Surgical pathology of the ENDOMETRIUM

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OF THE ENDOMETRIUM

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To my wife, Rosemary

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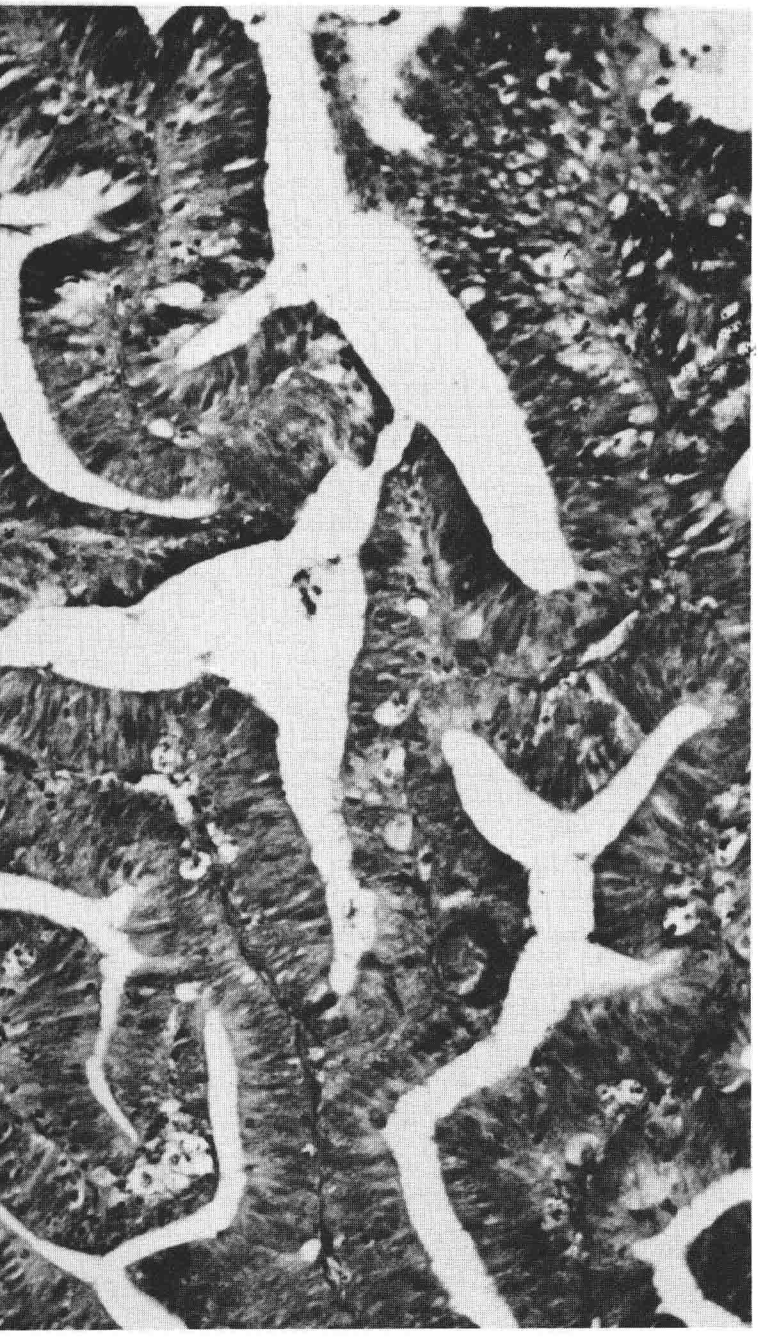
Surgical Pathology of the Endometrium

SURGICAL PATHOLOGY



Practical Aspects in Interpretation of Endometrial Curettings

J. B. Lippincott Company
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Preface

Surgical Pathology of the Endometrium is intended for use in community medicine by obstetrician-gynecologists and pathologists, and by the residents and students of those specialities who will also soon practice in the community. The emphasis is on the practical: no attempt is made to utilize techniques that are outside the reach of community practice. Nonetheless, the illustrations and discussion provided should assist any surgical pathologist "on the firing line" in the interpretation of one of the most frequent of specimens in surgical pathology, the uterine curettage.

Since it has been drawn so specifically for the community practitioner, this book covers all the facets of endometrial pathology that are dealt with on a routine basis in the community care of patients, namely biopsy and curettage specimens, abortion material, and cytopathology. For the surgical pathologist, the text is intended to provide guidance not only in the evaluation of uterine cancer and its precursors, but perhaps even more importantly for classification of the histologic patterns seen in nonneoplastic conditions of the uterus, which are often so difficult to correlate with the clinical status of the patient. Nagging points of differential diagnosis are illustrated and emphasized so that the perplexing features in routine specimens will be more clearly understood.

For the clinician, *Surgical Pathology of the Endometrium* provides an illustrated compendium of the language the surgical pathologist uses to explain what he sees. Finally, the volume adds to the conceptualization of endometrial pathology in several important areas:

1. The concept of lytic endometrium, how it differs from menstrual endometrium, and the part that incomplete hormonal stimulation plays in the histologic picture of endometrial sloughing at any point prior to true menstruation.

2. The concept that the histopathology of dysfunctional uterine bleeding, infertility, and amenorrhea often overlap, and that recognizable histologic patterns are frequently present which correlate with the patient's clinical status.

3. Emphasis on ever-present but seldom-discussed histologic features such as irritated stromal cells and the distinction between pseudoglands formed from strips of endometrial surface epithelium and endometrial adenocarcinoma.

4. A reclassification of endometrial hyperplasias and elimination of the "adenomatous hyperplasia" category.

5. Discussion and illustration of the less common variants of endometrial carcinoma. As in all other organs, variation in histologic pattern is characteristic in the neoplasms of the uterus.

Surgical Pathology of the Endometrium represents a first step in applying the practical approach to the teaching of surgical pathology. It is hoped that this approach will be useful.

Harvey Cove, M.D.

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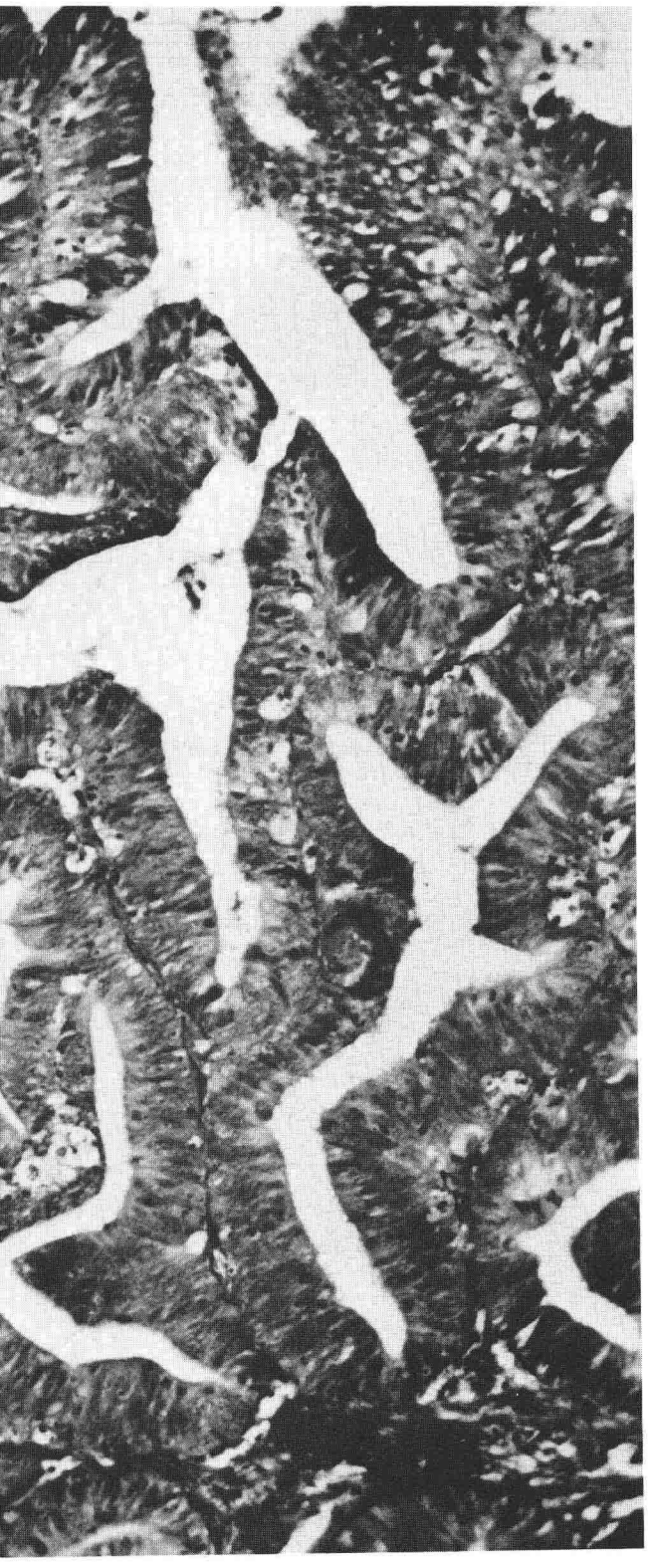


ONE

Surgical Pathology of the Endometrium

HARVEY COVE, M.D.

THE CURETTAGE SPECIMEN

A **frozen section** is seldom requested upon endometrial curettings, and some pathologists refuse to perform one. This results from a mistaken impression held by both clinicians and pathologists that frozen-section diagnosis is misleading and dangerous. Neither is true, provided that an accurate and complete history is available to the pathologist from the clinician. The clinician must realize that the diagnosis rendered is made only from a representative section; permanent sections of additional material may alter the final diagnosis. Unlike the practice for carcinoma of the breast, however, further surgery for cancer of the endometrium is usually deferred to a second procedure. Curettings which are abundant in older patients, or in which areas of necrosis are present, are the most suggestive of carcinoma. Nevertheless, pathologists should always bear the possibility of pregnancy in mind during a patient's reproductive years. I use an H and E frozen-section technique rather than a quick-staining procedure; a good H and E frozen section can be the equivalent of a good permanent section.

Frozen-section material is also required for enzyme and metabolic studies of the endometrium, but such studies are seldom undertaken outside research laboratories. Unfortunately, curettage specimens are infrequently submitted for electron microscopic examination, probably for two reasons. First, the whole specimen is usually embedded in paraffin so that the clinician will not miss focal changes. (Electron microscopy on paraffin-embedded material is possible but far from desirable.) Second, since frozen section is not often performed even on suspected malignancies, unusual tumors (for which electron microscopy might be rewarding) are not often recognized until it is too late.

I have occasionally been requested to perform frozen sections on abortion specimens in order to demonstrate chorionic villi in patients suspected of ectopic pregnancy. Gross recognition of chorionic villi may be difficult in spontaneous abortion specimens, but it should be relatively easy in therapeutic abortions. A double-wash technique is often helpful. Using two bottles of fresh saline, pick up fragments with small-specimen forceps, wash them free of blood in the first bottle, and then dip them into the second bottle. There the stalactitelike, grey-white chorionic villi will often be recognizable as they float toward the surface. If chorionic villi are grossly recognizable, only a representative section need be submitted to confirm intrauterine pregnancy. If chorionic villi are not recognizable, submission of multiple representative sections, and sometimes of the entire

specimen, is required. Occasionally a complete gestational sac, sometimes with intact fetus, may be identified.

It is sometimes useful in abortions or excessively bloody curettings, whether fresh or already formalin-fixed, to lyse the red cells with Bouin's solution. The residual fragments of tissue may be picked out for embedding. Although I prefer 10% buffered formalin for fixative, others use Bouin's or a variety of other fixatives.

Once processed, thin sections and good staining are essential. I utilize only H and E stains; all illustrations in this text exclusive of the cytology section are of H and E stained material

I regard endometrial curettings and biopsies as **"RUSH"** specimens, like biopsies from other sites. As such, interpretation should be available with other rushes on the following morning (including Saturdays).

ENDOMETRIAL BIOPSY AND CURETTAGE: INDICATIONS

By and large, two indications lead to endometrial biopsy or curettage. The first is abnormal uterine bleeding. In the younger woman, bleeding is often related to pregnancy; in older women, endometrial cancer or its precursors must be excluded. The second indication is infertility or amenorrhea. Here examination of endometrium serves three purposes: (1) to establish whether or not ovulation has occurred; if so, (2) to evaluate the effect of corpus luteum progesterone upon the endometrium; (3) to exclude other pathology (*i.e.*, tuberculosis, atypical hyperplasia). Endometrial biopsy is a minor operative procedure often performed in the outpatient setting. The discomfort of the patient varies from minimal to significant, but since cervical dilatation is not required (a narrow-gauge catheter is passed through the cervix into the endometrial cavity), general anesthesia is not necessary. Sampling can be performed with or without suction, and much of the endometrial surface can be sampled. Nonetheless, endometrial biopsy is a less complete procedure than endometrial curettage. If a lesion of more significance than that observed in the biopsy material is suspected, cervical dilatation and endometrial curettage, utilizing general anesthesia, are warranted. On the other hand, if the endometrial biopsy contains a carcinoma, the patient can be spared dilatation and curettage (D & C). Yet even endometrial curettage may miss a lesion hidden in the uterine cornu, for instance, or in a distorted endometrial cavity.

DATING THE ENDOMETRIUM

Development of the corpus luteum of the ovary is a dynamic process that evolves sequentially in a fixed time period, with each new event occurring at the same time in every normal cycle. Since the postovulatory development of the endometrium depends upon the effect of progesterone produced by the corpus luteum, its evolution also occurs sequentially and predictably.

TABLE 1-1. *Dating Hallmarks*

*Proliferative phase**
Simple tubular glands becoming coiled ("corkscrew")
Spindled stromal cells ("naked nuclei")
Glandular and stromal mitoses
Edema (midproliferative)
Secretory phase, first week postovulatory†
Day 14, 15: Morphological silence
Day 16, 17: Subnuclear vacuoles (SNV)
Day 18, 19: Loss of SNV, glandular dilatation, early secretion
Day 20: Maximal secretion of glycogen
Secretory phase, second week postovulatory‡
Day 21, 22: Stromal edema
Day 23, 24: Periarteriolar predecidual changes
Day 25, 26: Extension of predecidua
Day 26, 27, 28: Leukocytic infiltration and hemorrhage
Secretory phase in the cycle of gestation§
From day 24: Reestablished secretion, stromal edema, and decidual reaction
Menstrual phase‖
Lytic late secretory endometrium
Regenerative proliferative endometrium

* Because the proliferative phase, unlike the secretory phase, is varied in length from individual to individual, precise dating of the proliferative phase is not possible and it can only be categorized generally into early, mid-, and late stages.

† Dating in the first postovulatory week utilizes features found in the endometrial glands. The stroma resembles that of late proliferative endometrium throughout the cycle, until the predecidual changes are seen on about day 24.

‡ Dating in the second postovulatory week utilizes features in the stroma. The glandular changes are ignored for dating purposes.

§ Should pregnancy supervene, the features seen in sequence in the secretory phase are present in unison after day-24-secretions, stromal edema, and decidual change. These gradually develop into the well-recognized features of pregnancy: hypersecretory endometrium, Arias-Stella reaction, and decidua.

‖ Menstrual endometrium is lytic, *i.e.*, there is fragmentation and dissolution of the late secretory endometrium. In the beginning of menses, secretory-phase features are identifiable. Later in menses, degenerative changes and lysis are too extensive to allow identification of secretory features. Menstrual endometrium must be distinguished from other lytic endometria. Weak proliferative features signaling regeneration can be found intermingled with the lytic, late secretory endometrium, thus sometimes producing a mixed-pattern endometrium.

Dating of the endometrium is based upon an idealized 28-day cycle in which ovulation is numbered the 14th day by some (including this text) and the first day by others (Table 1-1). The length of a normal cycle varies from woman to woman, and, in any given woman with normal cycles, it may vary a few days ordinarily from month to month. The length of the

normal postovulatory or secretory phase does not vary from woman to woman but is 14 days plus or minus 1 day. The preovulatory or proliferative phase of the normal cycle is not fixed and does vary among women. Because of the fixed duration of the secretory phase, secretory endometrium can be dated. Preovulatory endometrium, on the other hand, cannot be dated precisely and is generally described only as early, mid, or late proliferative endometrium. The normal menstrual cycle varies from 25 to 35 days. Shorter or longer cycles, occurring regularly in a woman, may be normal; the variation reflects a range in the duration of the proliferative phase.

Many physicians who perform endometrial biopsy to establish whether or not ovulation has occurred delay the procedure until the onset of menses. This results in a large percentage of uninterpretable specimens, because there is dissolution and disruption of the stroma and glands, as well as regeneration, during menstruation. It may not be possible even to establish a diagnosis of secretory endometrium in such a specimen, much less to evaluate accurately the adequacy of the progesterone effect. This delay, of course, results from fear of disrupting a new implantation. However, it has been noted that in the infertility patient endometrial biopsy does not appear to result in increased fetal wastage, even if performed in a cycle of conception. Paradoxically, it may reduce fetal wastage, possibly as the result of an enhanced decidual reaction or other local factor.

Dating the endometrium has been shown to be accurate within 2 days about 80% of the time; it is based upon the time of ovulation as established by the drop in basal body temperature (BBT) prior to the sustained rise. The date assigned should be that for the most advanced features seen. (This does not apply, however, to the presence of subnuclear vacuolization (SNV) as an indication of ovulation because SNV can occur sporadically prior to ovulation. At least 50% of glands should contain SNV to establish that ovulation has occurred.) The onset of menses is not used for and does not correlate well with the date established histologically since bleeding may be premature following the biopsy procedure.

Biopsy is best obtained from the uterine fundus on the anterior wall. Material obtained from the lower uterine segment cannot be dated because it does not have the same cyclic development as the fundal endometrium. It is often difficult to decide how to interpret a fragment from the lower uterine segment, which is sometimes mistaken for a polyp, sometimes for a hyperplasia, and sometimes for basalis endometrium.

MENSTRUATION

Although broadly used to imply uterine bleeding whatever the source, **menstruation** really refers only to the cyclic shedding of menstrual endometrium that developed fully under ovarian hormonal stimulation in preparation for a pregnancy which has not occurred. The first day of menstruation is considered to be the first day of the idealized 28-day menstrual cycle. Curettage during menstruation not only demonstrates the degenerating late secretory endometrium but occasionally may also contain a newly regenerating, early proliferative endometrium.

PROLIFERATIVE ENDOMETRIUM

Proliferative endometrium (Figs. 1-1 to 1-10) has three characteristic features: simple tubular glands which become coiled into a corkscrew pattern when the length of the glands exceeds the thickness of the endometrium by the middle to late part of the proliferative phase; fibroblastlike stromal cells with hyperchromatic nuclei and little cytoplasm (naked nuclei); mitoses which increase in number as ovulation nears, both in glandular epithelial and in stromal cells. As noted above, the proliferative phase is variable and may be 10 to 20 days in length (although it is considered of 14 days' duration in the ideal 28-day cycle). It is not possible to date proliferative-phase endometrium, hence its specification as early, middle, or late phase. However, the proliferative phase is an estrogen-stimulated growth phase, and growth is reflected in heightening of the glandular and surface epithelial cells, with nuclear pseudostratification, increased numbers of mitoses, and glandular coiling. Mid-proliferative endometrium characteristically exhibits marked stromal edema. By the late part of the phase, the edema has largely regressed.

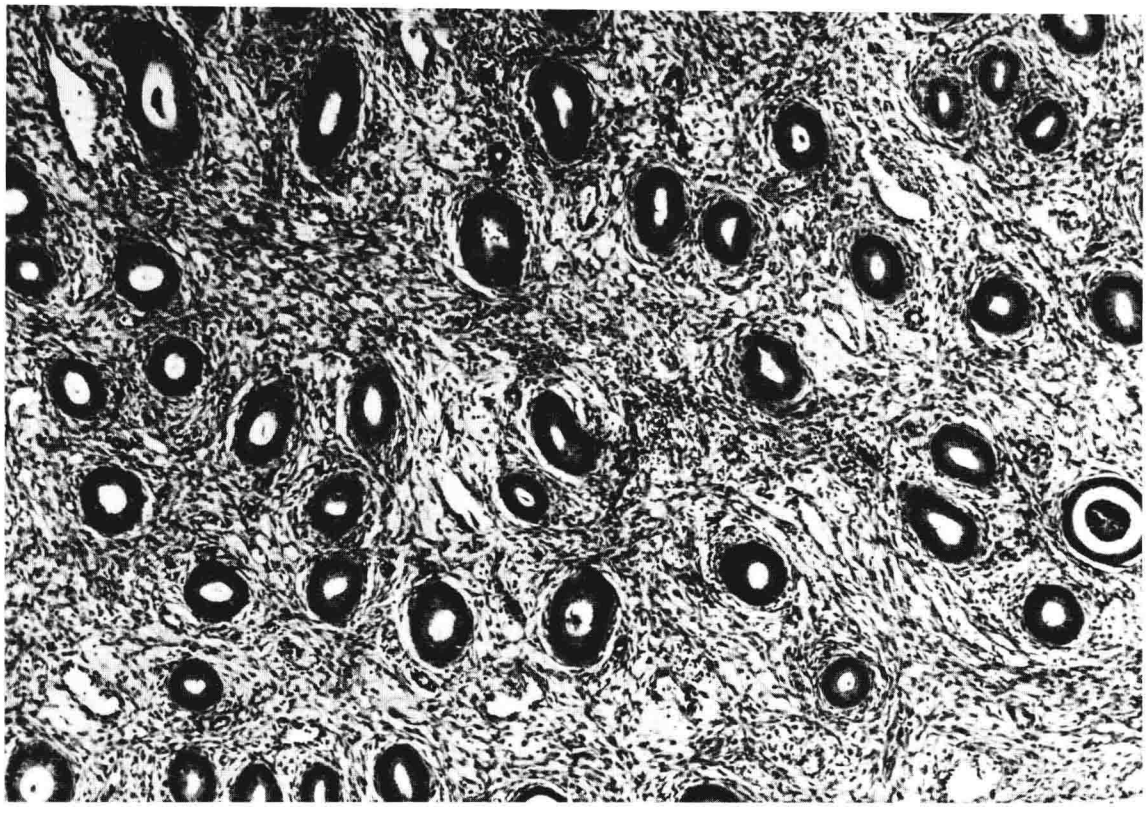
SECRETORY ENDOMETRIUM

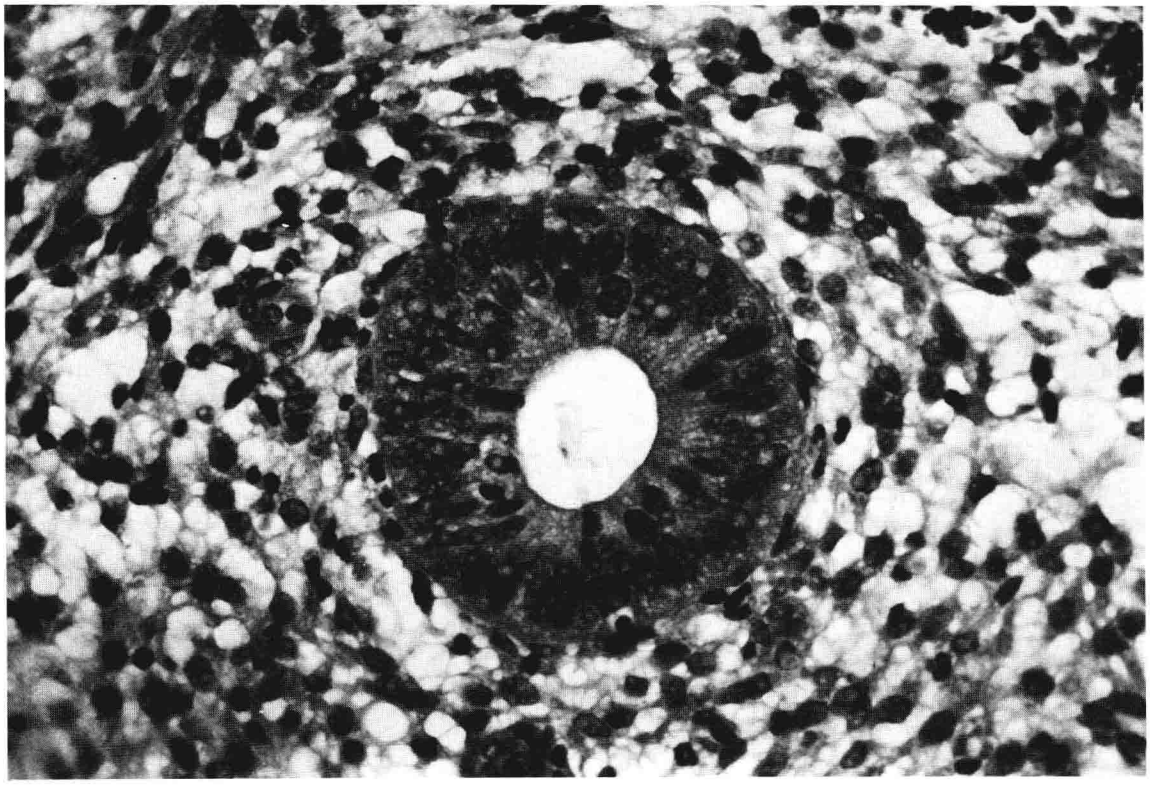
As noted above, the normal secretory phase in all women requires 14 days plus or minus 1 day. Development is not completely uniform throughout. However, by recognizing the most advanced changes in the sequential development of the secretory phase, we can assign a date to secretory endometrium (Figs. 1-11 to 1-27) equivalent to the number of days following ovulation that the sample was taken. As noted above, the day of ovulation, determined by the fall before the sustained rise in the BBT is considered to be day 14 of the idealized 28-day cycle. Ovulation, however, cannot be confirmed histologically until 36 to 48 hours after it has occurred, when SNV are recognizable in over half the endometrial glands (Figs. 1-12 to 1-14).

(*continued on p. 14*)

FIG. 1-1. Proliferative endometrium. Simple tubular glands cut in cross section.

FIG. 1-2. Proliferative endometrium. A simple tubular gland cut in cross section. There is slight pseudostratification of the nuclei and a mitotic figure. The stromal cells are typical of the proliferative phase and secretory phase until predecidual changes appear on day 24. They contain dark spindled ("naked") nuclei with little cytoplasm.





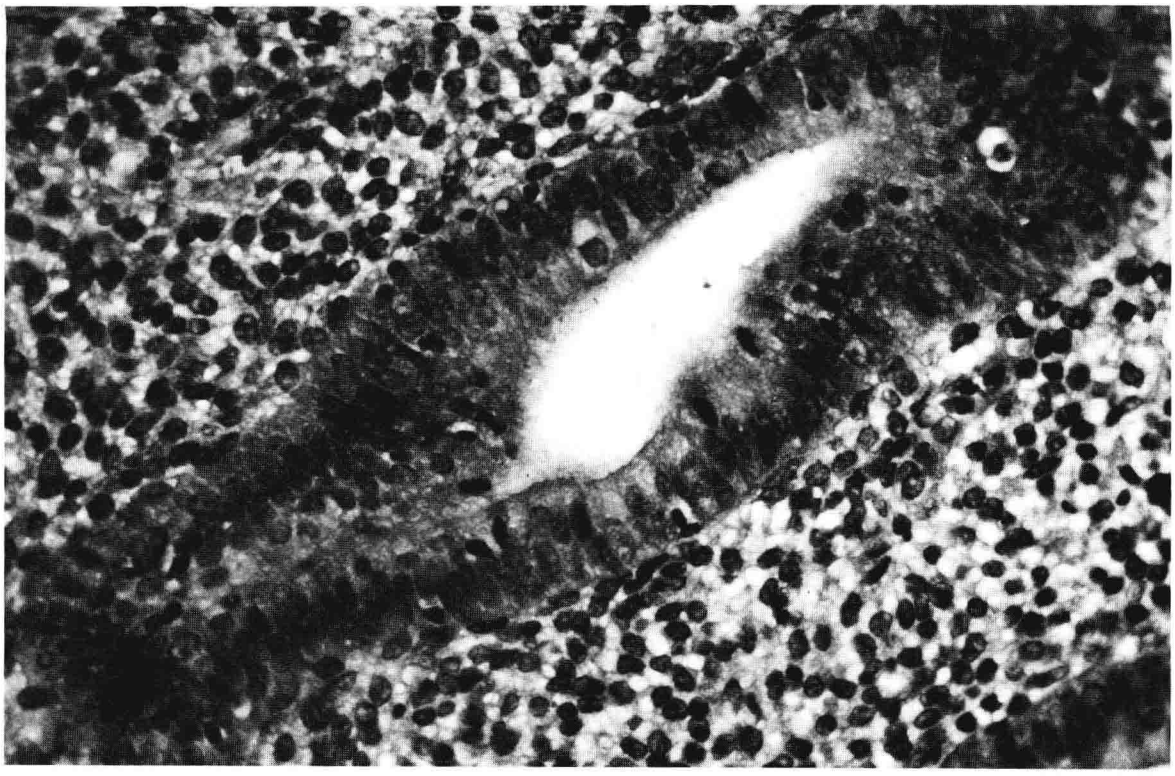


FIG. 1-3. Proliferative endometrium. Simple tubular glands cut in longitudinal section. Note the mitotic figures.

FIG. 1-4. Midproliferative endometrium. Marked stromal edema, simple tubular glands.

FIG. 1-5. Midproliferative endometrium (higher power of Fig. 1-4). The stromal edema is prominent.