

**ADVANCES
IN THE TREATMENT OF
MENSTRUAL DYSFUNCTION**

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Edited by

ALVIN F. GOLDFARB, M.D.

Assistant Professor of Obstetrics and
Gynecology, Jefferson Medical College,
Philadelphia, Pennsylvania

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PREFACE

WITH the recent increase in knowledge regarding menstrual physiology, it is felt that the transmission of this information to the practicing physician would be of interest. Moreover, the clinical application of this knowledge is such that an understanding of the basic sciences involved is important. It is for these reasons that a symposium on "Newer Developments In The Treatment of Menstrual Dysfunctions In Office Practice" was organized and was held on April 27, 1963, at Jefferson Medical College, Philadelphia, Pennsylvania.

The conference was divided into four major areas, (1) Basic Sciences, (2) Therapeutics, (3) Ovulation Control and (4) Reflections. The participants were all outstanding authorities in their respective fields.

Dr. Greenblatt presented recent data on the effects of progestins and a new experimental compound, Clomiphene, on the reproductive system. Dr. Lloyd discussed neuro-endocrinology and its influence on pituitary gonadal function. Dr. Paulsen presented evidence for the estrogenic activity that is inherent in the 19-nor testosterone compound. Dr. Landau reviewed and presented evidence describing the metabolic activity of progesterone and its effect on adrenal physiology.

In the second part dealing with therapeutics, several outstanding clinicians discussed many of the areas of gynecologic dysfunction and reviewed the management of these problems. Dr. Woolever presented a concise review of the management of dysfunctional uterine bleeding based upon a large volume of clinical data. Dr. Behrman presented a common sense method of treating and evaluating secondary amenorrhea. Dr. Roland reviewed the effect of steroids on the endometrium, a most important aspect of infertility. A clinician of experience, Dr. Riva, reviewed the use of a pseudopregnancy regimen in the management of endometriosis. His description of the endometrial changes in long-term progestin therapy demonstrates "secretory exhaustion."

Ovulation control was the subject matter of the third part of the conference. The role of ovulation control in child spacing

based upon eight years of experience was reviewed by Dr. García. The changes in the menstrual patterns in ovulation control were discussed by Dr. Flowers. In addition he discussed at length some new concepts with reference to dosage schedule and newer experimental steroids that are being used in ovulation control. Dr. Tyler discussed side effects and toxicity. In addition, he presented the experience of many workers throughout the world and their statistics regarding ovulation control.

The last part of this book presents three distinct contributions, one of which deals with the experience of a generalist in the area of progestin therapy. Dr. Shipps presented data to demonstrate the efficiency of progestins as a pregnancy test method. Dr. Sturgis made us all aware of the role of empathy in therapeutics and medical practice. Finally, as editor, I have taken the prerogative given me and summarized the papers. Discussions of the various presentations following each session have been included.

Dr. John B. Montgomery, Professor and Chairman of the Department of Obstetrics and Gynecology at the Jefferson Medical College, and Dr. Abraham E. Rakoff, Professor of Obstetric and Gynecologic Endocrinology, served as session moderators. A generous grant from the G. D. Searle & Co. made the symposium a reality. The conference and the publication have been most ably served by my secretary, Mrs. Robert Langman.

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Menstrual Physiology
Robert B. Greenblatt, M.D.

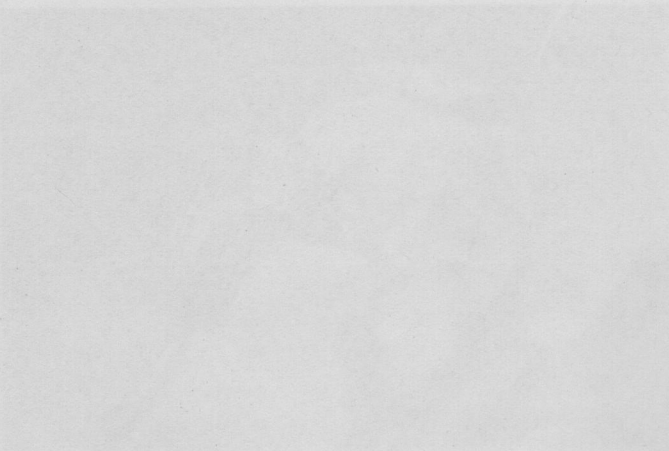
PART I

*The Physiology of the
Female Reproductive System*

REVIEW THE PHYSIOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM WITH THE PHYSIOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM AND SUPERFICIAL ASPECTS OF SUCH A REVIEW. SUCH A REVIEW OF THE PHYSIOLOGY OF THE FEMALE REPRODUCTIVE SYSTEM WOULD BE THE HIGHLIGHTING OF CERTAIN ASPECTS OF MENSTRUAL PHYSIOLOGY WHICH WOULD EMPHASIZING OR NEED CLARIFICATION.

The Ovarian Process

The precise moment of ovulation is a phenomenon not often observed or recognized at random laparotomy. The presence of a hemorrhagic bleb on the ovary should suggest that the moment of ovulation is at hand (Figure 1-1). Histologic sec-



Menstrual Physiology

Robert B. Greenblatt, M.D.

TO REVIEW THE VARIOUS FACETS WHICH DEAL WITH THE physiology of menstruation would be a long and superfluous task. Such information is available in any standard text book.^{1a, b} Germane, however, to the discussions to follow would be the highlighting of certain aspects of menstrual physiology which merit emphasizing or need clarification.

The Ovulatory Process

The precise moment of ovulation is a phenomenon not often observed or recognized at random laparotomy. The presence of a hemorrhagic bleb on the ovary should suggest that the moment of ovulation is at hand (Figure 1-1). Histologic sec-

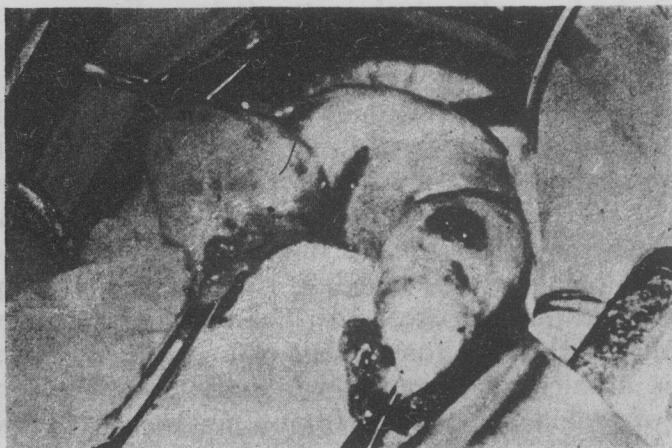


Fig. 1-1. Note the ovulatory bleb on the right ovary.

tion through such a bleb proved informative, for it revealed that several follicles were chosen to undergo some degree of ripening (Figure 1-2). Only one follicle, however, was selected

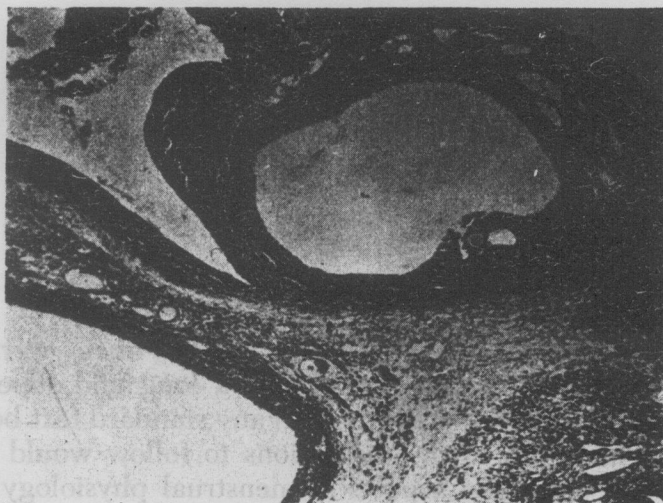


Fig. 1-2. Photomicrograph of histologic section through bleb shown in Figure 1-1. Note three follicles in various stages of maturation.

to go on to ovulation. In studying the histologic sections of the actual process of ovulation, in this instance, it was noted that there was dehiscence of the capsule, and the ovum with its cumulus of granulosa cells was on the way to be washed out of the collapsing follicle (Figure 1-3).

Menstrual Mechanics

Withdrawal of the hormonal support of an exogenously stimulated endometrium by estrogen and progesterone or the loss of endometrial support by a rapidly regressing corpus luteum is followed by necrosis and shedding of the endometrium, *i.e.*, menstruation. On the other hand, the bleeding which accompanies ovulatory failure or that following estrogen withdrawal or estrogen breakthrough bleeding is irregular and frequently prolonged and may be excessive. The endometrial biopsy obtained on the third or fourth day of an ovulatory menstrual period is usually very scanty, while the scrapings obtained in cases of prolonged bleeding from a persistently proliferative

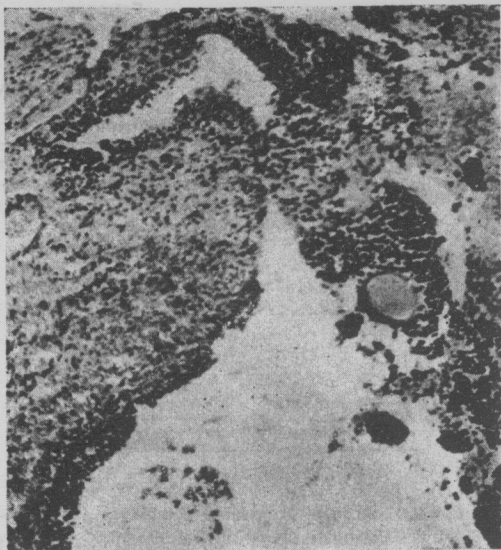


Fig. 1-3. Histologic section through follicle chosen for ovulation. Note dehiscence of the capsule and ovum with cumulus of cells about to be washed out into the peritoneal cavity.

type of endometrium are abundant, because of the failure of the endometrium to be shed.²

A rapid review of the contributions made to an understanding of the mechanisms involved in uterine bleeding is pertinent at this time. The simple factors involved in the induction of bleeding have escaped many clinicians and workers in the field. Allen demonstrated that removal of the ovaries in the adult macaque, regardless of the time during the cycle, is followed by uterine bleeding.³ This phenomenon was called "estrogen withdrawal bleeding." It had been known for a long time that after the excision of the active corpus luteum in the human, bleeding would follow within 48 hours.⁴ It was further shown that if an estrogen was administered immediately after castration of the macaque, the withdrawal bleeding could be postponed. However, if estrogens were given for a prolonged period of time then breakthrough bleeding frequently occurred. This was interpreted as "estrogen breakthrough bleeding." If the dosage of estrogens, however, was substantially raised and continued, the bleeding was arrested (Figure 1-4).

Furthermore, Corner proved that if progesterone was given

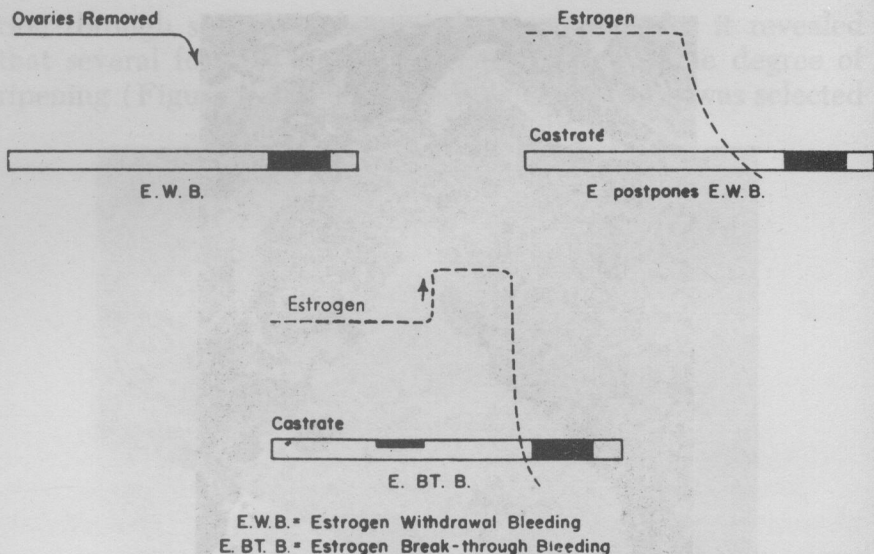


Fig. 1-4. Estrogen-withdrawal bleeding in the macaque. Experiments of Edgar Allen, George W. Corner, and others.

following the termination of the administered estrogen to the castrated macaque, the expected estrogen withdrawal bleeding could be prevented.⁵ On the other hand, when testosterone was given after discontinuing the estrogen, Engle showed that estrogen withdrawal bleeding could be delayed.⁶ The question arose, did testosterone behave in a manner similar to an estrogen or to a progestogen. It remained for Zuckerman to show, by an ingenious experiment, that if estrogen was administered and progesterone superimposed for a period of several days, withdrawal bleeding would take place regardless whether estrogen or testosterone was continued following termination of the progesterone.⁷ It was apparent to him that neither estrogen nor testosterone could prevent progesterone withdrawal bleeding (Figure 1-5).

The Delay of Onset of Menses

The question is frequently asked, can the due process of normal menstruation be postponed after ovulation has already occurred? In human experimentation, it has been shown that daily doses of 50 mg. of progesterone intramuscularly administered daily after ovulation has taken place will not delay the