MAZER & ISRAEL'S

DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY

FOURTH EDITION BY

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Preface to the Fourth Edition

The author of this edition accepts full responsibility for its content, the press of other duties having prevented the senior author from participating. The fourth edition could not have been possible, however, without the earlier preceptorship of, and the prior training, guidance, and instruction imparted by, Doctor Mazer.

Twenty years ago, when the first edition of this book was written, gynecic endocrinology was in its infancy. It was possible then for the clinician to keep abreast of the subject. It is now increasingly difficult for the practitioner to co-ordinate the advances of research with clinical usage in any field of medicine, let alone one touched by endocrinology. This edition, as were its predecessors, is intended as a guide for all physicians interested in the diagnosis and treatment of menstrual disorders and sterility. Contributions from workers in the fundamental sciences have been examined with the objective of translating their more pertinent findings into words of practical usefulness. Having been largely rewritten, this edition is almost a new book.

The references in this volume are but a small part of the flood of relevant articles that have been published during the last two decades. More recently, two new journals devoted specifically to the barren marriage, *Fertility and Sterility* and the *International Journal of Fertility*, have appeared. This vast quantity of material accounts in part for the relative lack of foreign-tongued references in comparison with those from sources in English.

The opportunity to re-evaluate the usage of hormones in practice has been an outstanding feature of this rewriting. Experience has shown that early enthusiasms for therapy do not always persist, the sievelike effect of time preserving only those of lasting value. Linked to these therapeutic emendations is an awareness that the way station between the innermost recesses of the brain and the peripheral organs, the hypothalamus, holds the

key to many of the ailments covered in this book. It is hoped that the reader will sense the necessity of a closely knit relationship between hormonal treatment and an encouragingly supportive attitude of the physician toward the patient and her surrounding life forces.

No book purporting to embrace the subjects of menstrual disorders and sterility would be complete without full discussions of both the thyroid and adrenals, as well as that of the role of the male in infertility. For these, it is a pleasure to acknowledge my great obligation to Drs. Charles W. Charny and Norman G. Schneeberg, whose by-lines duly credit their separate chapters. Thanks must also be expressed to Dr. Paul Decker, Assistant Director of the Ayer Laboratory of Pathology, Pennsylvania Hospital, for the many new photomicrographs that embellish this edition; to Mrs. Bernard Finneson whose patience enabled her nimble craftsmanship to express so well many of our ideas in graphs, diagrams, and drawings; to Mrs. S. Leon Israel for numberless hours in the library and for the diligence with which references were verified; to Dr. Harry B. Roitman for his seemingly effortless assistance in the solution of some of the problems of authorship; and, penultimately, to the tireless fingers and cooperative equanimity of Mrs. Viola Nelson and of Mrs. Ruth A. Davis who typed the manuscript.

Finally, there are no words remaining to convey properly my sense of gratefulness to Mr. Paul B. Hoeber and his ever-helpful, consistently gracious staff.

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Preface to the First Edition

In presenting this modest volume to the profession, it is the hope of the authors that it will especially serve as a guide to the family physician who is the first to see and treat the numerous women suffering from menstrual disorders and sterility. With this view in mind, the authors have described in great detail the office procedures employed in the diagnosis and treatment of menstrual disorders and sterility, and have merely mentioned those procedures which require special technical skill and hospital environment.

Menstrual disorders and sterility are essentially outstanding symptoms of various and diverse physiologic conditions. Academically, they should be considered under the heading of the conditions responsible for their appearance. Clinically, however, it is more expedient to discuss these symptoms as if they were distinct pathologic entities, not only because they are, in most instances, the only manifestations of the morbidity in question but also because each of them is so often the sole sign of multiple, coexisting, and totally unrelated pathologic conditions. For instance, adhesions obstructing the lumen of the fallopian tubes, anovulatory menstruation, chronic cervicitis, and testicular insufficiency may all enter into the etiology of a sterile union. Moreover, the underlying morbidity giving rise to amenorrhea or dysfunctional uterine bleeding is, in many instances, not discernible by all the means at our disposal, and the patient must, by necessity, be treated symptomatically.

Menstrual disorders and infertility are so closely related that any treatise on one or the other alone would not fulfill the requirements of the student and the family physician. The necessity of including a chapter on the diagnosis and treatment of male sterility is apparent, for treatment of the barren woman is incomplete without due attention to the degree of fertility of her husband.

The therapeutic procedures herein advocated are the well-tried and safe measures which the authors have employed for many years with a fair degree of success. The mention of those not yet generally accepted by the

profession is fortified by references to authoritative sources.

The authors have assiduously omitted description of laboratory procedures which cannot be carried out in the office. The clinical interpretation and evaluation of such tests are, we hope, adequately stressed; the original reference to the techniques are given.

In writing this volume, the authors have unavoidably drawn from their more recent articles which appeared in the *Journal of the American Medical Association*; the *American Journal of Obstetrics and Gynecology*; *Surgery, Gynecology and Obstetrics*; *Endocrinology*; the *Pennsylvania Medical Journal*; and *Medical Clinics of North America*. The courtesy thus extended by these periodicals is herein acknowledged.

Sincere appreciation is accorded Dr. Philip Getson for assistance in editing the text, Dr. George Baer for assembling much of the data employed in the tables, Dr. David R. Meranze for selecting many histologic preparations from our material at the Mount Sinai Hospital, and Dr. Elkin Ravetz for tabulating the index. Special credit also belongs to Mr. Joseph Poppel for his skill and patience in making most of the photomicrographs and to Miss Gladys E. Lande for the drawings. The authors acknowledge a deep indebtedness to their secretary, Miss Esther Weisman, and their laboratory technician, Mrs. Adele Boyle, whose indefatigable efforts served immeasurably to lighten the burden of authorship.

The courtesies of Mr. Paul B. Hoeber have made the final preparation of the manuscript a pleasant task. He is to be especially thanked for his unflagging efforts to keep the cost of the book within the reach of the student.

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CHAPTER 1

The Pituitary Gland

IT SEEMS only natural to begin a textbook devoted to menstrual disorders and sterility with a brief review of the physiology of the anterior hypophysis. It has become increasingly clear that the functions of the pituitary are controlled by the hypothalamus, in one way or another (see Frontispiece). Our knowledge of this relationship is not at all satisfying but sufficient is known to indicate that the gonadotropic function of the pituitary depends entirely upon stimuli received from the hypothalamus. Although this chapter will review briefly those functions of the pituitary, it is not intended to be a comprehensive endocrinologic discussion. Only those matters related to menstrual function and fertility will be discussed.

The three anatomic divisions of the pituitary gland are well known and need not be discussed here in detail (Fig. 1). The reader who is interested in details concerning the physiology of the pituitary, as well as its varied embryology, may find these matters clearly outlined in any of the current books dealing with endocrinology.

The interreactions between the hypothalamus and the pituitary gland are increasingly important, the subject of much current research. It is likely that our present concepts, vague as they are, will be on a sounder basis within the next few years.

The present knowledge of the general physiology of the anterior hypophysis was evolved mainly through extirpation and replacement experiments in animals. In 1927, Smith,[41] by employing a parapharyngeal method of surgical approach to the pituitary of the rat, demonstrated conclusively that hypophysectomy without injury to the hypothalamus results in genital atrophy and retardation of body growth and that these effects are easily remedied by means of implants or administration of extracts of anterior

lobe tissue alone. He further showed[42] that hypophysectomy in mammals results not only in arrested growth and atrophic gonads but also in involution of the adrenals and thyroid body.

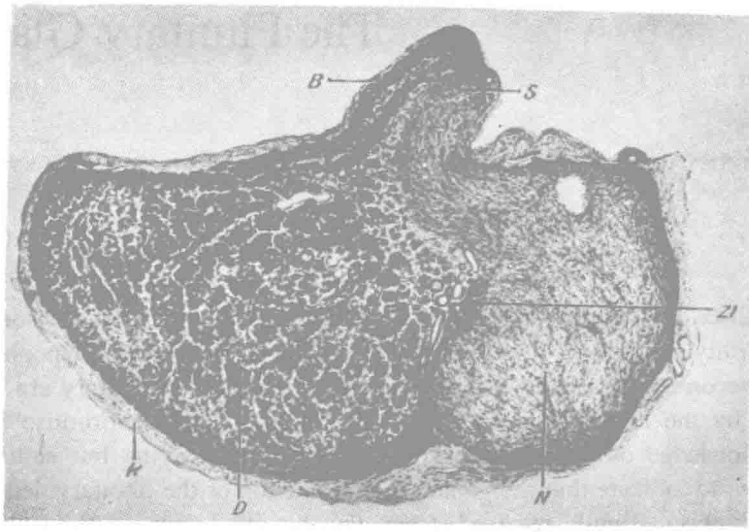

FIG. 1. Median section through the hypophysis of a 45-year-old man. (× 16) Note the anatomic divisions of the gland, as follows: *B*, infundibular portion of anterior lobe; *D*, anterior lobe; *K*, capsule; *N*, posterior lobe; *S*, stalk; and *Zl*, intermediate lobe. (From Schaffer.[40] Courtesy of W. B. Saunders Company.)

The use of hypophysectomy as palliative treatment for certain fatal diseases has, in the main, confirmed the observations made on hypophysectomized animals. Patients subjected to hypophysectomy[29, 31] or to destruction of the pituitary by implantation of radon seeds[12] develop weight loss, amenorrhea, mental and physical sluggishness, hypothermia, low basal metabolism, and hypoglycemia. These findings parallel the symptoms encountered in pituitary cachexia (Simmonds' or Glinski's disease and Sheehan's syndrome) wherein the secreting elements of the anterior pituitary gland disappear by necrosis.

HORMONES OF THE ANTERIOR LOBE OF THE PITUITARY. At the present writing, it is definitely established that there are at least six hormones produced by the anterior lobe of the pituitary, all of which have been isolated in pure form. Biologically, the follicle-stimulating, luteinizing (interstitial-cell-stimulating), and luteotropic hormones are *gonadotropic;* whereas, the growth, adrenocorticotropic, and thyrotropic principles may be termed

metabolic. Chemically, the six hormones are divisible into two classes of proteins, namely, the simple proteins and the glycoproteins. They may also be categorized chemically by their solubility characteristics. There is some evidence, albeit still controversial, to support the contention that a specific mammogenic hormone is also elaborated by the pituitary (Chap. 9). Moreover, it must not be overlooked that the growth hormone, *somatotropin,* exerts multiple actions related to the metabolism of foodstuffs and the functions of enzymes, and thus aids the effects of the other pituitary hormones.[28]

To understand clearly menstrual disorders and infertility, knowledge of the three gonadotropic hormones is essential. Description of the other principles of the anterior hypophysis is, by the necessity of space, omitted.

The Gonadotropic Hormones of the Anterior Lobe of the Pituitary

The complete dependence of the ovarian cycle upon hormonal stimulation from the anterior lobe was demonstrated in 1927 by the independently performed, classical experiments of Smith and Engle[43] and of Zondek and Aschheim.[49] They succeeded in evoking temporary estrus and ovarian growth in intact infantile rodents by means of hypophyseal implants. It was later shown that specific extracts of anterior pituitary lobe tissue produce the same effects in the immature animal and also repair the gonadal damage produced by hypophysectomy. The product of no other endocrine gland is capable of evoking these phenomena in the immature intact or hypophysectomized adult animal. Today, it is realized that the anterior pituitary lobe is the "motor" of gonadal function in both male and female. The effects of the gonadotropic hormones on the gonads of either sex are as follows:*

Ovary	*Testis*
1. Ripening of follicles, with secondary production of estrogen.	1. Proliferation of the epithelium of the seminiferous tubules.
2. Maturation of ova.	2. Spermatogenesis.
3. Luteinization of mature granulosa and theca cells, with secondary production of progesterone.	3. Stimulation of interstitial tissue, with secondary production of testosterone.

* Only the ovarian changes are illustrated in this volume. Space does not permit the illustration of testicular effects, except as they relate to male infertility (Chap. 28).

THE TRIAD OF PITUITARY GONADOTROPIC HORMONES. The anterior hypophysis secretes three essential gonadotropic hormones, namely, the follicle-stimulating fraction (FSH), the luteinizing hormone (LH) (also known as the interstitial-cell-stimulating hormone [ICSH]), and the luteotropic hormone (LTH) (also known as the lactogenic hormone or prolactin).[25] Each of these yields an almost individual ovarian stimulation.

The follicle-stimulating hormone (FSH) is gametokinetic in either sex, causing growth of follicles and of seminiferous tubule epithelium. In the female, the stimulative action of the follicle-stimulating hormone results in maturation of the antrum-type follicle and the ovum contained therein, until the follicle reaches the graafian stage of development (Fig. 2). Electro-

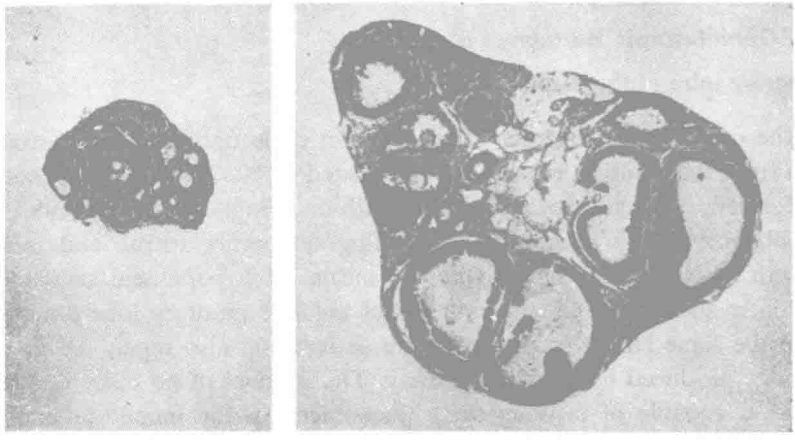

FIG. 2. Ovaries of 22-day-old (infantile) mice. (×35) *A*. Ovary of control animal, showing only primordial follicles. *B*. Ovary of animal injected with pituitary gonadotropin, showing first effect—maturation of follicles—Reaction I.

phoretically pure FSH, as shown experimentally in rats and mice, does not evoke secretion of estrogen. Physiologically, however, FSH is probably not secreted alone but rather together with some LH, which is responsible for secretion of estrogen by the cells of the growing follicle. The estrogen, in turn, has a marked trophic effect on the ovum itself.[14]

The luteinizing hormone (LH), acting in conjunction with the follicle-stimulating hormone, not only causes secretion of estrogen but also evokes ovulation and causes the cells of the ruptured graafian follicle to be transformed into lutein cells (the corpus luteum) which secrete progesterone as well as estrogen (Fig. 3). The pure luteinizing hormone is incapable of

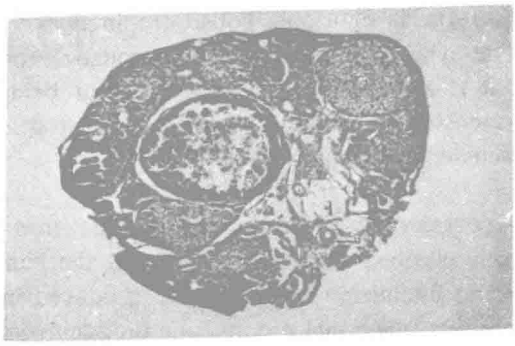

FIG. 3. Ovary of a 22-day-old (infantile) mouse injected with pituitary gonadotropin, showing a hemorrhagic follicle in the center—Reaction II. (× 35)

producing growth of the follicle, estrogen secretion, and ovulation; FSH must be present in proper ratio.

The luteotropic hormone (lactogenic hormone), LTH, is neither follicle-stimulating nor ovulatory. It is, however, capable of maintaining and prolonging the life and function of the corpora lutea of the experimental animal (Fig. 4). Like the luteinizing hormone, LH, it also produces hy-

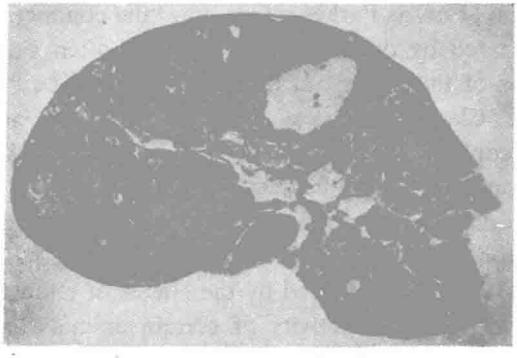

FIG. 4. Ovary of a 22-day-old (infantile) mouse injected with pituitary gonadotropin, showing the formation of corpora lutea—Reaction III. (× 35)

peremia of the infantile rat ovaries, as seen in the two-hour pregnancy test.[25] Since LTH causes progesterone to be secreted by the corpora lutea of an hypophysectomized rat, it is assumed, perhaps debatably, that it is responsible for progesterone secretion in the human. It will not prolong the dura-

tion of luteal function as chorionic gonadotropin does.[4] However, it has been shown to be synergistic with chorionic gonadotropin.[13] Perhaps, as Jones suggests, it is also synergistic with LH, that being its physiologic function in the menstrual (ovarian) cycle.[21] The lactogenic effects of this hormone are discussed in Chapter 9.

SOURCE OF PITUITARY GONADOTROPINS. The electron microscope and cytochemistry have clarified the cellular origin of the gonadotropins. Follicle-stimulating and luteinizing hormones are produced in the basophiles, of which there are two functional groups, one producing gonadotropic hormones, the "gonadotrophs," and the other secreting thyrotropic hormone, the "thyrotrophs."[11, 38] The fact that only the "gonadotrophs" respond to estrogen deprivation (castration) and replacement in the female rat supports the contention that there are two kinds of basophiles.[30] Prolactin (LTH) arises from one of the acidophile types of cell, the identity of the specific variety still being in question.[2]

The problems involved in cytochemical study of the anterior hypophysis may be appreciated by perusal of a recent textbook on histochemistry.[37]

NEUROHORMONAL CONTROL OF SECRETION OF GONADOTROPINS. The anterior pituitary may no longer be regarded as "the conductor of the endocrine orchestra." For, as Parkes points out, "the conductor is really just a marionette, activated by different strings pulled, often simultaneously, by various members of the orchestra, as well as by members of the environmental audience. Clearly, this is no ordinary orchestra, and the fact that physiological cacophony is comparatively infrequent shows that the elaborate co-ordination is surprisingly effective."[36]

Experimental data have long indicated that reproductive function of animals could be influenced by environmental changes of either physical or social character. This is exemplified by the effects of alteration of light and of nutrition upon hormonal activity of certain animals, subjects recently reviewed in detail by Hammond[17] and by Meites,[35] respectively. Thus, gonadotropic function of the anterior pituitary is controlled in two ways, either peripherally by sensory perception and by alterations in levels of gonadal steroid hormones or centrally by emotional reactions. All these stimuli, hormonal or neural suprahypophyseal regulators of gonadotropic function, are transmitted to the anterior pituitary through the hypothalamus (Frontispiece). The latter "may be thought of as an important information center, for the translation of messages from other parts of the brain into

visceromotor or endocrine impulses."[6] Evidence derived from either experimentally inflicted lesions[15] or clinical observations[3] leave little doubt concerning the hypothalamic control of hypophyseal gonadotropic activity. Whether the governing pathway is entirely nervous, being transmitted via the complex hypothalamo-hypophyseal tract entering through the posterior lobe,[46, 51] or neurovascular involving the hypophyseal portal system,[48] remains unsettled. Good evidence favors the passage of stimuli from hypothalamus to anterior pituitary through the vascular route.[18] However, the nature of the alleged chemotransmitter and its possible interactions are still moot.[9] Finally, Zuckerman's extirpation and implantation experiments lead him to question the essentiality of the portal vessels in the hypothalamic-hypophyseal system.[52]

The importance of the hypothalamic-hypophyseal system in the etiology of menstrual disorders is outlined in detail in Chapter 13.

CLINICAL USE OF PITUITARY GONADOTROPINS. The pituitary gland, although producing considerable quantities of gonadotropic hormones, stores so very little of them that extracts thereof are usually insufficient to produce appreciable gonadotropic effects clinically. They are available in low potency for clinical experimentation but must be given intramuscularly. FSH and LH are, moreover, water soluble and are, therefore, too rapidly absorbed to be effective when given parenterally. LTH is alcohol soluble but cannot be given intramuscularly in large quantities. All are totally ineffective when given orally. At best, the administration of pituitary gonadotropins is purely substitutive in cases of pituitary deficiency, for none will effect ovulation in the human. Even as substitutive therapy, pituitary gonadotropins cannot be employed for any length of time without long intervals of rest because, as shown conclusively by Maddock[32, 33] and others, sufficient antihormones form within two months to vitiate completely the effects of injected pituitary gonadotropins. In women with primary (intrinsic) ovarian deficiency, it is likewise useless to administer pituitary gonadotropins, because the pituitary gland is already producing excessive quantities of the hormones, especially the follicle-stimulating fraction.

Extrapituitary Sources of Gonadotropic Hormone

Larger, more potent, and clinically active quantities of gonadotropic substances are available from sources other than the pituitary gland, namely,

the blood serum of pregnant mares, human pregnancy urine, and the combination of pituitary and chorionic gonadotropins.

The urine of castrated and menopausal women also contains appreciable quantities of pituitary gonadotropins (mostly the follicle-stimulating fraction) but the quantity is, nevertheless, insufficient for widespread clinical use.[23]

BLOOD SERUM OF PREGNANT MARES (EQUINE GONADOTROPIN). In 1930, Cole and Hart[7] reported that the blood serum of mares contains large quantities of a gonadotropic substance during the mid-period of pregnancy. This substance, unable to pass the renal filter, is excreted in the mare's urine in minute quantities. As recovered from the blood of the pregnant mare, it is biologically identical with the hypophyseal gonadotropic hormones, in that injections of it produce both follicular growth and luteinization in either hypophysectomized or intact immature female animals, as well as spermatogenesis in male animals.[7]

On this basis, it was at one time heralded widely as a panacea to evoke ovulation in instances of anovular menstruation and to stimulate spermatogenesis in infertile men. Unfortunately, this has not proved to be the case.

Equine gonadotropin is *standardized* on the basis of an international unit (I.U.). It is the specific gonadotropic activity of 0.25 mg. (250γ) of the standard preparation in the possession of the World Health Organization and stored at the National Institute for Medical Research, London. The product, being a protein derivative, must not be given without testing the patient for sensitivity by the intradermal method and without questioning her concerning reactions to prior injections of serums. It should not be employed in those who develop wheals with pseudopodia or give a history of allergic tendencies. The few therapeutic indications for its use are mentioned in the respective chapters.

HUMAN PREGNANCY URINE (CHORIONIC GONADOTROPIN). The pituitary-like luteinizing principle, chorionic gonadotropin, is a derivative of cytotrophoblast,[22, 44, 47] the Langhans' cells. It is excreted in steadily increasing quantities from the beginning of gestation, being detectable a few days prior to the first missed period and reaching a maximum level during the third month of pregnancy. From then on, excretion of this hormone rapidly diminishes, disappearing entirely two weeks after parturition. A high concentration of the pituitary-like gonadotropic principle is likewise present in the blood and urine of women with either hydatidiform mole or chorionepi-