

Gynecologic and Obstetric
pathology

With Clinical and Endocrine Relations

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Fourth Edition

With 683 Illustrations, 25 in Color

Emil Novak

A.B., M.D., D. Sc. (Hon., Trinity College, Dublin; Tulane),
F.A.C.S., F.R.C.O.G. (Hon.)

Late Assistant Professor Emeritus of Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore; Fellow and Past President, American Gynecological Society.

Edmund R. Novak, A.B., M.D.

Assistant Professor of Gynecology, The Johns Hopkins Medical School; Gynecologist, Johns Hopkins, Bon Secours, Hospital for the Women of Maryland, and Union Memorial Hospitals, Baltimore, Maryland.

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Preface to the Fourth Edition

This will be the last edition of this textbook in the names of Novak and Novak, for the senior author passed away on February 3, 1957. Although in ill health for a number of months, he was able to write until the end, and contributed more than a little towards the context of this edition. For this reason the authorship of Novak and Novak seems fully justified.

Because of the irrevocable nature of his disease, it was natural that my father and I discussed the future of many things, including the ultimate disposition of this text; for reading, writing and teaching were almost as vital to him as breathing. Very close to my Dad, as well as to me, has been Dr. Donald Woodruff, who is in charge of our Gynecological Pathology at Johns Hopkins, and he will be co-authoring future editions with me. I am sure that I can speak for both of us in stating that we are under no illusions as to completely filling the departed shoes. Both Dr. Woodruff and I of course were so intimate with my father that we have a pretty good idea regarding his reactions to various concepts, trends of thought, and worthwhile articles by different authors. Because of the basically sound framework devised for this book, we hope to be able to keep up the unique position of this text in gynecological and obstetrical pathology.

Various changes have been made in this edition. Recent cytological developments have indicated a need for more discussion, and Dr. John K. Frost, who is in charge of the Cytology Laboratory at the Johns Hopkins Hospital and the University of Maryland has been kind enough to provide a chapter on this rather new subject. Dr. Robert E. L. Nesbitt, Professor of Obstetrics and Gynecology at the University of Albany, has completely revamped the chapters dealing with Placental Abnormalities, Implantation, and Placentation. Increasing commitments by Dr. Louis Hellman have made it impossible for him to continue with this phase of the book, and we are most grateful for his past contributions. It has seemed inadvisable to continue with a chapter on Breast Pathology; space limitations were too strict, and in any case there are several excellent treatises on breast lesions.

In addition to a general revision with added bibliography, we have attempted to amplify such important and equivocal pathological problems as the relationships of basal cell hyperactivity and intra-epithelial cancer, endometrial hyperplasia and adenocarcinoma and pelvic tuberculosis. At the same time it has seemed wise to delete certain portions that were becoming more or less archaic. We have tried to replace old illustrations by more appropriate and better ones, but, as in past editions, can only apologize if proper credit is not always given, for many outside sections are sent into our laboratory. This does not imply lack of appreciation, but simply inability to properly catalogue the large amount of material so that appropriate thanks can be given.

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We are most indebted to a number of individuals whose ideas or illustrations are incorporated—above all, Dr. Donald Woodruff. Thanks as always go to the “Grand Old Lady of the Hopkins Gyn. Lab.,” Miss Eva Hildebrandt, Sister Mary Lucy, Mrs. Nancy Schueler of the Bon Secours Laboratory, and Miss Helen Clayton at the office for invaluable help. We should also like to express our gratitude to the many nice people associated with the Saunders Company who were so helpful and cognizant of the various difficulties associated with compiling this edition. Thanks again go to the Williams and Wilkins Company for permission to use various illustrations and figures.

Lastly, there is the problem of keeping future editions of this book on the past high level. This will be an almost impossible assignment, for I sincerely believe that my father had a general knowledge and literary style unparalleled in modern medical literature. All I can promise is a sincere effort to do our best by both Dr. Don Woodruff and myself.

EDMUND R. NOVAK

January, 1958

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Chapter One

The Endocrinology of the Menstrual Cycle and Pregnancy

Introduction. While gynecologic and obstetric pathology represents merely the application of general pathologic knowledge to the special field of the female reproductive organs, there are other considerations than the special structure of the tissues and organs concerned which make this field a very special one. Chief among these are the histologic changes produced by the hormones involved in menstruation and in pregnancy. It is probably correct to say, therefore, that in no field of pathology is there a greater need for the correlation of anatomic and physiologic considerations. Since most of what we know concerning the physiology of the cycle pertains to its endocrinology, it is evident that a basic knowledge of reproductive endocrinology is essential for the proper interpretation of the cyclic histologic changes which one encounters in most of the constituent organs of the female reproductive apparatus. It seems sensible, therefore, before discussing the pathology of the various diseases of the reproductive tract, to review briefly the endocrinology of the menstrual cycle and of gestation.

The Hormones of Menstruation

Endocrine Function of the Ovarian Follicles. A good starting point in the discussion of the cycle of menstruation is the phase immediately following menstruation. In the ovary at this time a considerable number of follicles begin to mature and to produce increasing quantities of the estrogenic hormone. One of these follicles for some unknown reason outstrips its fellows, which are blighted at various phases of development through the process which we designate as *atresia folliculi*. The one follicle which characteristically goes on to full maturity and ovulation reaches its maximum at a point approximately midway in the usual four-weekly cycle, though sometimes considerably earlier, sometimes considerably later.

From our present standpoint of endocrines, it is important to stress that the maturing follicles produce increasing quantities of a hormone substance which in the past was called by many different names, such as *female sex hormone*, *folliculin*, *estrin*, and *theelin*. It occurs in various closely related forms, but the common characteristic is the ability of the members of this group of substances to produce estrus in castrated animals. For this reason the generic name *estrogen* is now applied to them. The chief forms of

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estrogen found in the body are *estrone*, *estradiol*, and *estriol*. All of them are to be found in the urine of women during reproductive life. The evidence indicates that it is in the form of estradiol that the hormone is actually given off from the ovary.

The various estrogenic principles differ very markedly in the degree of their estrogenic potency. They are very tangible substances, for their exact chemical composition and molecular structure are now known, and they can be isolated in crystalline form. They can even be prepared synthetically, and their potency can be increased in various ways, as by esterification. There are many other interesting characteristics of this group of substances, such as their relation to various carcinogenic agents, and to certain estrogenic chemicals, such as the *stilbene derivatives*, which are highly estrogenic though chemically not related to the natural hormones. The most important representative of this group is the substance called *diethylstilbestrol*, commonly spoken of as stilbestrol, and this has achieved wide clinical usage as a cheap and effective substitute for the natural hormones when estrogen therapy is indicated. These subjects need not, however, be discussed in this brief review of cyclic endocrinology as related to the histology of the genital canal.

Endocrine Function of the Corpus Luteum. After the rupture of the follicle and the extrusion of the egg, the collapsed follicle undergoes a metamorphosis into the corpus luteum. The latter, therefore, is not a totally new structure, but simply a transformed follicle which then enters upon a second or corpus luteum phase of its life. The estrogenic hormone, hitherto produced by the follicle, is now secreted by the corpus luteum, which in addition gives forth a second hormone, much more characteristic of it than estrogen, and known as *progesterone*. And yet the two hormones, while producing very different effects upon the uterus, are quite closely allied chemically, as might be expected from the close kinship of the follicle and corpus luteum. It is thus evident that estrogen is found throughout the cycle, being produced first by the follicle and then by the corpus luteum. On the other hand, progesterone is present only after ovulation, being produced by the corpus luteum alone.

Like estrogen, progesterone can be isolated in purified, crystalline form, and various derivatives are known. Moreover, it has been established by the work of Venning and Browne that a substance found in the urine, and known as *pregnanediol*, represents the excretion form of progesterone.

Astwood has described a third principle, *luteotrophin*, which he believes in animals motivates the liberation of progesterone, but whether or not it plays any such role in the human is, to say the least, still very uncertain. As a matter of fact, an increasing number of investigators believe that luteotrophin is identical with prolactin, which is produced of course in the pituitary gland and is usually thought of as a stimulus to milk production in the postpartum breast.

Effects of Estrogenic Hormone. What are the effects produced by these two hormones upon the genital tract, and especially upon the uterus? In the first place, the estrogenic hormone is best thought of as a growth hormone with a special action upon tissues of müllerian origin, that is, upon the tubes, uterus, and the upper part of the vagina. In all of these it calls forth a growth response which increases from the end of one period to the beginning of the next, with also increasing hyperemia. This growth effect is especially pronounced upon the endometrium, though the myometrium is

likewise affected. In addition to this, it seems to have been established that it is the estrogenic hormone which is responsible for the normal rhythmic activity of the uterine musculature. This same hormone, becoming operative even before the time of puberty, brings about the appearance of the menstrual period and the various secondary sex characters, and it exerts a growth effect upon mammary tissue, in which it brings about duct proliferation.

Effects of Progesterone. Progesterone, on the other hand, exerts its effects upon an endometrium which has been previously built up by estrogen, producing, in such an endometrium the secretory picture noted in fullest degree before the onset of menstruation, the so-called *progestational phase*. As regards the effect of progesterone on the myometrium there is a difference of opinion. While many have believed, and still believe, that progesterone is the normal inhibitant of the characteristic contractility of the uterine musculature (Reynolds, Knaus), there is an increasing number of investigators who have produced evidence that progesterone has no such inhibiting effect. It is, however, an inhibitor of ovulation, which therefore does not occur so long as there is a normally functioning corpus luteum. In certain animals, like the rabbit, it is absolutely essential to the maintenance of pregnancy in its early stage. In the human it is certainly not indispensable, though undoubtedly it is of considerable importance from this standpoint. Finally, in the breast it produces the so-called lobular development, in contradistinction to the ductal proliferative action of estrogen.

Relaxin. This was described as a third ovarian hormone by Hisaw in 1929. There have been sporadic inconclusive reports about a non-steroid hormone commonly associated with pregnancy. Its status has always been extremely uncertain and must be regarded as such at this writing. Use of this agent in the treatment of dysmenorrhea, premature labor, cervical dystocia and threatened abortion has met with rather equivocal results. For fuller details the reader is referred to a recent publication by Eichner who was careful to warn against premature conclusions.

Anterior Pituitary Gonadotrophic Sex Hormones. Important as the two ovarian hormones are in the physiology of menstruation, there are other endocrine factors concerned which are just as important. It has long been known that the pituitary gland is in some way linked up with the gonads, but it was not until 1926 that the nature of this relationship was established, chiefly through the work of Philip Smith and his co-workers in this country, and that of Zondek and Aschheim in Germany. This is not the place to review the historical aspects of this work, but suffice it to say that it has established the fact that the anterior pituitary dominates the functional activity of the ovary, and that this control is exerted through *two gonadotrophic sex hormone principles*. One of these makes possible follicle maturation and thereby the production of the follicle hormone. It is therefore spoken of as the follicle-ripening or follicle-stimulating principle (FSH). The other, the luteinizing hormone (LH), is responsible for luteinization and therefore for the secretion of progesterone. Unlike the two ovarian hormones which have been isolated in crystalline form, the gonadotrophic pituitary hormones have not yet been isolated, and we know nothing as to their chemical structure. It has been postulated that the LH principle is composed of different fractions, one of which initiates ovulation while the other maintains the corpus luteum. However, many of us believe that, as noted by Holmstrom and others, ovulation occurs when an optimal ratio

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between FSH and LH is reached. Obviously there is much to be learned about the different actions and functions of the pituitary gonadotrophins.

Antihormones. In 1932 some confusion was thrown into the endocrine problem, particularly in the field of therapy, by Collip's publication indicating that the endocrines are capable of exciting the production in the blood of antihormonal substances. It is obvious that the acceptance of such a concept would have a bearing upon both experimental and clinical endocrinology, as the production of antihormones would be expected to lessen or nullify the effect of prolonged estrogen administration. A considerable controversy, as yet not completely resolved, has developed as to whether this antihormone production is of specific nature, or whether it represents merely a protein reaction. It cannot be said that the concept of antihormones has as yet had any noteworthy effect upon clinical organotherapy.

Summary of Menstrual Endocrines. To summarize, therefore, the estrogenic hormone produced by the growing follicle brings about a steadily advancing proliferative phase in the endometrium. With the rupture of the follicle the newly formed corpus luteum, through its secretion of both estrogen and progesterone, produces a still greater endometrial development, distinguished especially by increasing evidence of the secretory response evoked by the progesterone. The corpus luteum begins to regress, according to the recent investigations of Brewer, on about the twenty-second or twenty-third day of the cycle. The resulting withdrawal of the ovarian hormones is, as a matter of fact, believed to be the cause of the menstrual bleeding.

The mechanism whereby this is brought about is not yet entirely clear, though there is little doubt that the immediate factor is to be sought in the effect of these hormone changes upon the vascular apparatus of the endometrium. The important studies of Daron, Markee and others have thrown much light upon this problem, indicating that the endometrial degeneration and desquamation of the bleeding phase are due to ischemia resulting from intense and prolonged vasoconstriction of the spiral arterioles of the endometrium.

The blood supply of the endometrium is furnished by two sets of arterioles, the *straight*, and the *spiral or coiled*. The former serve a merely nutritional function, but the latter, passing upward from the basalis well into the functionalis, play an important part in the physiologic and histologic cycle of the endometrium.

Through the study of endometrium which had been transplanted to the anterior chamber of the eye in monkeys, Markee has shown that the spiral arterioles undergo a periodic vasoconstriction and vasodilatation, producing the so-called "blushing-blanching" phenomenon, the pulsations alternating at intervals of 60 to 80 seconds.

As the cycle advances, the spiral arterioles lengthen more rapidly than the endometrium increases in thickness, so that the vessels accommodate themselves to the endometrium by increased coiling, which in the premenstrual period becomes so marked as to slow down the blood flow and brings about a stasis. It is the latter which Markee believes is responsible for the endometrial necrosis and the degenerative blood vessel changes which lead to hemorrhage by both rhexis and increased diapedesis. The possible contributing role of arteriovenous anastomoses is still a matter of dispute.

Shortly before the onset of menstrual bleeding, the vasodilatation gives