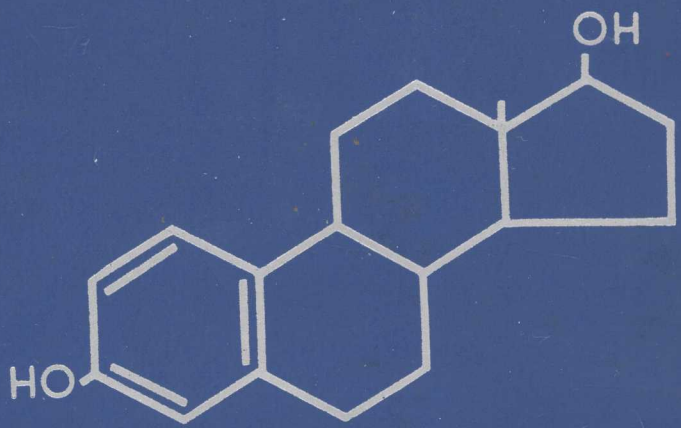
CLINICAL USE OF SEX STEROIDS

James R. Givens, editor



CLINICAL USE OF SEX STEROIDS

EDITOR
JAMES R. GIVENS, M.D.

ASSOCIATE EDITORS
RICHARD N. ANDERSEN, PH.D.
BRIAN M. COHEN, M.B. CH.B., M.D.
ANNE COLSTON WENTZ, M.D.

Based on the proceedings of the Fourth Annual Symposium on Gynecologic Endocrinology held May 7 – 9, 1979 at the University of Tennessee, Memphis, Tennessee

YEAR BOOK MEDICAL PUBLISHERS, INC.
CHICAGO • LONDON

Library of Congress Catalog Card Number: 80-53576

International Standard Book Number: 0-8151-3528-9

CLINICAL USE OF SEX STEROIDS

Annual symposia on gynecologic endocrinology
held at the University of Tennessee and
published by Year Book Medical Publishers, Inc.

Volume 1
GYNECOLOGIC ENDOCRINOLOGY (1977)

Volume 2
ENDOCRINE CAUSES OF MENSTRUAL
DISORDERS (1978)

Volume 3
THE INFERTILE FEMALE (1979)

Dedication

JOSEPH W. GOLDZIEHER, M.D.

THE FOURTH ANNUAL UNIVERSITY OF TENNESSEE REPRODUCTIVE MEDICINE SYMPOSIUM, "Clinical Use of Sex Steroids," is dedicated to Dr. Joseph W. Goldzieher. Stimulated initially toward a career in chemistry by his studies under Dr. Louis Fieser at Harvard, Dr. Goldzieher was ultimately guided by a family tradition in medicine going back to his great-grandfather in his choice of a career. The medical and scientific worlds have been greatly enriched by the contributions of the physician-chemist that these two major influences produced.

Dr. Goldzieher is a graduate of Harvard University and New York University Medical School. His training spans the fields of internal medicine (at Bellevue Hospital) and pathology (at New York City Hospital). Dr. Goldzieher next went to Duke University where his work

with Dr. E. C. Hamblen on the use of estrogens for treatment of amenorrhea marked the beginning of his fruitful and extensive studies of steroids. He is a diplomate of the American Board of Clinical Chemistry.

Returning to New York, he was in private practice with his father for several years and Director of Research at St. Clare's Hospital where he studied adrenal steroidogenesis.

Dr. Goldzieher's move to the Southwest Foundation for Research and Education in 1953 opened up new opportunities for his scientific pursuits in the ensuing years. He was Chief of the Endocrine Laboratory and Chairman of the Department of Endocrinology at the Foundation prior to taking his current position as Director of Clinical Sciences and Reproductive Biology at the Foundation.

A long-standing period of collaborative work with Dr. L. R. Axelrod that began in 1956 has resulted in major advances in our knowledge of steroidogenesis in both normal and pathologic specimens of the adrenals and ovaries.

Studies of orally active progestational compounds also began in 1956 in conjunction with pharmaceutical companies. This work was followed by the first clinical trials of oral contraceptives in association with Drs. Warren Nelson, Gregory Pincus and Eddy Tyler. By 1973, data on more than 100,000 cycles had been accumulated.

The discovery that mestranol was a contaminant of the early preparations of Enovid-E in large enough amounts to account for its contraceptive effect led to the development of the theoretically appealing sequential oral contraceptives.

Continuing studies of combined oral contraceptives have examined the question of the safety of these preparations on a multinational basis and have included a critical evaluation of the epidemiology of these preparations with a heavy statistical emphasis. Additional work has added greatly to our knowledge of the pharmacokinetics and metabolism of oral contraceptives as well as their effects on carbohydrate metabolism and lipid profiles of oral contraceptive users.

What of the future? There is still an urgent need for improved and alternative antifertility methodologies in spite of the success of oral contraceptives. Joe Goldzieher is right there, at the forefront of this area of work.

RICHARD N. ANDERSEN, PH.D.

Preface

THIS VOLUME presents the proceedings of the University of Tennesee Fourth Annual Symposium on gynecologic endocrinology, which was titled Clinical Use of Sex Steroids. The symposium was held in Memphis, May 7–9, 1979, and was sponsored by the Division of Reproductive Medicine of the Departments of Obstetrics and Gynecology.

The authors submitted prepared manuscripts of their presentations; the panel discussions are edited transcriptions. The purpose of this symposium was to discuss the indications, contraindications and side effects of those sex steroids used in clinical practice. The physiology and pharmacology of both natural and synthetic agents were discussed during the first half-day of the program. The use of sex steroids in the management of menopause, osteoporosis, hypogonadism, contraception, dysfunctional uterine bleeding, precocious puberty and corpus luteum insufficiency were discussed in the next day and a half of the program.

The last day of the symposium was devoted to potential complications and/or side effects associated with sex steroid therapy, including carcinoma of endometrium and breast, liver dysfunction, hypertension, deranged carbohydrate-lipid metabolism and teratogenic effects.

Willingness of the Faculty members to participate and prepare a manuscript is gratefully acknowledged. Appreciation is again expressed to Dr. Preston V. Dilts, Jr., Chairman of the Department of Obstetrics and Gynecology, for continued support of this symposium. The expert assistance of the Continuing Education Division members in conducting the symposium is gratefully appreciated. The continued, faithful secretarial assistance of Ms. Caroline Minga and Ms. Linda Lay is acknowledged. Drs. Anderson, Cohen and Wentz ably served as associate editors and contributed their unique talents to various sections of the volume. The professional editorial assistance of Fran Kelsey and Gabriela Wallenstein made the publication of this volume possible.

JAMES R. GIVENS, M.D.

Contributors

RICHARD N. ANDERSEN, M.D., PH.D.
Division of Reproductive Medicine, Department of Obstetrics and Gynecology, University of Tennessee College of Medicine, Memphis, Tennessee

G. WILLIAM BATES, M.D.
Associate Professor, Department of Obstetrics and Gynecology, The University of Mississippi School of Medicine, Jackson, Mississippi

PAUL BECK, M.D.
Professor of Medicine, North Carolina School of Medicine, Director, Medical Teaching Service, Raleigh, North Carolina

GARY S. BERGER, M.D.
Assistant Professor of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina

DAVID A. BLAKE, PH.D., M.D.
Associate Professor, Gynecology/Obstetrics and Pharmacology, The Johns Hopkins University School of Medicine, Baltimore, Maryland

BRIAN M. COHEN, M.B.CH.B., M.D.
Associate Professor, Department of Obstetrics and Gynecology, Head, Section of Reproductive Surgery–Infertility and Andrology, Division of Reproductive Medicine, University of Tennessee Center for the Health Sciences, Memphis, Tennessee

RICHARD P. DICKEY, M.D.
Associate Professor, Department of Obstetrics/Gynecology, The Louisiana State University School of Medicine, New Orleans, Louisiana

MARION DUGDALE, M.D.
Professor, Departments of Internal Medicine and Pathology, University of Tennessee Center for the Health Sciences, Memphis, Tennessee

RICHARD A. EDGREN, PH.D.
Associate Medical Director, Syntex Laboratories, Palo Alto, California

JAMES R. GIVENS, M.D.
Professor of Medicine, Head, Section of Reproductive Medicine, University of Tennessee College of Medicine, Memphis, Tennessee

ALVIN F. GOLDFARB, M.D.
Clinical Professor, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

JOSEPH W. GOLDZIEHER, M.D.
Department of Clinical Sciences and Reproductive Biology, Southwest Foundation for Research and Education, San Antonio, Texas

GILBERT S. GORDAN, PH.D., M.D.
Professor of Medicine, University of California, San Francisco, California

CHARLES B. HAMMOND, M.D.
Professor, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, Duke University Medical Center, Durham, North Carolina

NORMAN M. KAPLAN, M.D.
Professor of Internal Medicine, The University of Texas Health Science Center, Dallas, Texas

NATHAN KASE, M.D.
Professor, Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut

PETER A. LEE, M.D.
Associate Professor, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland

MARTIN M. QUIGLEY, M.D.
Assistant Professor, and Director, Reproductive Endocrinology, Division of Obstetrics and Gynecology, University of Texas Health Science Center, Houston, Texas

ALBERT SEGALOFF, M.D.
Clinical Professor of Medicine, Tulane University School of Medicine, New Orleans, Louisiana

EDWARD S. UMSTOT, M.D.
Division of Reproductive Medicine, Department of Obstetrics and Gynecology, University of Tennessee College of Medicine, Memphis, Tennessee

CYNTHIA VAUGHAN, R.N., M.A.
Formerly Clinical Coordinator of Nursing, University Hospital, New York University Medical Center

NICHOLS VORYS, M.D.
Clinical Associate Professor, Department of Obstetrics/Gynecology, Ohio State University College of Medicine, Columbus, Ohio

ANNE COLSTON WENTZ, M.D.
Professor, Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, University of Tennessee College of Medicine, Memphis, Tennessee

EMERY A. WILSON, M.D.
Associate Professor, Department of Obstetrics and Gynecology, The University of Kentucky College of Medicine, Lexington, Kentucky

Contents

Progestagens

RICHARD A. EDGREN, PH.D.

Associate Medical Director, Syntex Laboratories
Palo Alto, California

IN 1971, MCGUIRE AND DEDELLA[1] summarized a series of studies indicating that radiolabelled progesterone was preferentially concentrated by the mammalian uterus and that this uptake of progesterone was depressed by incorporation of unlabelled progestational agents. This study followed closely the collection of evidence suggesting specific association of other steroid hormones with "binding sites" in hormone-sensitive tissues. Such "activating sites of attachment"[2] have been demonstrated to exist for estrogens,[3] androgens,[4] mineralocorticoids[5] and glucocorticoids.[6] Studies on the binding of steroids have led to a general theory of steroid action that is based on this binding, and a number of paradoxical problems concerning the biologic actions of progestagens appear to be clarified by this theory. I therefore propose to review the biologic effects of the progestagens commonly used in therapy (alone and in combination with estrogens) from the vantage point of the receptor binding hypothesis.

The Receptor Binding Hypothesis

Circulating steroids appear to pass readily in both directions through the plasma membranes of cells in most vertebrates. However, in the specific target tissues of steroid action, these substances are sequestered by receptor proteins and intracellular hormone concentrations are increased markedly (Fig 1, A).

The complexes of steroid and receptor are then translocated into the nucleus of the cell, where they are bound to the chromatin and become a portion of the synthetic apparatus of the genome (Fig 1, B). The trans-

8151-3527/80/0004-001-029-$03.75

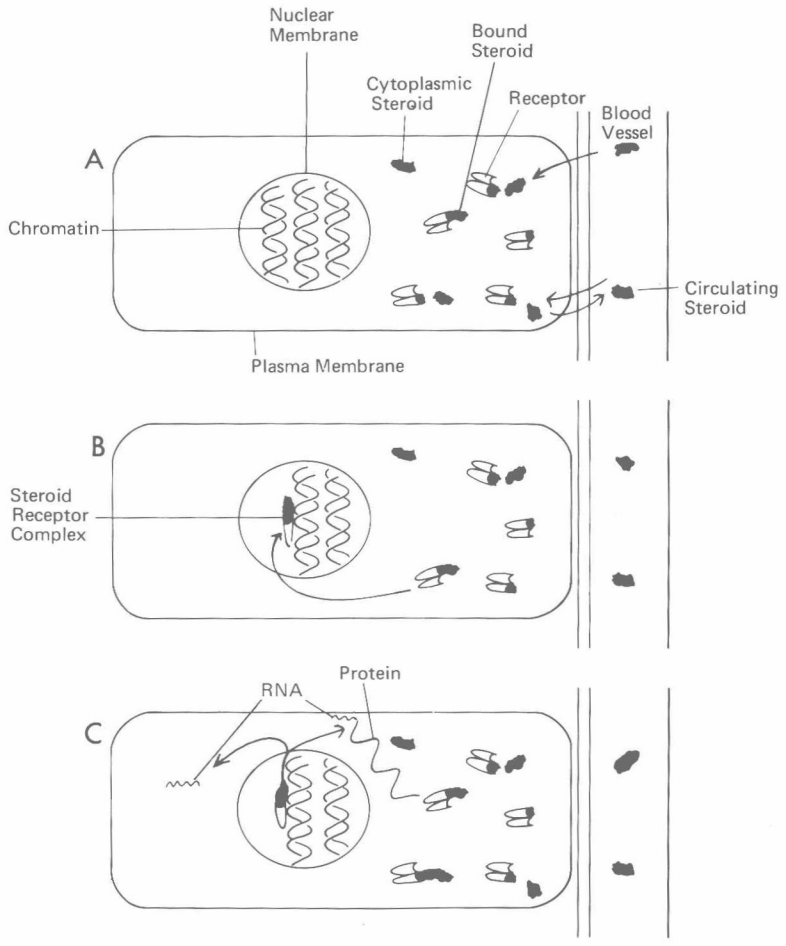


Fig 1. – Diagrammatic representation of the steroid bindings hypothesis. **A,** circulating steroids pass readily through the plasma membranes of all cells. In target tissues, the steroid molecules are sequestered by binding to proteinaceous receptors in the cytoplasm. **B**, the steroid receptor complex is translocated; it passes into the nucleus and binds to the genome; *m*RNA production is altered. **C**, the *m*RNA passes back into the cytoplasm, where it affects protein synthesis, leading to differentiation, growth or secretion.

location process does not occur through passive diffusion, but appears to require active processes, which are still imperfectly understood.

Sherman and Miller[7] have shown that the progesterone receptor can be divided into subunits and that only a portion of the "holoreceptor" enters the nucleus in association with the steroid molecule.

In the nucleus, the new complex of genome, receptor and steroid alters the production of messenger ribonucleic acid (*m*RNA); the latter passes back into the cytoplasm and affects protein production (Fig 1, C).

The sequence of stages for all steroid action appears to be as follows:

(1) Passive diffusion of steroid through plasma membrane into target cells
(2) Binding to receptor
(3) Translocation of steroid/receptor complex into the nucleus
(4) "Binding" of complex to genome
(5) Synthesis of *m*RNA
(6) Passage of *m*RNA into cytoplasm
(7) Synthesis of new protein, leading to growth, differentiation, synthesis, etc.

In this sequence, binding of the steroid to the receptor is critically important since it appears to be specific, and may be defined as the first link in the chain of effects that constitute the "action" of a steroid hormone; a substance *must* bind to a receptor before a hormonal effect is produced. Furthermore, the receptors are reasonably specific in structural requirements for binding, and these binding requirements parallel many of the usually cited pharmacologic requirements for steroid action. Thus, binding affinities to the estrogen receptor are high for compounds with aromatic A-rings and the progesterone receptor normally associates poorly with steroids having anything but the Δ^4-3-oxo configuration.

Chemical Structures

Chemically, progestational agents used therapeutically belong to two classes of steroids, i.e., derivatives or relatives of progesterone and derivatives or relatives of testosterone, usually 19-nortestosterone.

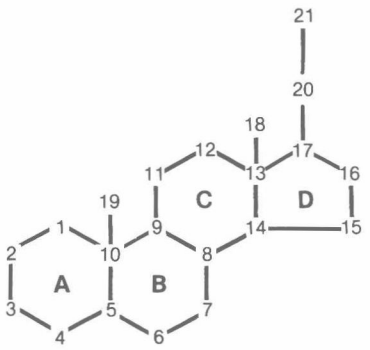


Fig 2. – The lettering system for the rings of the steroid nucleus and the numbering system for the carbon atoms; each number represents one carbon atom.

Structurally, all steroids have nuclei composed of 4 rings: 3 are 6-membered and one is a 5-membered ring. The lettering system for the rings and the numbering of the carbon atoms is shown in Figure 2. For comparative purposes the structures of the most important natural sex steroids are shown in Figure 3. The 3 estrogens, estradiol, estrone and estriol, have aromatic A-rings and hydroxyl groups at carbon 3. They differ in the nature and positioning of oxygenated groups at carbons 17 and 16. Estrogens of equine origin used in therapy also contain such substances as equilin and equilenin, which are structurally similar to estrone but have unsaturation in the B-ring, i.e., double bonding at 6–7 and 8–9 for equilin and 7–8 for equilenin. Testosterone and progesterone are Δ^4-3-oxo-steroids; testosterone has a hydroxyl group in the β-position of carbon 17, whereas progesterone has an acetyl group at 17.

Remarkable increases in potencies of progestational agents were achieved in experimental animals by structural modifications. Examples are shown in Figure 4. Progesterone, the standard, was defined as having a potency of 1 in the Clauberg test for uterine glandular proliferation in rabbits (this test will be detailed in the next section). The 17α-acetoxy derivative of progesterone was about 10 times more potent than the parent compound when given parenterally, but it had little activity when administered orally. Oral and parenteral potencies were markedly increased by incorporation of a methyl group at carbon 6. Increasing B-ring unsaturation by incorporation of a double bond be-

Fig 3. – Chemical structures of the important, natural sex steroids of humans.