



Novak's

# GYNECOLOGIC AND OBSTETRIC PATHOLOGY

With Clinical and Endocrine Relations

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FIFTH EDITION

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*In Memoriam*

EMIL NOVAK

February 3, 1957

To Our Families

## PREFACE TO THE FIFTH EDITION

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This is the first edition of *Obstetric and Gynecologic Pathology* in which Emil Novak did not play at least a partial role. He created the book and, alone, carried it through two revisions. His terminal illness prevented application of the full measure of his great energies to preparation of the Fourth Edition, but he did make definite contributions. The present authors are carrying on his work in the laboratory at the Hopkins and share his enthusiasm for both gynecologic pathology and its expression in this text. A spur to keeping the book fresh and vigorous is the realization that it stands as a monument to accomplishment of one of his major aims in life—the establishment of pathology as an important feature of the residency training program in gynecology.

In planning the Fifth Edition we invited Dr. Robert E. L. Nesbitt, already a significant contributor, to add a new section on Abortion. Dr. John K. Frost has substantially revised and brought up to date his chapter on Cytology. A number of chapters, such as those on Uterine Sarcoma and on the Vulva, have been completely revamped. Many of the old illustrations have been replaced with better ones and many completely new photographs added.

A change has been made in the bibliographies. Older references have been deleted and recent ones substituted in their place. We have taken this step on the basis that those who do want identification of the older classic papers can find them in the bibliographies in previous editions.

We wish to thank formally here those who have been good enough to send material to our laboratory. In all cases in which we have used such material we have attempted to give proper acknowledgment, but we may have inadvertently omitted credit in a few instances. On occasion we have utilized pictures that may not be of the highest technical quality, but we feel that this course is justifiable if it allows illustration of lesions only rarely encountered.

We are most indebted to a number of individuals whose ideas or illustrations are incorporated. Thanks as always go to the "Grand Old Lady of the Hopkins Gyn. Lab.," Miss Eva Hildebrandt, and to 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 Wilkin-

Company for permission to use various illustrations and figures, which we have done without specific indication.

Finally, let it be stated that the responsibility of carrying forward this book on something approaching the level

of the earlier editions does not rest lightly on the authors. Our effort will be sincere and intense.

EDMUND R. NOVAK

DONALD WOODRUFF

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# THE ENDOCRINOLOGY OF THE MENSTRUAL CYCLE AND PREGNANCY

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## Chapter One

### **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 endocrin-

ology of the menstrual cycle and of gestation. A complete résumé of the hormonal interrelations would require a separate textbook.

### **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-week cycle, though this may occur considerably earlier or 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 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.

It is also well established that certain androgenic substances are produced in the female and are measurable by urinary determinations of the 17-ketosteroids and other androgenic steroids. The usual source of these steroids is the adrenal gland but in certain conditions (Stein-Leventhal syndrome, arrhenoblastoma, etc.) the ovary may be responsible.

#### **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*.

In the pregnant woman, it is, of course, progesterone that is responsible for the decidual reaction that is merely an exaggerated progestational response. 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 inhibitor of the characteristic contractility of the uterine musculature (Reynolds), 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 in 1929, and there have been

sporadic inconclusive reports about a nonsteroid 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 publication by Eichner who is 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. 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 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 (LH) and is similar to the interstitial cell stimulating hormone (ICSH) in the male, while the other maintains the corpus luteum (LTH). However, many believe that, as noted by Holmstrom and others,