direction by the action of the enzyme RNA polymerase II. The primary transcript is a large mRNA precursor, which is processed by cutting out introns and splicing the remaining exons together before delivery to the cell cytoplasm. In the cell cytoplasm, mRNA acts as a template for protein synthesis. ATG indicates the initiation codon for transcription, codon to codon, until a specific termination codon (TAA, TAG, or TGA) is reached. The polyadenylate (poly A) tail is added to the 3′ end of the mRNA to direct its exit from the nucleus for translation. The promoter elements act to localize the exact start site for transcription, control the quantity of RNA, and regulate tissue-specific expression of the gene.

at the 3′ end, there is a termination triplet (TAA, TAG, or TGA). Sequences that are upstream (to the left in a DNA strand reading left to right) are of particular importance in the regulation of the level of transcription of mRNA. These upstream regulatory regions or promoters are important in initiating and controlling the rate of gene transcription. Elements such as proteins produced by other genes that may regulate genes may be on the same chromosome (called *cis*-acting elements) or on a different chromosome (called *trans*-acting factors). Those regulatory nucleotide sequences that lie in the regions of DNA upstream to the transcription start site may undergo mutation and silence the structural gene or cause it to act inappropriately. In contrast to promoters, other DNA regulatory elements may occur in unpredictable locations, often at a considerable distance from the transcription start site. These "enhancers" augment transcription from the gene promoter. The promoter regions of genes tend to have common motifs, whereas enhancer regions do not share many sequences.

Gene Expression

The first step in gene expression is the transcription of a full-length RNA copy of the DNA. These RNA transcripts then serve as templates or messengers for protein synthesis. For a gene to be expressed, an enzyme, RNA polymerase II, slides along a DNA strand and splices free ribonucleotides into an mRNA chain based on the DNA template. The strand of DNA that is copied or transcribed into mRNA is then decoded or translated by the protein synthesis machinery of the cytoplasm. The mRNA comprises a single-stranded polynucleotide chain with a sugar phosphate backbone in which the order of bases is the complement of the transcribed DNA strand of the gene. In RNA, thymine (T) is replaced by a closely related base, uracil (U), which will also base pair with adenine (A). The gene for gonadotropin-releasing hormone (GnRH) is unique in that one strand of the DNA encodes for GnRH, whereas the other strand encodes a different protein.[4] There are now several other examples of mammalian genes in which two different genes are transcribed from opposite strands of the same DNA locus.[5] The expression of eukaryotic protein coding genes can be regulated at a variety of levels from transcription to translation.

Gene Expression

$$\text{DNA} \xrightarrow[\text{Transcription}]{} \text{RNA} \xrightarrow[\text{Processing}]{\text{Translation}} \text{Protein}$$

Transcription is regulated by a variety of factors mediated through the promoter sequences that are upstream or 5′ to the structural gene. These regulatory sequences have specific regions that direct the enzyme RNA polymerase II to the correct site to initiate transcription. The initial RNA transcript must undergo a highly regulated process called splicing in which the introns are removed to create the mature mRNA (see Fig. 1–1). The process by which introns are removed and the flanking exons (expressed regions) are stitched back together is called pre-mRNA splicing. This process of splicing depends on a large molecular apparatus containing RNA and protein molecules, called the spliceosome. Spliceosomes are biochemical machines similar to ribosomes in size and complexity. Sometimes the same mRNA may be spliced differently in different cells to produce entirely different transcripts. The gene for calcitonin is a good example in which differential splicing or processing will generate different mRNAs in different tissues.[6] The best example of post-translational modification is the pro-opiomelanocortin gene or protein.[7]