

every doctor who sees the woman patient

Gynecologic Endocrinology

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University of Michigan Medical School

Foreword by Norman F. Miller, M.D.



A HOEBER HARPER BOOK

GYNECOLOGIC ENDOCRINOLOGY

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Foreword

The title of this book may suggest to some that gynecologic endocrinology is a specialty in itself. This, of course, is not the case. The terminology is used merely to indicate that the author has endeavored to cull from a broad and diverse field of glandular physiology those features that apply specifically or prominently to the human female. Attention is deliberately focused upon the functional and dysfunctional activity of the female reproductive organs.

The author presents in a concise manner the endocrine status of the female during the several phases of her life. In addition, there is a section describing the technique, value, and limitations of many endocrinologic diagnostic procedures.

Every branch of medicine has contributed to, and benefited from, the rapid advancement of our knowledge of endocrinology. It is doubtful, however, that any specialty has more energetically encouraged investigation in the field of endocrinology than obstetrics and gynecology. This is not surprising since the human reproductive process, with which these fields of endeavor are chiefly concerned, is in large measure dependent upon normal endocrine physiology. Furthermore, adequate comprehension of this discipline is essential to our understanding and rational treatment of dysfunctional disturbances of the reproductive organs.

Doctor Riley is particularly well qualified to present gynecologic endocrinology in a manner that will appeal to the clinician. In addition to being an outstanding endocrinologist and cytologist, he has consistently worked with clinicians in their endeavor to solve and treat dysfunctional gynecologic disorders. He knows our problems and is familiar with the questions to which the clinician commonly seeks an answer. It is because of these qualifications plus his ability to portray clearly through the medium of the written word those endocrine aspects we need to know that his *Gynecologic Endocrinology* achieves importance.

The section dealing with the **pituitary gland** furnishes a comprehensive survey of the chemical and biologic **properties** of this important structure. Presented in succinct format, the text provides a convenient source of information concerning the fundamental properties and the various hormonal factors attributed to this tiny, but complex, organ.

Of particular interest is the author's summary of the physiologic factors responsible for the rhythmicity of endometrial behavior. Although the suggested sequence of hormonal changes is based upon classic as well as current concepts, the reader must be mindful of the fact that there remain many gaps in our understanding of this complicated mechanism. Attention is properly directed to the fact that available procedures do not always provide complete or satisfactory hormonal recovery and, consequently, that assay methods may lack specificity, accuracy, and clinical usefulness.

In dealing with hormone production during pregnancy, Doctor Riley includes newer knowledge regarding the adrenal steroids and their fluctuations during gestation. A brief description of the interrelationship between hormonal activity and the breast tissue of the human female serves to emphasize the paucity of basic information and our deficiencies in this important area.

The endocrine status of the fetus in utero as well as in the newborn is dealt with in Chapter 6. The important interrelationship between mother and fetus, including the possible modifications of genital organs in the newborn due to hormone administration to the mother during pregnancy, is an increasingly important field for contemplation because of the large quantities of hormone sometimes advised during the pregnant state.

Although abnormal sexual development occurs infrequently, it is certainly an important problem. Chapter 9 covers this subject in considerable detail.

One of the more important contributions is consideration of the endocrine aspects of infertility. In the absence of discernible physical cause for infertility, the physician has turned to the endocrinologist for aid. While much on this subject remains to be solved, the author skillfully covers some areas wherein endocrine dysfunction is a factor.

The section dealing with the cytologic, chemical, and biologic procedures used in the evaluation of endocrine activity in the human body will truly serve as a useful laboratory manual for those interested in the technical aspects of the many endocrinologic studies commonly used. Many clinical readers will be especially grateful for a simple presentation of the chemical nature of the steroid hormones and their function in both normal and abnormal states.

The formulary of pharmaceutical endocrine preparations should be helpful to the busy clinician seeking to keep up with the rapid progress of our chemists and pharmaceutical houses.

Gynecologic Endocrinology should serve as an excellent review of the hormone status, both physiologic and abnormal, as it applies to the female during all ages of life. It represents an excellent text for students on the subject as well as a rapid reference for practitioners who wish to know more about gynecologic endocrinology.

NORMAN F. MILLER, M.D.

Preface

This presentation of the fundamentals of reproductive physiology, the endocrine aspects of gynecologic dysfunction, and details of useful diagnostic procedures is based in part upon a previous effort to cover these subjects in the handbook entitled *Essentials of Gynecologic Endocrinology*, first printed in 1950. The intervening years have been marked by rapid advances in all phases of endocrinology, including that particular phase which deals with the endocrinology of the female. The use of improved assay methods has provided more precise information concerning the endocrine levels prevailing during the menstrual cycle and in various types of gynecologic dysfunction. The effective application of such methods and better understanding of the physiological significance of the laboratory findings have led to more rational approaches to treatment. A surge of interest in the diverse aspects of infertility has stimulated investigation in this field that has led to greater optimism in dealing with the frustrating problems of the childless couple. The availability of corticoid steroids has provided effective therapeutic approaches to the hitherto insurmountable problems of virilism and pseudohermaphroditism. It is intended that this book will reflect these many encouraging advances.

Though it is impossible to overlook the tremendous contributions derived from investigations in laboratory animals, the author has chosen, for the most part, to present the endocrine facts as they obtain in the human. Thus, for example, there is but brief reference to the path-finding observations of the effects of estrogenic substances on the reproductive tract of the rat or guinea pig, whereas detailed descriptions are given of the effects of these agents on the human uterus and vagina. It is appreciated that this arbitrary restriction of source material occasionally results in a brief or inconclusive presentation of some phase of endocrine physiology. However, it is felt that such brevity or uncertainty will serve the useful purpose of emphasizing the paucity of information on many aspects of human endocrinology.

In recent years the journals have devoted much space to articles attempting to explain the etiology of so-called functional disorders and to papers describing the merits of one type of endocrine therapy or another. The frequent appearance of contradiction in the literature, the not uncommon reliance upon speculation, and the readiness with which concepts are formulated and retracted increase the difficulty of presenting a lucid summary of the cause of the functional disorders and make an evaluation of the therapeutic measures seemingly hopeless. In the present text, those theories of etiology or methods of treatment are presented which appear to have the merit of being based on sound thinking or critical investigation. Others are included because they have achieved recognition by virtue of their thought-provoking nature rather than because they have gained general acceptance.

In the chapter dealing with the clinical manifestations of various gynecologic disorders such as amenorrhea and hypermenorrhea, the author is concerned primarily with the endocrine implications of these conditions. This limitation of viewpoint would seem to direct disproportionate attention to the functional aspects of these disorders. It cannot be too strongly emphasized that one must first investigate the possibility of organic, systemic, constitutional, or psychic causes before delving into the frequently controversial and obscure aspects of endocrinal etiology.

During the writing of a book and its preparation for publication, the author finds himself acquiring indebtedness to many individuals. Acknowledgments are small recompense for help and criticism so generously given.

The author wishes to acknowledge his indebtedness to Dr. Norman F. Miller, Chairman of the Department of Obstetrics and Gynecology, University of Michigan Medical School, for encouraging the writing of this book and for his ever-continuing interest in its preparation. His critical appraisal of our laboratory procedures and hesitancy to accept overly enthusiastic conclusions, with always a neat blend of encouragement, have been a stimulus to improvement in our work in this field.

The author has benefited for many years from association with successive groups of young men in training in this department, and any insight into the clinical aspects of gynecologic endocrinology that he may have stems in large measure from this association.

Thanks are due to Mrs. Jean Alfrey, whose interest in the project and secretarial talents made the final stages of preparation less of a burden to the author. I wish to acknowledge the many helpful suggestions of Mr. Roland Burd, Chief Medical Photographer, and of Mr. Gerald Hodge, Department of Medical Illustrations, University of Michigan Medical School, and the numerous courtesies of their respective staffs. To my laboratory staff I am indebted for their cooperation in carrying out the

innumerable laboratory procedures that have contributed greatly to our better understanding of gynecologic dysfunction. I would also like to acknowledge the help of Dr. John Gosling, who generously provided microscopic material for illustrating normal phases of the endometrium and ovarian neoplasms.

I am most grateful to my wife for her constant encouragement, her continued interest in the progress of the work, her valuable assistance in the preparation of the manuscript, and especially for her critical proofreading.

G. M. R.

Ann Arbor

Introduction

ENDOCRINOLOGY is the study of the glands of internal secretion. The term *internal secretion* was first introduced by Claude Bernard in 1855 to identify those substances which pass directly from a gland into the blood circulation. Bayliss and Starling, discoverers of secretin, coined the term *hormone* for a chemical substance which, produced by one organ, is carried by the blood to other tissues where it produces its effect. The term *endocrine*, derived from two Greek words meaning "to separate within," was later introduced to distinguish the hormone-producing glands from those whose secretions are eliminated through excretory canals or ducts. These glands have also been referred to as the *ductless glands*.

Endocrinology has advanced with amazing rapidity since the isolation of the first crystalline hormone, epinephrine, in 1901. The ensuing years have seen the isolation of active principles in pure or highly purified form from all the glands of internal secretion, with the exception of the parathyroids.

In each instance the isolation of the crystalline hormone or active substance was preceded by intense and brilliant work in the field of experimental endocrinology—the recognition and clarification of the physiological role of the endocrine gland, the development of methods for detecting and measuring the internal secretion, and the preparation of active extracts of the hormone.

Perhaps no phase of endocrinology has received more attention or shown more rapid progress than that concerned with the physiology of reproduction. Indeed, Berthold's¹ demonstration of the dependence of the masculine characteristics of the cock upon the presence of the testis was the first experimental proof of internal secretion. A single generation witnessed the elucidation of the endocrine role of the gonads, the isolation of their hormones, and the establishment of their interrelationships with other glands of internal secretion.

Impetus to investigations in the field of gynecologic endocrinology was given by Edgar Allen's description of the vaginal smear method² for assaying the follicular hormone and Corner and W. M. Allen's use of the endometrial response for the corpus luteum hormone.³ The isolation of the male sex hormone was preceded by the outstanding work of Moore and his collaborators on the physiology of the testis hormone and the development of the capon-comb test for measuring this hormone by Gallagher and Koch.⁴ Great is our indebtedness to P. E. Smith⁵ for the concept of the hypophyseal regulation of the reproductive glands and to Herbert M. Evans and his brilliant associates for isolating highly purified pituitary hormones. Only now are we beginning to appreciate the significance of Hisaw's isolation of relaxin from the corpus luteum. Du Vigneaud's synthesis of polypeptides with pressor and oxytocic activities comparable to those of posterior pituitary extracts is a milestone in the continuing progress of endocrinology.

The recognition of the major endocrinopathies, the appreciation of glandular dysfunction as distinct from organic pathology, and the availability of potent endocrine preparations are in large part responsible for the rapid advance of clinical endocrinology.

The availability of crystalline hormonal preparations has led to new problems. Not infrequently these preparations are used in the absence of clear-cut indications. Such medication may obscure or delay the correct diagnosis and expose the patient needlessly and at considerable expense to the effects of potent endocrine agents. Promiscuous use of endocrine therapy has been encouraged by the introduction of relatively inexpensive synthetic products, notably estrogenic substances.

The treatment of gynecologic functional disorders is greatly handicapped by lack of accurate and practical methods of measuring the activity of those glands responsible for cyclic function. Consequently, it is seldom that the etiology of menstrual dysfunction is fully understood. Without this understanding it is not surprising that these disorders often remain unresponsive to treatment.

New phases of endocrine research are rapidly developing. Attention is being directed to the cytochemistry of the endocrine glands, the importance of the role of the receptor organ, and the complexities of glandular interdependence. The recognition of the properties of such chemical agents as thiouracil and alloxan and the availability of radioactive isotopes have provided new tools with which to attack the problems of glandular function. Stimulated by Huggin's demonstration that estrogenic therapy affords marked relief to patients suffering from carcinoma of the prostate, intensive research has been directed toward the broad problem of the relationship of hormones to cancer.

There remain great opportunities for research in the field of gynecologic

endocrinology. There are many shortcomings in our understanding of various types of menstrual dysfunction that prevent prompt and accurate diagnosis and preclude effective therapy. Although much has been learned concerning the endocrinology of pregnancy, seldom is the cause of an abortive process known and rarely can such a process be therapeutically prevented or arrested.

In the field of human reproduction, problems relating to infertility are legion: a more accurate and practical method for detection of ovulation is needed and the predictable induction of ovulation has thus far not been attained. The complexities of the human reproductive process and differences between the human menstrual cycle and the reproductive cycle of nonprimate animals have led to a close alliance between the research laboratory and the clinic. G. W. Corner⁶ has said, "In this field, beyond all others in medicine, the clinician and the basic science investigator must work together to make laboratory findings useful in practice."

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Section I

Endocrine Physiology

